PROPHYLAXIS OF ENDEMIC GOITER WITH IODIZED OIL IN RURAL PERU

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Three Andean villages at altitudes of 3,100 to 3,500 meters above sea level were studied in order to determine the prophylactic effect of iodized oil administration on endemic goiter and cretinism (1). At the time of the study the population in these villages was approximately 4,000, with an annual growth rate of about three percent. In a group of 3,000 subjects examined in a house-to-house survey, the visible goiter rate, as defined in an accompanying paper (2), was 55 percent. However, when the occurrence of palpable goiter was considered as well, the incidence of goiter rose to 83 percent. Fifty percent of the children in the 0-5 yr age group were goitrous and of these, 20 percent demonstrated visible goiter. Goiter prevalence increased with age, as did nodularity. An example of this is shown in Fig. 1. In some families every member was found with goiter as illustrated in Fig. 2. Goiter was also found among the domestic animals. The percentage of defective persons in the three villages ranged from 1.0 to 3.6 percent. Although these villages are accessible by automobile, they are still quite remote and isolated.

Measurement of iodine excretion in these three villages averaged 17 µg per 24 hr, and the radioactive iodine uptake averaged approximately 75 percent. The mean value of the total serum iodine was 5.5 µg per 100 ml and the total thyroxine

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Fig. 1. Huge nodular goiters are more prominent among adults as shown in this 74 yr old mother and her 39 yr old daughter from the endemic area of Tapo.

Fig. 2. Clinical appearance of a group of four brothers and two sisters all of whom have diffuse goiters of Grade I and II. The boy on the top right and the girl below were six and seven years old respectively. The other four children were below five. A six month old baby sister who does not appear in the picture was not goitrous as yet.

was 4.1 µg per 100 ml measured as iodine, with a range of 1.7 to 6.4 µg per 100 ml. As a result, many persons were below the accepted normal range for a population without endemic goiter; however, these patients had no clinical evidence of hypothyroidism.

In October, 1966, 1,700 persons from these villages were injected either with iodized oil or placebo, and were reinjected three years later along with a new group of persons injected for the first time. The program design is described elsewhere (1,2).

In order to control carefully the progress of women in the child-bearing age and to follow as many pregnancies throughout gestation as possible from both the iodized and placebo groups, a full-time physician was appointed to rotate continuously among the villages. Newborn infants were recorded at the time of delivery.

This report is particularly concerned with the evaluation of these children who were born into the program and now have been followed up to five years after injection of their mothers. The marked effects of thyroid hormone deficiency during intrauterine and early post-natal life, resulting in physical growth and mental retardation, have already been demonstrated in human beings (3-6) and in animals (7-9). Though hypothyroidism has been reported among children (10) and developmental delay is well known in cretins from iodide-deficient endemic goiter areas, as yet it is not well established that the deficiency of iodine alone is the only cause, or whether any developmental delay actually occurs in non-cretin children. We hope, therefore, at this time to provide additional information on the role of iodine deficiency in early development as well as the effect of iodine supplementation in mothers-to-be.

The negative effect of chronic iodine deficiency on maternal thyroid hormone synthesis, but not necessarily on the fetus, is described in an accompanying paper (II).

SUBJECTS AND METHODS

A total of 456 newborn children was registered, of whom approximately 44 percent belonged to the placebo or iodine-deficient (Group D) and the other 56 percent to the iodized group (Group I). Of these, 84 percent have been covered by comprehensive follow-up evaluations which included the following:

1. *Physical examination*, including the assessment of goiter.

2. *A full anthropometric series* including body weight, stature or supine length, sitting height or crown-rump length, head and chest circumferences, as well as upper arm circumferences, triceps,

subscapular and waist skinfold thickness and biacromial and bi-ilicristal diameters in order to characterize the nutritional status of the subject. The measurements were made according to recommendations given by WHO (12). A Lange caliper was used for the skinfold measurements.

3. *Radiology studies* made from birth through several different ages in order to demonstrate bone maturation according to standard methods. The examination included a PA x-ray of the left hand and wrist using a Bucky field-portable x-ray unit at a tube to film distance of 91.5cm. The bone age was then calculated according to the patterns of Greulich and Pyle (13).

4. *Motor and neuropsychological appraisal* in 60 percent of these children utilizing the Gesell test (14). In some cases, a more critical neuropsychological development was measured by the Stanford-Binet (15) and the Brunet-Lézine (16) tests. The Stanford-Binet evaluation was employed in the two to four yr-old group only and the Brunet-Lézine in those under two yr of age. In a few children older than two yr, but with a marked mental retardation, the Brunet-Lézine test was employed. Audiometry, voice, buccofacial praxis, articulation praxis and verbal expression and comprehension were tested by methods adapted to our environment by Dr. Cáceres' team (17). The more critical studies were done only in the village of Huasahuasi.

5. *Electroencephalographic studies* made with an eight channel Nikon Kode portable unit on 15 subjects in each group between the ages of two and four yr. These studies were carried out under sleeping conditions after Seconal administration (.025-.075 gm) in most of them.

6. *Urinary excretion of iodide (UEI)* measured in a sampling of the overall newborn population, between the ages of two and 4 1/2 yr according to methods previously described (1).

The above studies were mainly cross-sectional. On some occasions, semi-longitudinal evaluations were carried out. All investigators were unaware of the injection status of the subjects throughout the determination of the above parameters. Grouping of results according to protocol injection of the mothers occurred only after the qualification of the studies was concluded.

RESULTS AND COMMENTS

At the time of birth there was no difference in the children of placebo or iodized-oil injected mothers, although there did appear to be a slight tendency for weight to be higher in the iodized group. Head circumference and Apgar scores were in the

normal range in both groups. Placental weights were lower than in usual standards, but they were not different from those expected in any population at 3,500 meters above sea level (18). Mean values of the data recorded at birth are included in Table 1.

Table 1. Data at birth of children born to iodized and placebo mothers

	Weight (gm)	Length (cm)	Cephalic Circumference (cm)	Apgar	Placental wt. (gm)
PLACEBO	2981 ± 69*	44.7 ± 3.2	33.9 ± 0.3	9.0 ± 0.2	488 ± 50
IODIDE	3197 ± 181	49.4 ± 0.3	34.2 ± 1.2	7.9 ± 0.7	413 ± 157
P VALUE	ns	ns	ns	ns	ns

*Mean ± SE

Birth rate was slightly higher in the iodized group than in the placebo one. Two hundred fifty-four births were registered among 390 fertile-aged women in the former while in the latter there were 202 births among 402 fertile-aged women. Infant death rate, on the other hand, although significantly higher when compared to well-developed countries, was similar to other rural areas in Peru (19), with no significant difference between iodized and placebo groups - i.e. approximately 11 percent in the former and 12 percent in the latter during the first two years of life.

No congenital goiter was found in either group. The data obtained in regard to height and weight were similar in both placebo and iodized groups in both sexes as shown in Figs. 3 and 4. These factors beyond 12 months of age are in the third percentile for North American standards (20), but when compared to another population in Peru (21) not involved with endemic goiter, the figures are comparable. Thus, these changes appear to be characteristic of the rural Peruvian population rather than of the endemic area alone. A slow and prolonged growth pattern has been demonstrated in high altitude Peruvian natives (22). However, there appeared to be little difference between the iodine and placebo groups as both attained nearly the same stature year by year. The iodine group tended to show slightly higher growth rate values, but there was considerable overlap (Table 2). Post-natally there was an observable tendency for weight to increase more than height, which might suggest that there is no severe malnutrition among these children. Additional support for this theory was provided by the skinfold and upper arm circumference measurements as shown in Table 3. While both groups

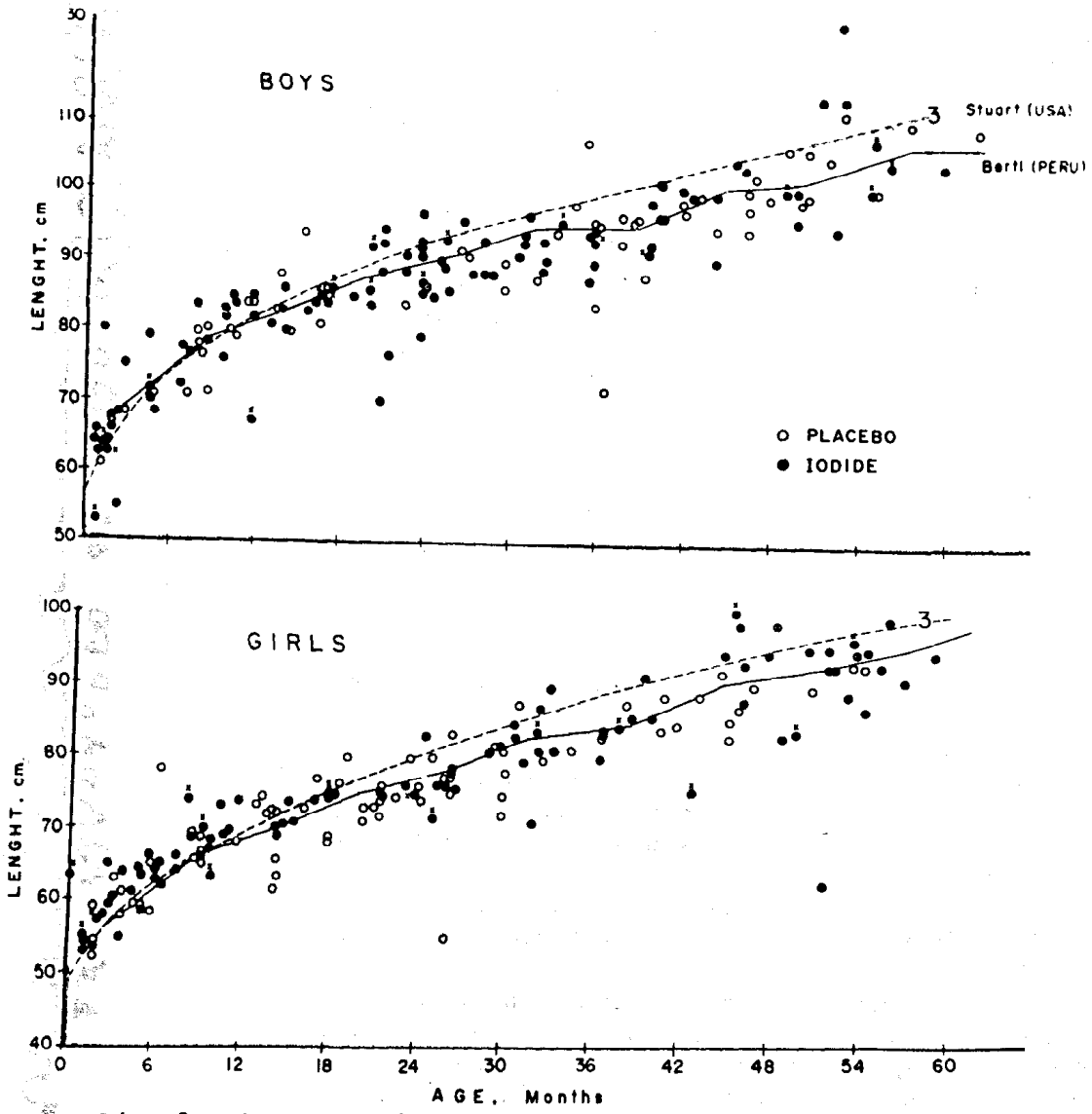

Fig. 3. Stature and supine length of a cross-sectional sample of 0-5 yr old children, as compared to North American patterns and to another non-goitrous rural population in Peru.

appeared to have nearly the same upper arm circumference, the sums of skinfolds were slightly, but not significantly, greater in the placebo group. Although it seems unlikely that this finding may reflect a slow thyroid function in the iodine-deficient group, this possibility has not been ruled out. In any event, whatever the factors responsible for the slightly greater fat deposition of the placebo group, they did not appear to be reflected in taller statures. Moreover, in both groups there was a drop in the skinfold values from birth through 12-18 months of age.

Birth x-rays disclosed no evidence of intrauterine hypothyroidism as indicated by the appearance of ossification (23). In only two subjects was there any indication of retardation in bone maturation and this was not definite. It is interesting to

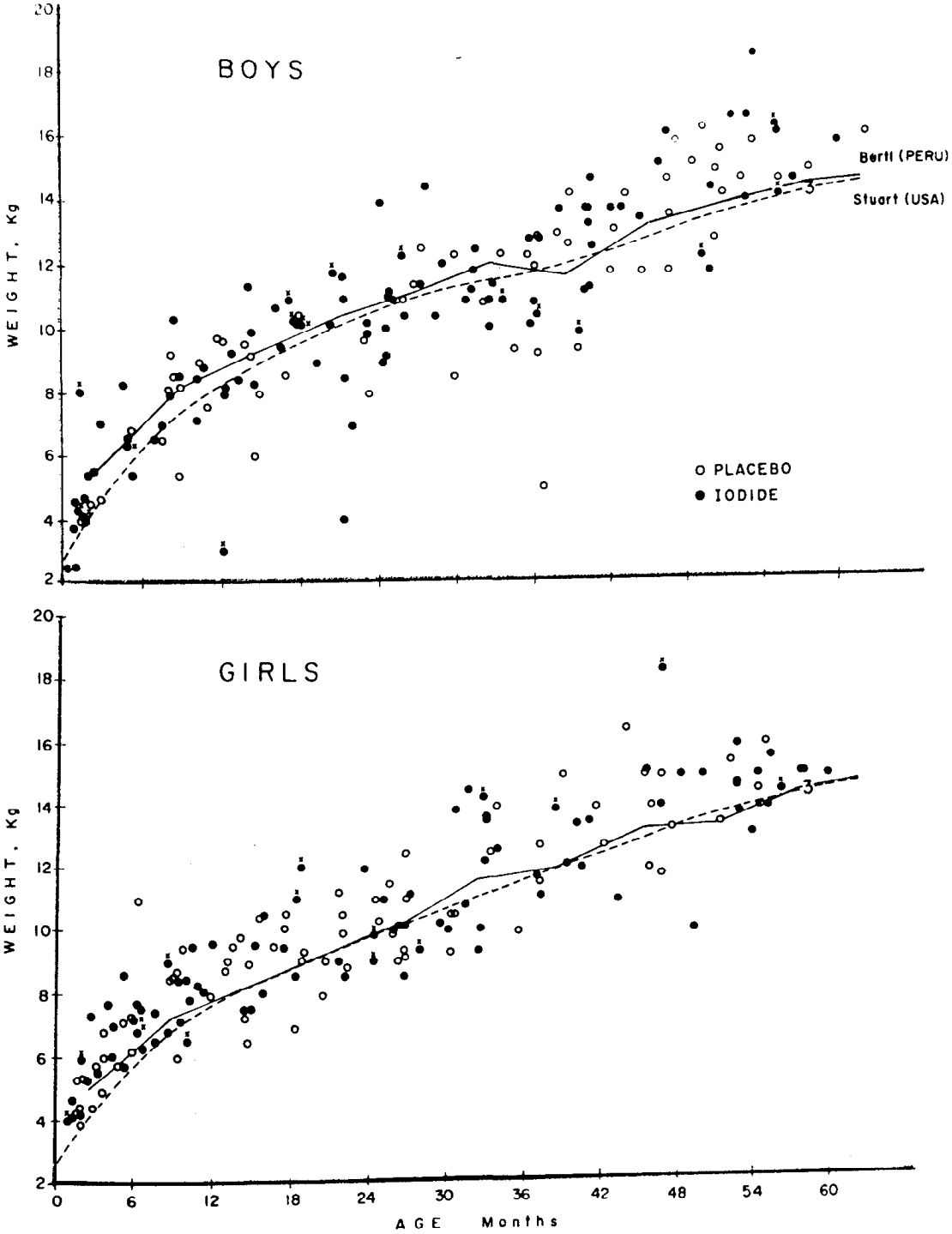

Fig. 4. Weights of the same cross-sectional sample as described in Fig. 3.

Table 2. Growth Rate (cm/month) in children born to iodide deficient (placebo) and iodide treated (iodide) mothers

Age Months	0-6	6-12	12-24	24-36
PLACEBO	2.52	1.58	0.85	0.55
IODIDE	3.16	1.75	0.83	0.84

Table 3. Skinfold thickness (mm) and upper arm circumference (cm) of children born to iodide-deficient (P) and iodide-treated (I) mothers

Age	Group	N	Triceps	Scapula	Waist	Sum of Skinfolds	Upper Arm Circumference
2 - 6 months	P	17	7.4	5.9	5.8	19.1	13.1
	I	28	6.5	5.1	4.5	16.1	12.6
6 -12 months	P	15	7.9	5.6	5.5	19.0	14.4
	I	15	6.6	4.5	4.4	15.5	13.8
1 - 2 years	P	19	7.8	4.2	4.0	16.0	14.0
	I	21	7.0	3.9	3.4	14.3	14.1
2 - 4 years	P	44	8.3	4.1	3.7	16.1	14.8
	I	23	7.9	3.8	3.8	15.5	14.8
4 - 5 years	P	14	8.0	4.1	3.9	16.0	15.0
	I	21	7.5	3.6	3.8	14.9	15.5

note that post-natal bone maturation continued quite normally until the 12th to 18th month, when there was evidence of some slowing down which resulted in a 12 months' lag with respect to chronological age through the third year and a lag of up to 25 months through the fifth year. However, there was no difference between the iodized and the non-iodized group (Fig. 5). It is possible that this bone retardation is related to weaning and weaning diarrhea, as well as to other significant factors

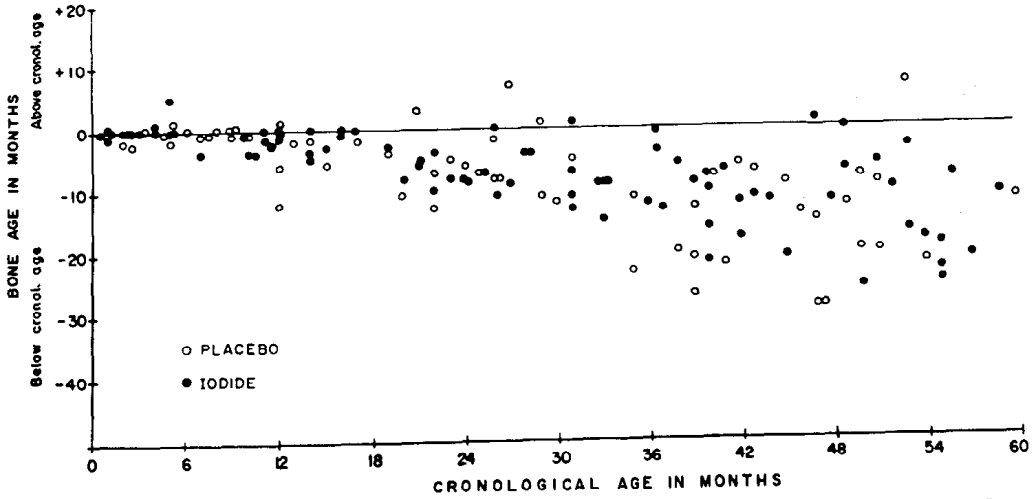

Fig. 5. Bone age maturation as compared to chronological age. A progressive "delay" is apparent beyond the 12th-18th months of age in both groups.

in rural areas of developing countries. The possibility that this bone delay, when coupled with nutritional factors, may be a genetic characteristic of our populations, has not been ruled out. If true, comparison to North American standards would be inappropriate. Our results are consistent with similar findings reported by Baker et al. (24) in other non-endemic areas in the highlands of Peru as well as with those reported by Israel et al. (25) in children from endemic goiter areas of Ecuador.

The motor and neuropsychological results which we have obtained applying the Gesell tests to about 70 percent of the newborn population from both iodized and placebo groups are shown in Fig. 6. An interesting pattern was observed: both groups appeared to follow the normal curves until approximately 18 months, at which time they began to fall below normal developmental patterns. There were 20 to 30 percent of the subjects who scored below 90 during the first 12 months, but this percentage did not differ between the two groups. Scores were more affected by linguistic defects than by inadequate motor or social skills.

The Stanford Binet and Brunet-Lezine assessments were carried out in 49 subjects in the placebo group and 43 in the iodized oil group. For the purpose of statistical analysis, however, exclusion has been made of those children born to mothers

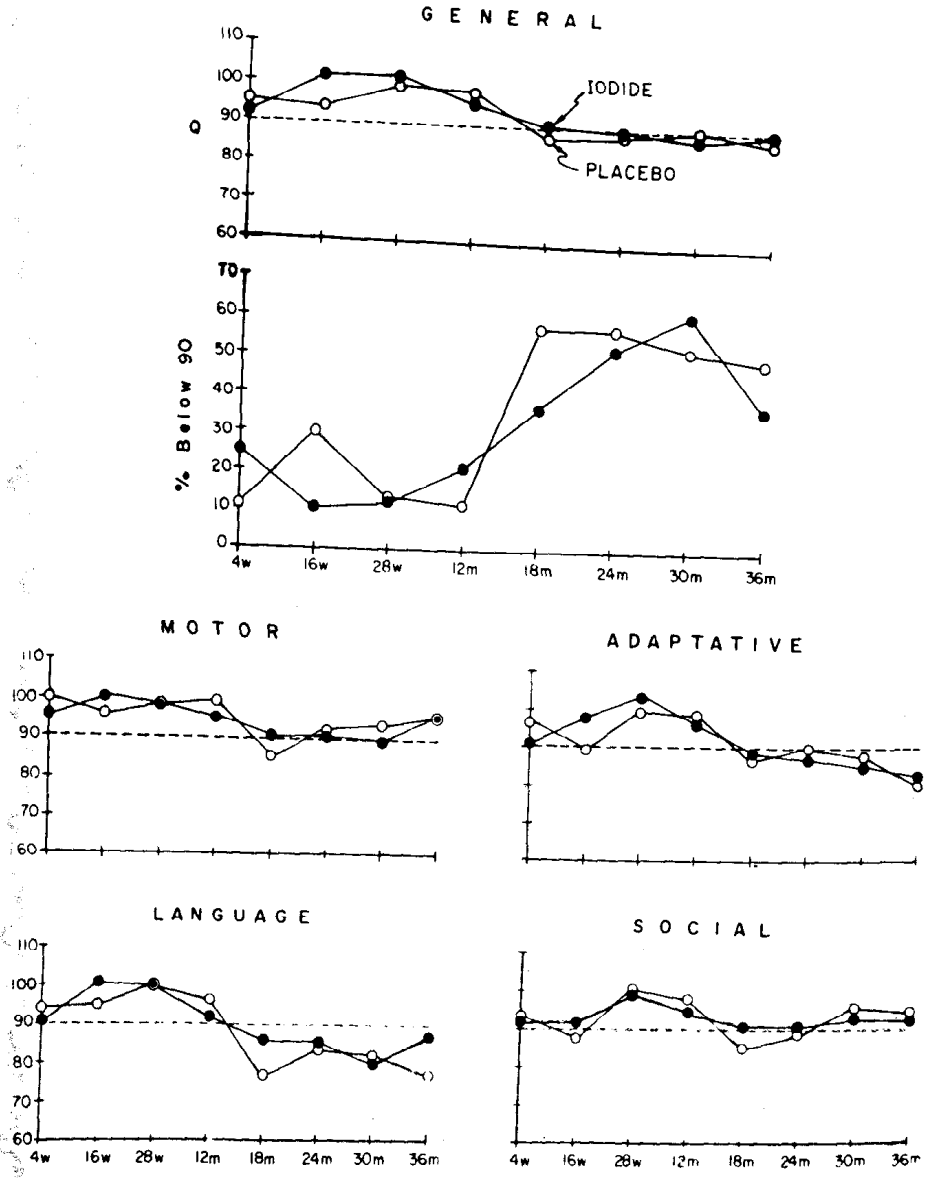

Fig. 6. Developmental quotients assessed by Gesell tests.

injected while already pregnant. Therefore, the results illustrated in Table 4 and Fig. 7 apply only to those children of mothers who received iodized oil or placebo prior to conception. While differences in the mean IQ scores shown in Fig. 7 were not significant between the two groups, there was a tendency for higher results in the iodized group regardless of the age interval. Moreover, Table 4 demonstrates that while only 15 percent of those in the placebo group obtained IQ scores of 90 or over, 26 percent were in the 80-90 "dull" range and 59 percent were in the below normal category. In the iodized group 34 percent demonstrated

Table 4. Percent distribution of iodine-deficient (D) and iodine-supplemented (I) children according to their IQ scores

	AGE, Months						TOTAL	
	3-12		13-24		25-58			
	D(10)	I(8)	D(11)	I(12)	D(25)	I(15)	D(46)	I(35)
Normal	20	50	0	25	20	33	15	34
Dull	30	37	18	17	28	27	26	26
Borderline	40	12	9	25	28	27	26	23
Mental Deficiency	10	0	73	33	24	13	33	17
Language Deficiency	10	0	64	42	72	73	58	46
Hearing Deficiency	0	0	11	0	14	0	11	0

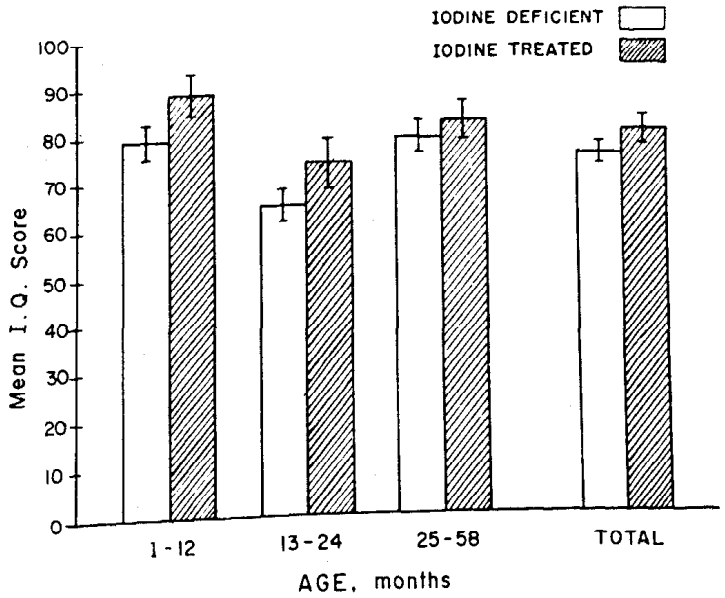

Fig. 7. Comparison of intellectual status in terms of intelligence quotients (IQ) between children born to iodine-deficient and iodine-treated mothers.

an IQ higher than 90 with 26 percent also in the borderline area, but only 40 percent in the below-normal category. Language and hearing deficiency was also more frequent among the placebo children, and 11 percent of these showed some hearing impairment but not deafness.

Electroencephalographic studies were done on a sample of Huasahuasi children. Those children born to mothers injected after conception were excluded from the results, leaving 12 in the iodine-deficient group and nine in the iodized group. All but one EEG showed normal traces. The abnormal one was in the iodine-deficient group and showed disorganized background activity with bursts of theta and delta activity and scattered low waves, which is suggestive of mildly diffuse, disorganized activity. The small number of observations prevented drawing firm conclusions from this study.

The urinary excretion of iodide in a sample of 32 children born to iodine-deficient mothers demonstrated a mean value of 27 µg per 24 hr. In 11 children with an age span of 24 to 57 months born to iodized mothers UEI values ranged from seven in the older children to 107 in the younger ones with a mean value of 42 µg per 24 hr. It would seem from these data, that iodized mothers are capable of supplementing their offspring with adequate amounts of iodide through placental transfer and through lactation after birth for periods of up to 24 months.

Unfortunately, the results of this study still do not permit us to arrive at definite conclusions about the benefit of iodide supplementation on the physical and neuropsychological development of children born to mothers previously injected with iodized oil as compared to children born to iodine-deficient mothers. A comparable delay in development was similarly observed in both groups and was also found to be true in a separate parallel study (26). Although a more critical neuropsychological evaluation showed a tendency for higher IQ mean values in the iodized group, on an individual basis there was no significant relationship between physical growth and intelligence status. This latter observation is consistent with those made in children even more mentally retarded (27). Recent information from New Guinea (28) and Ecuador (29) on the prevention of easily detectable neurological damage amongst children born to iodized mothers is strong evidence in favor of the important role played by iodine deficiency in the pathogenesis of cretinism. However, the drop in the percentage of defectives seen in Ecuador in their control group from the original 10 percent found in the overall population before starting the iodized oil program to only two percent in the population born over a five yr period, while the iodine deficiency remained the same, supports the assumption that this deficiency

is not the only cause of cretinism, but rather is a permissive factor. Medical care and possibly an improvement in the socio-economic conditions introduced in this area might have been contributing to these changes. There is also a general consensus as to the underlying role of heredity in the pathogenesis of defects associated with endemic goiter as demonstrated by the variability in the percent of cretinism amongst villagers suffering the same degree of iodine deprivation (30). Heredity possibly accounts for the occurrence of few defectives, since the base-line prevalence of defectives in our series ranges from 1.0 to 3.6 percent, which is significantly lower than the 10 percent observed in Ecuador. It is also possible that, although no obvious cretins have been detected in our series, the IQ difference between iodized and control groups observed in Huasahuasi village, where the prevalence of defectives was the lowest, might become more significant in the other villages where the higher prevalence is possibly due to a genetic trait.

We have examined one patient recently from the iodized group who is now nearly two yr of age, but is unable to walk and is markedly retarded. She demonstrates hypertelorism, her Stanford-Binet score was 71, and her bone age was retarded to five months. She is clearly retarded in comparison with her sibs. We intend to investigate the cause of this retardation. A single case of Down's syndrome has also been observed in the iodized group as well as one well-documented patient with a 21 trisomy in her karyotype in the iodine-deficient group.

Therefore, we must conclude that if one is to judge the actual benefit of iodine supplementation alone as a means of eliminating the development of handicapped children from the world-wide endemic areas, not only must more sophistocated neuropsychological assessments (other than that used to identify cretins), more than one psychological instrument and the electroencephalogram be employed, but also, factors other than iodine deficiency must be taken into consideration. Minor mental handicaps, aside from the gross abnormalities seen in cretinism, must be recognized as well in children protected by iodine prophylactic programs.

SUMMARY

Studies in agrarian villages in highland Peru have been conducted in order to determine the effectiveness of iodized oil prophylaxis against endemic goiter and cretinism. After random injections in the population, observations have been made over a period of five years which have not yet disclosed definite differences between the control children and those born to mothers who received iodized oil prior to conception. Both

groups have shown some delay in neuromotor and physical development beginning some time between the 12th and 18th months of life. Thus, our data do not enable us to conclude at present that iodized oil prophylaxis in itself is significantly beneficial in terms of neuropsychological or physical development in our population groups. The existence of a tendency for higher IQ's in the iodized group, however, cannot be ignored and needs further investigation. As both groups were under the same socio-economic and ecological circumstances, other climatic, nutritional, social and economic factors have undoubtedly played a major role which may obscure the effect of iodide administration. The importance of heredity in cretinism and mental defects also cannot be overlooked.

ACKNOWLEDGEMENT

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DISCUSSION BY PARTICIPANTS

PRETELL: A study on nutrition in these Andean villages was carried out by the National Institute of Nutrition and showed a low intake of animal protein. Most of these people eat meat perhaps once a week. Caloric supply is about normal.

ERMANS: I think there is some danger in comparing the effects of iodized oil in a population with control patients living in the same area. In a previous study, a survey of goiter prevalence was made in a given village of Idjwi using as controls two groups of untreated subjects, the first one being a group of subjects living in the same village, and the second, subjects living in a neighboring village in which iodine prophylaxis was not introduced. After one year, the non-injected subjects living in the village treated with iodized oil showed a clear-cut regression of goiter size and prevalence. In the neighboring village no change at all occurred. This result seems to be related to recirculation of iodine in the areas in which large amounts of iodine were given. Another interesting point is the observation by a zoologist (S. O.) who is measuring the size of the thyroid glands in rats captured in the goitrous region. These glands were found to be initially enlarged, but after administration of iodized oil to the inhabitants of the village, the size of these glands was definately reduced.

IBBERTSON: I wonder if Dr. Ermans would agree that it is possible to increase body iodine stores without materially influencing the amount of iodine appearing in the urine. I agree that it is difficult to maintain a control population. In the Himalayas all the human excreta goes into a pile of leaves in the bottom of the household and once a year this is carried out in the fields and dumped. The iodine comes back in the crops and the whole population becomes iodized as a result, so that a control population in this sort of setting is useless.

PRETELL: I agree. We have been able to measure the urinary excretion of iodine in the non-treated group to 19 months after the program was started. We also noted, as will be demonstrated, a small drop in the prevalence of goiter in the non-treated population, but the uptake and the urinary excretion of iodine were the same.

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