

Prophylaxis and Treatment of Endemic Goiter with Iodized Oil in Rural Ecuador and Peru¹

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WITH FEW EXCEPTIONS endemic goiter continues as a major health problem in those areas of the world where the disease has been known for generations. Substantial understanding of its pathogenesis, simple and effective preventive measures, and a rising world economy have done little to reduce its prevalence on a worldwide scale. This state of affairs is due principally to the low priority accorded to the disease by health authorities and to the ubiquitous conflicts of interest between the public and private sectors.

One of the most extensive and severe focuses of endemic goiter occurs in Latin America. The disease is widespread throughout Central and South America but is concentrated in the mountain ranges extending along the Pacific coast from Mexico to Chile. As an estimate, over 10 million people may be affected by this condition. Precise figures cannot be obtained because morbidity statistics are in-

complete or unavailable and because surveys have been limited in geographic scope or to special age groups (1, 2).

If endemic goiter implied only an enlargement of the thyroid, it could be dismissed as a trivial affliction. In fact, severe endemic goiter is accompanied by a substantial incidence of cretinism and deaf-mutism. Furthermore, there is good reason for suspecting that, in many cases, the mental retardation (apart from overt cretinism), neuromuscular disturbance, and short stature that usually accompany severe endemic goiter may in fact be causally related. In addition, it has been suggested that the disease may have an unfavorable effect on general health and educational capacity.

In view of the magnitude and severity of the problem, the Pan American Health Organization (PAHO) has maintained an active program of technical assistance in this field during the past 2 decades. Of the 26 member governments, 17 have a defined problem of endemic goiter, and endemic cretinism is known to exist in several of these afflicted areas. Fifteen of the 17 countries have enacted legislation requiring the iodization of salt, and the remaining 2 have legislation under consideration. Despite this expression of official concern, effective programs have been established in less than half of the countries affected, and many of the most serious areas of endemicity are still without any preventive

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measures. In view of this, the PAHO decided to look for alternate methods of prevention of endemic goiter and cretinism. This decision in no way conflicted with the priority given to salt iodization but rather was directed to finding an interim solution. The PAHO also recognized that some of the most severely affected populations are so isolated from normal commercial channels that the people will continue to use primitive sources of uniodized salt even if salt iodization is implemented on a national scale.

Among various alternative methods for supplying dietary iodine, one has been provision of parenteral iodine to establish long-term body stores. A number of years ago a program of goiter prevention by the injection of iodized oil was begun in New Guinea. Information available from those surveys (3-5) indicated that prophylactic programs were effective in reducing the prevalence of goiter and that the procedure was practical and safe. The results obtained in New Guinea, however, have not provided enough information regarding the effectiveness of this form of prophylaxis in reducing incidence and have given virtually no information regarding prevention of those disabilities that are epidemiologically associated with severe endemic goiter. With these considerations in view, field studies were begun in 1966 to determine the feasibility and effectiveness of parenteral administration of iodized oil in prevention and treatment of endemic goiter and the defects that may accompany it.

Two neighboring countries of South America, Ecuador and Peru, were selected for study since both presented areas with high prevalence of goiter and cretinism, and no preventive programs were being undertaken.

THE PROGRAM IN ECUADOR

Two villages, Tocachi and La Esperanza, were selected because of their re-

moteness and because, in both, endemic goiter is severe and cretinism is commonplace. They are about 70 km north of Quito, 6 miles apart, and ethnically, socially, and biologically comparable (6). The villagers have unusually limited social mobility and contact with the outside world, characteristics shared with hundreds of others in the South American Andean region.

The socioeconomic situation is precarious in both villages (Table 1). There is a high infant mortality rate, a high incidence of illegitimacy, a low level of literacy, and a great poverty reflected by the low per capita income and small percentage of artisans. Chronic iodine deficiency is severe in both villages, and prevalence of goiter and associated defects is high (Table 11). Salt used by the villagers contains 0.24 $\mu\text{g/g}$ iodine.

Iodine was given to the Tocachi population, while La Esperanza served as a control village. The program was started in March 1966. The iodized oil was Ethiodol (37% iodized poppy seed oil, each milliliter containing 475 mg of iodine, obtained from E. Fougere, Inc., Hicksville, L. I., New York). Disposable plastic syringes were used to avoid problems of sterilization at high altitudes. The following dosage schedule was used:

up to 2 years old:	0.2 ml of iodized oil
2-6 years old:	0.5 ml of iodized oil
6-12 years old:	1.0 ml of iodized oil
12 years old and up:	2.0 ml of iodized oil

The oil was administered intramuscularly into the gluteal region of small children and into the deltoid region of adults. Drawback was practiced to ensure that oil was not injected intravenously. Merthiolate was used for skin sterilization.

Thyroid size was evaluated by a modification of the classification of Pérez et al. (7).

Grade Oa:

not palpable

Grade Ob:

palpable, but not visible with the head raised

Grade I:

easily palpable with head in normal position and visible with the head raised; those glands presenting easily palpable nodules with head in normal position but not visible with head raised were included in this grade

Grade II:

easily visible with head in normal position

Grade III:

visible at a distance

Grade IV:

monstrous goiters

For epidemiologic purposes glands were considered abnormal when *grade Ob* or larger. These glands were recorded as diffuse or nodular.

Examination of selected children included an X-ray of the left hand and observation for gingival emergence of the deciduous and permanent teeth. Hand X-rays were taken using Kodak no-screen Ready Pack medical X-ray films, at a tube-to-film distance of 91.5 cm (36 inches) with a Bucky field-portable X-ray unit. Anthropometric measurements were also made. For evaluation of cretinism, the fundamental fact taken into account was the mental deficiency of the subject. The degree of deficiency was obvious to the surveyor and confirmed by the manner in which the subject lived in relation to the rest of the community.

Shortly after the completion of the injection program a physician and a midwife were assigned full time to Tocachi and La Esperanza. These villages had not had a physician in residence before. Small dispensaries were established for administering to the general medical needs of the communities, but particularly to keep continuous close observation on the effects of the prophylactic program and on the progress and results of pregnancies as they might occur. All pregnancies in both villages have been followed and neuromotor development and physical growth of all of the children born in both villages have been studied since March 1966. Epidemiological surveys for goiter prevalence and

TABLE I
Socioeconomic conditions in two Ecuadorian villages

	Tocachi	La Esperanza
Percent of subjects born in the village	97	91
Percent of infant mortality	43	29
Percent of unwed mothers	26	14
Percent of subjects who are illiterate	31	34
Percent of subjects who have visited the coast region	5	9
Percent of artisans	5	5
Annual income per capita (\$)	90	85

TABLE II
Prevalence of goiter and of neural and motor abnormalities, percent of total population (March 1966)

	Tocachi	La Esperanza
General goiter	69.7	52.8
Nodular goiter	41.1	23.4
Diffuse goiter	28.6	29.3
Endemic cretinism	8.2	6.0
Deaf-mutism (severe impairment in hearing and speech)	4.5	2.5
Deafness (severe impairment in hearing)	1.6	0.0
Mutism (severe limitation in speech)	0.4	0.4
Motor abnormalities	1.0	0.8
Other congenital malformations	0.4	1.2

incidence have been conducted at 6, 12, 20, and 25 months after the injection program.

THE PROGRAM IN PERU

The plan in Peru has been similar in most respects (8). Three central sierra villages, Tapo (3,311 m), Huasahuasi (3,531 m), and Ataquero (3,100 m) were selected. A net growth rate of 3% per annum assured a high percentage of children.



Tarma, a nearby town equipped with laboratory and hospital facilities, served as headquarters for the field work. More detailed laboratory work was carried out in Lima, about 5 hr away by automobile.

Iodized oil or a placebo was injected into 1,771 subjects. The placebo was poppy seed oil without iodine. Nine hundred and twenty-three subjects in the three villages were injected with iodized oil (GrI) and 848 with the placebo (GrP). Injections were done in females up to 45 years of age and in men up to 18. Among the schoolchildren, groupings for the placebo and the iodized oil were predetermined at random within a given age. Care was taken to match the size of goiter. In other groups randomization was accomplished by consecutive alternation of iodine and placebo injection. The doses used were the following:

less than 1 year old:	0.5 ml
from 1 to 5 years old:	1.0 ml
over 6 years old:	2.0 ml

In adult women with nodular goiter the dose was reduced to 0.2 ml. All injections were performed in the 1st week of October 1966.

Surveys were also made for bone and neurological maturation. Reevaluation of the prevalence of goiter was made at 6, 12, and 18 months after injection. At the time of reevaluation, the examiners were ignorant of both the prior estimated gland size and the type of injection. Clinical assessment was made by members of the same team throughout the program.

Particular attention has been paid to the females in the child-bearing age (16–45 years old). As many pregnancies as possible occurring in both the GrP and GrI groups were followed throughout gestation. Newborns were recorded for the purpose of future evaluation. In addition, serum levels of thyroid hormone were investigated in pregnant women, as well as iodine content in milk from lactating women.

RESULTS

Goiter Prevalence

Administration of iodized oil in Tocachi caused a regular and consistent fall in the prevalence of goiter for 20 months, both in the total population and in men and women taken separately. The ratio of goiter in women to that in men increased while the prevalence of goiter in the total population decreased (Fig. 1). After the 20th month the prevalence began to rise again.

At the time of the survey 6 months after iodization, nodular goiter had increased noticeably while diffuse goiter had decreased, but in the following surveys (up to the 20th month) nodularity also steadily decreased. The Ethiodol produced a distinct decrease of the incidence of *grade II* goiters and larger, and this decrease continued into the survey conducted 25 months after iodization. Although the decrease in size of large goiters was achieved at the expense of an increase in the incidence of *grade I* goiters, after the survey at 12 months *grade I* goiters also tended to diminish. This trend persisted after 20 months. After the 20th-month survey, however, this type of goiter (but not those of larger size) tended to increase in the total population. It seems certain that the sharp increase of nodular goiter found 6 months after iodization was a result of involution of hyperplastic thyroid tissue.

The degree of reduction in goiter diminished as age increased. The maximum reduction was seen during the first 18 years of life. There was minimal reduction after 40 years of age. Reduction at 25 months after iodization was 36% for the total population. There was not a single instance of palpable thyroid in children born in Tocachi to iodized mothers. Eighteen percent of the children of La Esperanza up to 2 years of age who were examined at the time of the 25th-month survey presented palpable glands. As to overall goiter prevalence in La Esperanza, the re-

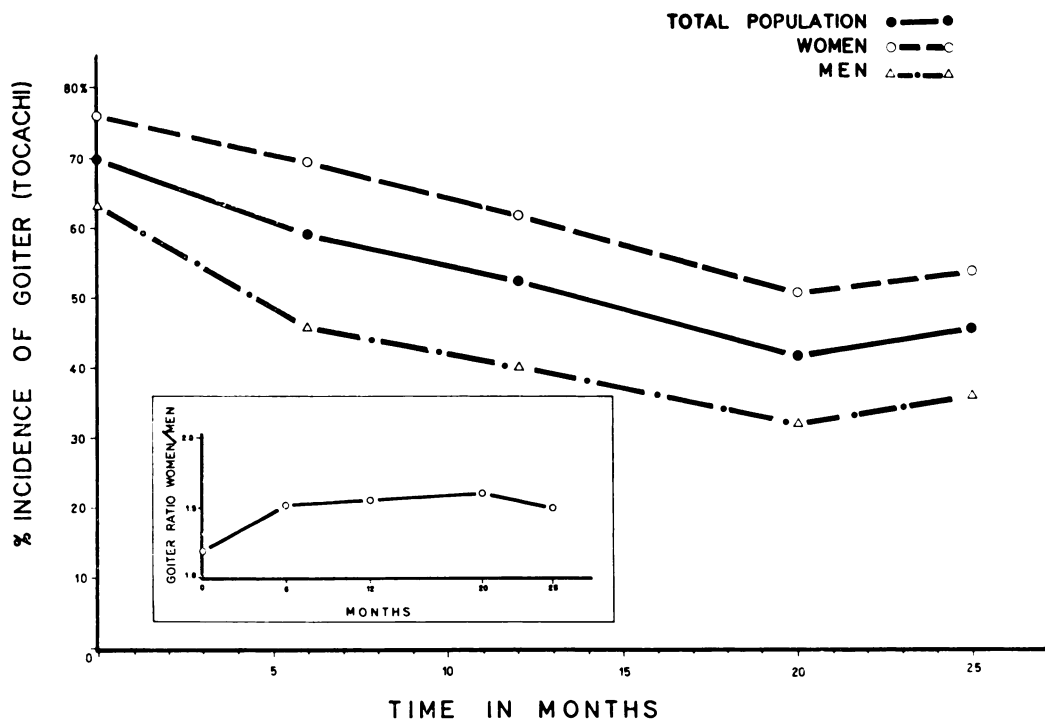


FIG. 1. Effect of administration of iodized poppy seed oil (Ethiodol) on the incidence of goiter in a village of rural Ecuador. Insert shows the ratio of goiter in women and men.

sults indicated that there was a significant increase during the same period.

The findings in the three Peruvian villages were similar. Fifty percent of the population were affected with goiter during the first 5 years of life. This was primarily of the *Ob* degree; thereafter, more than 90% were goitrous. Size of goiter and nodularity increased with age. The prevalence of "endemic cretinism" and other defects varied from 1.0% to 3.6% in the three villages.

Goiter prevalence in the iodized group in Peru decreased steadily for 18 months after the injection program (Fig. 2). A striking fall from 58 to 16% in visible goiter as well as from 86 to 52% in palpable goiter occurred in the iodized group, while the placebo group changed only slightly from 52 to 45% in the former and 81 to 78% in the latter. In both groups the decrease was more marked in males than in females. In addition, the decline appeared

to be more pronounced in the 13- to 18-year- and under-6-year-old groups than in the 6- to 12-year-old subjects.

Thyroid Function and Iodine Metabolism

In the Ecuadorian study, uptake of ^{131}I by the thyroid proved to be depressed at the time of the survey at 6 months. A restoration toward normality was observed in successive control surveys (Fig. 3). The urinary excretion of iodine (UEI) (Fig. 4) followed an exponential pattern. Since the subjects on whom UEI determinations were done were adults who had received 2 ml of Ethiodol (950 mg), elimination of those 950 mg would be virtually accomplished at the 40th month after injection. These results imply that a dose equal to half of that used would reduce the total effective time by only 5 months.

Changes in thyroid function tests at different stages of the Peruvian study are shown in Fig. 5. The 24-hr thyroid uptake

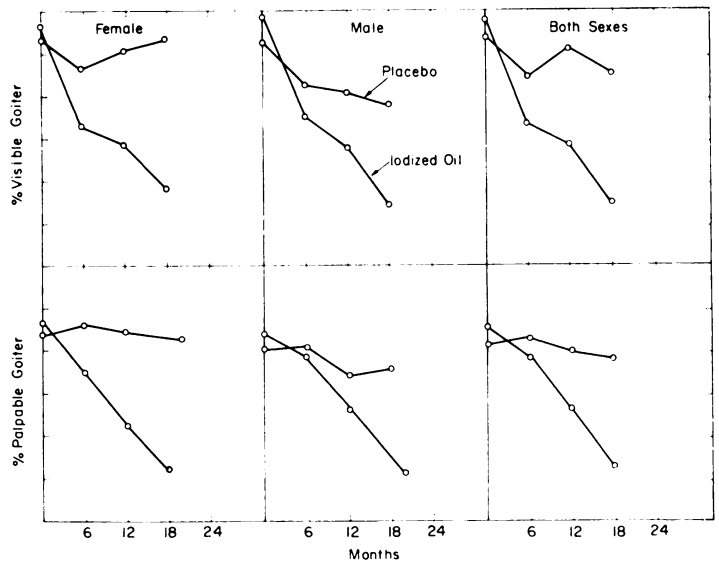


FIG. 2. Decline in goiter in three Peruvian villages after the administration of iodized poppy seed oil. A comparison is made with subjects injected with noniodized oil. In each case the ordinate is from 0 to 100%.

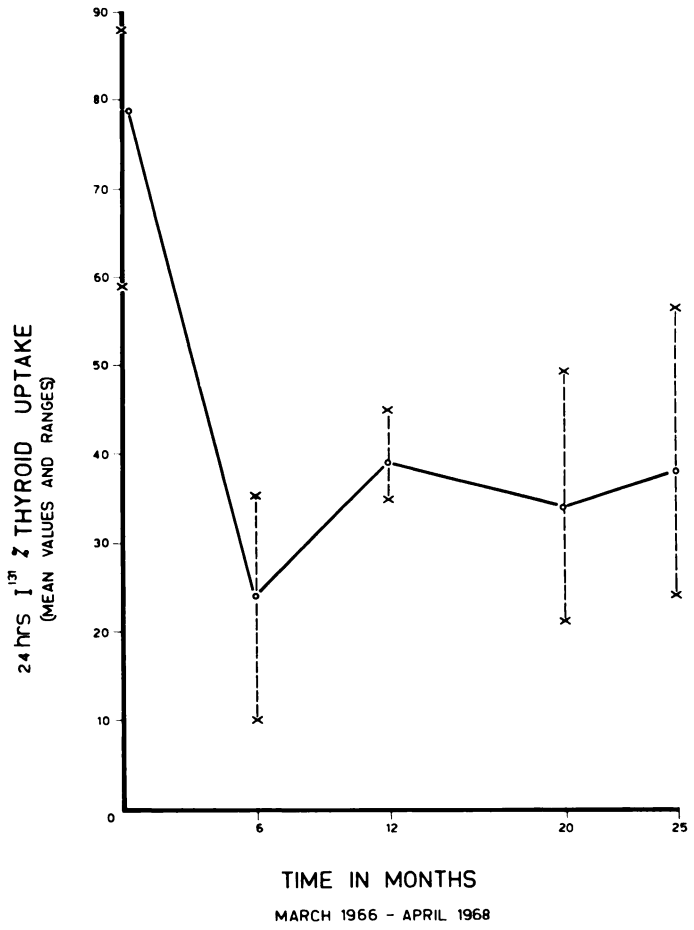


FIG. 3. Effect of administration of iodized oil on radioactive iodine uptake by the thyroid.

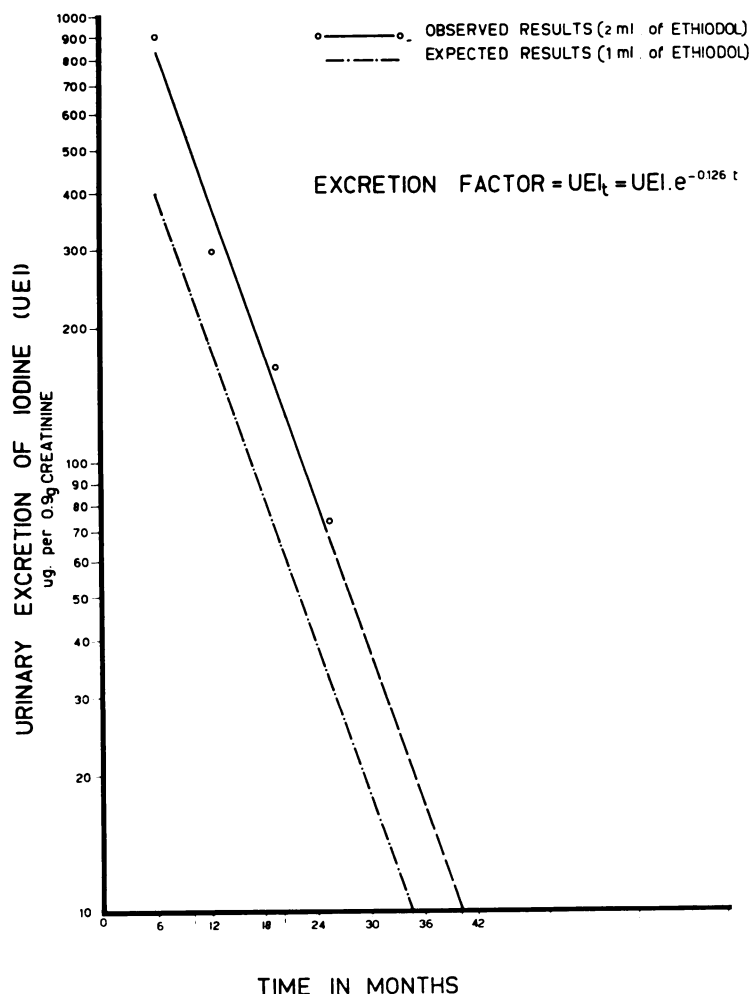


FIG. 4. Urinary excretion of iodide following administration of iodized oil. The iodide is excreted exponentially.

fell from a control level of $75.1 \pm 0.9\%$ to $15.8 \pm 1.4\%$ at 9 months but increased slightly to $19.5 \pm 0.3\%$ and $21.9 \pm 1.1\%$ at 13 and 19 months, respectively. This change corresponded to a rise above normal levels of both serum iodide and PBI. These reached maximum levels by the 9th month and then fell to normal by the 19th month. Serum thyroxine remained within normal limits. The values for urinary excretion of iodide (UEI) in relation to the dose of Ethiodol at two different age levels appear in Table III. The 6- to 12-year group, which received about double the dose of iodine per kilogram of body weight

(41.5 mg), had a higher UEI at 6 months than the 13-year-and-over groups, which had an average dose of 23.0 mg. However, values in both groups continued to fall to equivalent levels throughout the later periods. The UEI for the latter group fell exponentially after 6 months. The slopes, and therefore the $T_{1/2}$, were similar for both 2.0 ml and 0.2 ml doses in this group (Fig. 5).

Effects in Infants and Children

A total of 92 deliveries was recorded among the women of child-bearing age in the three Peruvian villages. Of these, 58

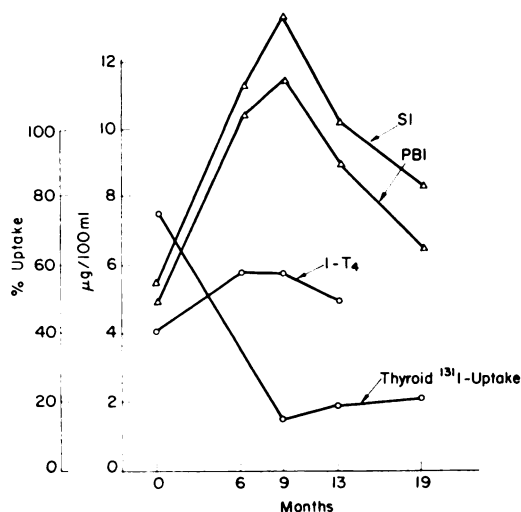


FIG. 5. Effect of iodized oil on radioactive iodine uptake, plasma thyroxine iodine (I-T₄), protein-bound iodine (PBI), and total serum iodine (SI).

were in the iodized group. The plasma thyroxine levels in the pregnant noniodized group had a mean value of $5.2 \pm 0.4 \mu\text{g}/100 \text{ ml}$ during the last 5 months of pregnancy, and thus failed to rise, as normally occurs. The mean value in the iodized subjects was $7.9 \pm 0.7 \mu\text{g}/100 \text{ ml}$. The content of iodine in milk from 9 women injected with 2 ml of iodized oil was $9.7 \pm 1.2 \mu\text{g}/100 \text{ ml}$, whereas it was $1.9 \pm 0.7 \mu\text{g}/100 \text{ ml}$ in women injected with 0.2 ml iodized oil, and 0.0 to $0.5 \mu\text{g}/100 \text{ ml}$ in four given the placebo oil.

Ninety children were born in Tocachi from March 1966 to April 1968 (to iodized mothers); 16 (17%) died and 2 (2%) went

away. One hundred seventy-seven children were born in La Esperanza (to untreated mothers) during the same period; 17 (9.6%) died and 5 (2.7%) went away. The children of both Ecuadorian villages subsist in a generally poor environment; there is high infant morbidity and mortality. Children of Tocachi presented a higher degree of morbidity and also showed a higher degree of undernutrition.

Special emphasis has been placed on the effects of iodized oil on growth and development of infants and children. These studies have been materially enhanced by the availability of a full-time physician and a midwife for the program in Ecuador. Particular attention has been given to the perinatal period. Somatic growth has generally been similar in children from Tocachi and La Esperanza. It has been lower in both villages than in a low income infant group from Quito, and relatively lower still when compared with American standards.

There was a falloff in developmental averages of children around 6 months old. Gains in weight and height lagged more markedly after this age. The percentage increase in height 12 months after delivery was 37% in Tocachi and 40.5% in La Esperanza. Thus, in Tocachi there is the same kind of handicap in height as is found in adults. The expected normal increment for height is, at this age, 50%. The weight and height deceleration are obvious signs of undernutrition, possibly

TABLE III
Urinary excretion of iodine per 24-hr period after administration of Ethiodol

Age in years	Dose		Months after injection				
	Ethiodol, ml	Iodine, mg/kg	6	9	13	15	19
6-12	2.0	41.5 ± 1.1	$1,079 \pm 101$	497 ± 49	346 ± 29	274 ± 24	169 ± 15
13 or over	2.0	23.0 ± 0.7	859 ± 64	621 ± 47	345 ± 29	253 ± 25	168 ± 16
13 or over	0.2	2.0	230 ± 45		76 ± 16	62 ± 6	48 ± 4

Values are in micrograms.

including iodine undernutrition, and the high incidence of disease.

The increase in head circumference in both villages and for each group was lower than the American standard. However, it was interesting to note that averages in Tocachi were slightly better than those in La Esperanza in all age groups.

A large number of infants and young children were found in La Esperanza with *Ob* thyroids and 4% had *grade I* diffuse goiter. No case of thyroid enlargement was found in Tocachi in the comparable age group.

Levels of neurologic maturation (Gesell's standards) were reached in both villages at older ages than is considered normal. There was progressive behavioral retardation in both villages as tested by manipulative, perceptual, linguistic, and gross motor tasks. Average developmental quotient in Tocachi was 92.77% (normal). It was 89% in La Esperanza (low normal).

Possible Toxic Effects

In the survey conducted 6 months after administration of Ethiodol, there were about 15 subjects in Tocachi who presented a clinical picture suggesting hyperthyroidism. They were taken to Quito for hospitalization and examination. The disease was confirmed in three women, all elderly and with large nodular goiter. The laboratory tests useful for their diagnosis were the basal metabolic rate and the butanol-extractable iodine serum, since the other tests were exactly the same as for other iodized subjects who were not suspected of having hyperthyroidism. All three responded satisfactorily to therapy.

Neither iodine thyroiditis, "iodism," nor local reactions were observed. Most of the newborn were seen within a few days or weeks after delivery, and none was found to have goiter. Treatment with thyroid was begun at once when a diagnosis of cretinism was made.

COMMENTS

Endemic goiter and its accompanying defects are found today in their virgin form in some of the rural communities of Andean Ecuador and Peru. Iodization of common salt has not been implemented in the highland regions of these countries. The socioeconomic conditions of the Andean people, basically composed of Amerindian and mixed European stock, have varied little since Spanish colonial times. Everything points to an endemic of ancient date, the primary causative factor of which has been a deficiency of iodine.

Because of economic strictures and geographical isolation there is little expectation that national programs for manufacture and distribution of iodized salt will reach some of these rural populations in the near future. Accordingly, it has been necessary to consider alternative forms for supplying iodine. One of these is by parenteral administration of iodized oil, since these preparations release their iodide at a slow rate and may fulfill iodide needs for many months after a single injection.

The results that have been obtained conform to the reports of similar field trials in New Guinea and recently in Africa (9) and indicate that this method of distributing iodine is technically simple, free of serious risk, and effective to a considerable degree. Sequential surveys in the iodized population in both the Ecuadorian and the Peruvian studies have disclosed a gratifying reduction in goiter size and, compared to control groups, a failure of goiter to appear. In the Peruvian group a decline has been more evident in visible goiter than in palpable goiter at all intervals (72% and 40%, respectively, by the 18th month) as a result of progressive shrinkage of goiters of large size. Many of these have not completely disappeared and remain as palpable goiters of *Ob* degree. Whether they will completely disappear in time remains to be seen. Similar

results have been obtained in Ecuador, but a small rise was seen in the occurrence of goiter between the 19th and the 25th month. The effectiveness of the iodized oil treatment as a preventive method is demonstrated by the fact that only 1.5% of new cases were recorded in iodized children versus 7.2% in the controls.

A finding of possible significance is that in pregnant women the physiologic rise of PBI during normal pregnancy failed to occur in the group that did not receive prophylactic iodine. Many of these values were in the hypothyroid range, and corresponding plasma thyroxine values were even lower. Although a genetically impaired thyroxine-binding protein system may have been the cause of this phenomenon, this possibility seems to be ruled out by normally rising values in iodized pregnant women. The fetal thyroid undoubtedly shares with the mother's gland the low iodine supply from the diet. This sharing results in a lower amount of iodine being available for the mother's gland, which in turn is unable to maintain the required hormone levels. In any case, it may be expected that the hormone contribution of the mother to the fetus must be small, because free T_4 in all subjects is decreased during pregnancy. Whether the fetus is capable of synthesizing its own T_4 is unknown.

It is too early to know the effectiveness of the iodization program in terms of linear growth, boney development, psychological and neurological growth, and learning ability. Data presently available are consistent with, and suggestive of, a dramatic effect on the prevention of cretinism, but the numbers involved are presently small. The data on boney development, dentition, and linear growth show little improvement resulting from the single fact or change, i.e., injection of iodine. Mental performance seemed improved in one large, but admittedly preliminary, survey

among young schoolchildren. It will require at least 2 additional years of observation before the impact of the program on many aspects of health can be appraised. Meanwhile, there seems to be every reason to advise an extension of the program to other communities where endemic goiter is severe and where there is no present possibility of an effective program of salt iodization.

SUMMARY

Endemic goiter continues to be a significant health problem in many areas of the world. In some areas the disease is so severe that cretinism and other associated defects are found. In many areas, geographic, economic, and other factors prevent the use of iodized salt as a preventive measure.

A pilot program using iodized poppy seed oil has been instituted in two rural communities in Ecuador and three in Peru. Results after approximately 2 years indicate the feasibility and effectiveness of the programs. There has been a sharp reduction in the incidence of goiter. Cretinism has not yet appeared among the progeny of the population injected with iodized oil, but several instances have appeared in control groups. The use of iodized oil as a public health procedure for the prevention of endemic goiter and its associated defects is an acceptable measure in regions where salt-iodization programs cannot be presently undertaken.

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