

## CHAPTER 26

## IODIZED OIL IN THE PREVENTION OF ENDEMIC GOITER AND ASSOCIATED DEFECTS IN THE ANDEAN REGION OF ECUADOR

I. PROGRAM DESIGN, EFFECTS ON GOITER PREVALENCE, THYROID FUNCTION, AND IODINE EXCRETION<sup>1</sup>

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## INTRODUCTION

In South American countries which made up the Inca Empire, the Quechua word coto is synonymous with goiter. In Quechua, coto means mound or protuberance, and the Indians used coto in reference to tumor in the neck (10, 11, 20, 22). Goiter was frequent among the Indians of the Andes at the time of arrival of the Spaniards (27). The recent discovery of a pre-Colombian figure with a prominent goiter testifies to the commonplace nature of the affliction (Figure 1).

The Spanish conquest of the Inca Empire caused a rapid disintegration of the economy. In 1543 Agustín de Zárate (37) had referred to the great number of llamas which existed in the Province of Quito, and Cieza de León, in 1547, stated that "the people are peaceful, and there is an abundance of bread and grains." (9) By 1596 Father Cobo was already worried about the state of poverty and degeneration of the Indians. Thus the socioeconomic patterns which the Europeans imposed upon this continent placed a great stress upon the normal biologic and cultural development of the American natives. In the eighteenth and nineteenth centuries, Jorge Juan and Antonio de Ulloa (26), Humboldt (25), Caldas (6), Boussingault (5), Orton (31), and Wolf (36) noted the extreme poverty which reigned among the Indians and half-breeds of the rural zones of the Andes. They remarked upon the great number of goitrous, deafmute, and defective persons in this region.

The Spanish and their direct descendents also had goiter on an important scale, and travelers of that time refer to this condition. The small sculptured pieces of the eighteenth century support this observation (Figure 2), especially since the Quitenian images of that time were almost entirely of a religious nature.

<sup>1/</sup> This study is supported in part by the Pan American Health Organization, U.S. National Association for Retarded Children, and U.S. National Institutes of Health Grant HD-362.

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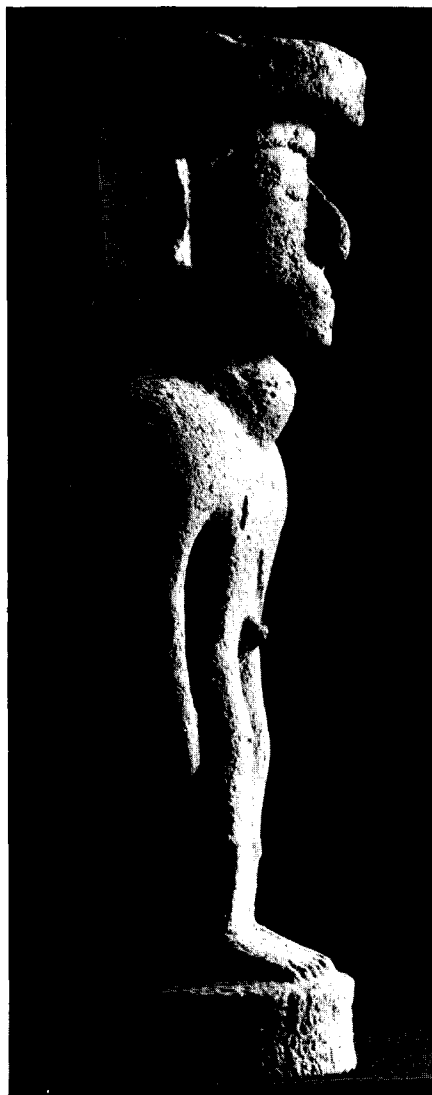


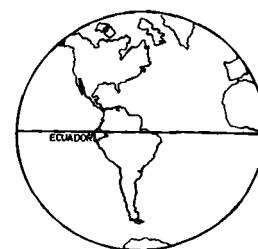
Figure 1. Pre-Colombian sculpture (50 cm high), showing the "Colorado" people who once resided in the Andean region of Ecuador, in the basin of the Guallabamba River. From there they migrated to the coast. The age has been calculated at 800 years. Now in the Anthropologic Museum of Quito.



Figure 2. Small sculpture (15 cm high) from Quito in the last of the eighteenth century. Now in the Convent "El Carmen Alto," Quito.

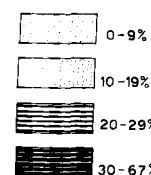
In 1958 the Ecuadorean Institute of Nutrition conducted a survey (18) and found endemic goiter to be a grave problem in the Andean Region (Figure 3). It was observed that the prevalence of goiter varied between neighboring villages, that the size of goiter diminished in villages located at more than 3,200 meters above sea level, and that the mentally deficient persons, deaf-mutes, and deaf who were observed during the survey did not present the characteristics aspects of hypothyroidism. Studies of iodine metabolism indicated iodine deficiency as the principal causative factor (13, 16). The results were similar to the findings of Stanbury et al. (34) in endemic goiter in the Andean Region of Mendoza, Argentina.

Ecologic, ethnic, and socioeconomic studies in eight rural villages of the Ecuadorean Andean region in 1965 (19, 20) supported the following conclusions: (1) For endemic goiter to exist in a community, man must live under



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Figure 3. Geographic territorial divisions by the capital of the country, including Toca of each one was made program.

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There are, unfortunate salt is not feasible at pres prevention by the injection tion available from those su grams were effective in redu dure was practical and safe. failed to provide entirely s of this form of prophylaxis tically no information regar been demonstrated to be in e ter, such as endemic cretin deformities, and endemic mer

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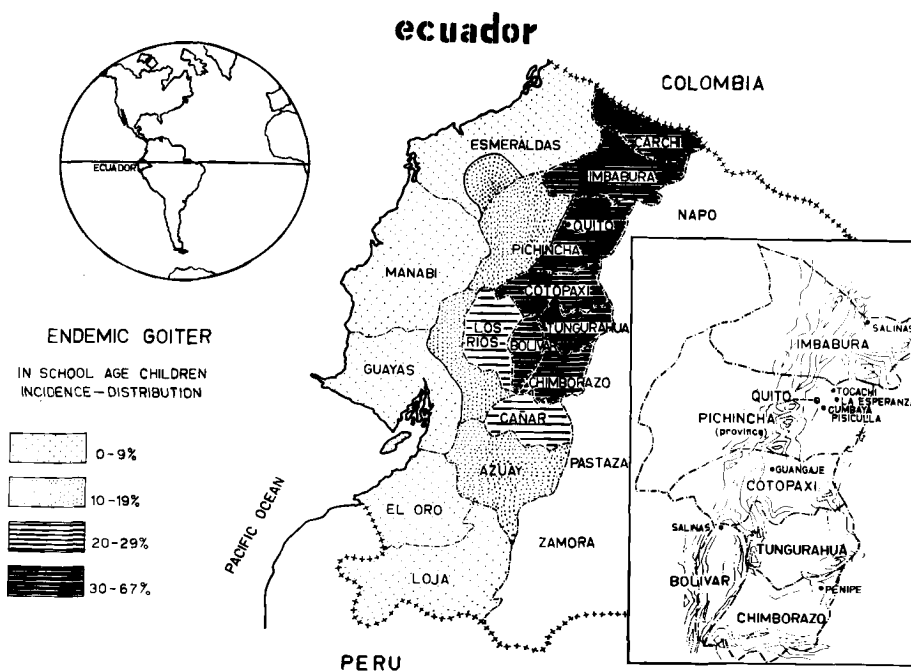


Figure 3. Geographic location of the Republic of Ecuador, and partial map of its territorial divisions by provinces. In the Province of Pichincha is included Quito, the capital of the country. In the frame is shown the location of the eight rural villages, including Tocachi and La Esperanza. Inventory of the total population of each one was made one year before the start of the iodized oil prophylactic program.

chronic iodine deficiency. (2) Severity of the endemic is related to the magnitude of iodine deficiency, but intercurrent socioeconomic and biologic factors in the community may modify the incidence of goiter. (3) These intercurrent factors are of themselves incapable of causing the endemic. (4) The prevalence of endemic cretinism, deafmutism, and motor abnormalities is highly correlated with the intensity of endemic goiter.

There are, unfortunately, many regions of the world where iodination of salt is not feasible at present. 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 (24, 28) 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, failed to provide entirely satisfactory information regarding the effectiveness of this form of prophylaxis in reducing the incidence of goiter and gave practically no information regarding prevention of those disabilities which have been demonstrated to be in epidemiologic association with severe endemic goiter, such as endemic cretinism, endemic deafmutism, deafness, mutism, bone deformities, and endemic mental retardation.

Iodization of common salt has not been implemented in Ecuador. The socioeconomic conditions of the Andean people, basically composed of Indians

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conducted a survey (18) in the Andean Region (Figure 1). The incidence of goiter varied between neighboring villages located at more than 1000 feet. The survey did not present the results of iodine metabolism indicator (13, 16). The results (34) in endemic goiter

In eight rural villages of the Andean Region, the following conclusions were reached: man must live under

and half-breeds, have varied little since the Spanish colonial times or have changed at a very slow pace. Thus, everything has pointed to a virgin endemic of an ancient date, the primary causative factor of which has been a severe chronic deficiency of iodine. On the basis of these facts, we elected in March 1966 to carry out a program for prevention of endemic goiter and associated defects in two isolated villages of the Ecuadorean Andean region by means of the intramuscular administration of iodized oil.

#### MATERIALS AND METHODS

A socioeconomic inventory of the total population of eight rural villages in the Andean Provinces most affected by goiter (Figure 3) was made one year before administration of the iodized oil. The inventory was performed by one medical doctor and three medical students. Accompanying them was a representative of the Ecuadorean National Planning Board. He studied the economic status of each community by means of a survey on complete families taken as a random sample.

Two previously studied villages were chosen for the prophylactic program, Tocachi and La Esperanza (Figure 3). They were selected because of their remoteness and because in both of them endemic goiter is severe and cretinism is commonplace. They are situated about 70 kilometers north of Quito. They are six miles apart and are ethnically, socially, and medically entirely comparable. They are remote from any medical facility. The villagers have unusually limited social mobility and contact with the outside world. These villages share many characteristics with hundreds of others in the South American Andean region.

We elected to give iodine to the Tocachi population, since the population concentration was ideal. La Esperanza remained as the control village. The program was started in March 1966. The iodized oil was Ethiodol (37 per cent iodized poppy seed oil, each ml containing 475 mg of iodine, from E. Fougera, 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 two years.....	0.2 ml of iodized oil
2 - 6 years.....	0.5 ml of iodized oil
6 - 12 years.....	1.0 ml of iodized oil
12 years old and up.....	2.0 ml of iodized oil

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

The studies were done just before or at the same time as the iodized oil administration. A nutritional survey was conducted by sampling. Fifty families from Tocachi and 75 from La Esperanza were chosen.

Goiter prevalence was determined by five teams (each comprised of one medical doctor, two medical students, and one local leader). Four of the five teams were in charge of the four sections into which each village was divided.

Precise data had been provided in each house, names of family members, and a team was stationed at the village. Special studies were examined and found to be excellent in both villages.

Evaluation of the results of Pérez et al. 1961, and

Grade 0<sub>a</sub>

Grade 0<sub>b</sub>

Grade I

Grade II

Grade III

Grade IV

For epidemiologic purposes larger. These glands were needed for the response and type (diffuse or nodular) to the Tocachi population. 96 per cent (960) of the Tocachi refused the injection. The exception for one of transitory

For evaluation of cretinism was the mental deficiency of the subject lived in relation to be considered by his family the average inhabitants of the village. This criterion was employed because the characteristics were characterized by residents of an urban area.

Examination of selected as well as observation for teeth. Hand x-rays were taken of films, at a tube-to-film distance, portable x-ray unit. Anthropometric measurements of children.

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Precise data had been prepared on each section regarding house location, fami-  
 lies in each house, names and ages of all members of a family, etc. The fifth  
 team was stationed at the priest's house, where subjects previously chosen for  
 special studies were examined. The attitude and cooperation of the people were  
 excellent in both villages.

Evaluation of the thyroid size was in accordance with the classification  
 of Pérez et al. 1961, and modified by us. This is:

- |                      |   |   |
|----------------------|---|---|
| Grade O <sub>a</sub> | - | not palpable;   |
| Grade O <sub>b</sub> | - | palpable, but not visible with the<br>head raised;  |
| Grade I              | - | easily palpable with head in normal<br>position and visible with the head<br>raised;<br><u>Those glands presenting easily<br/>palpable nodules with head in<br/>normal position but not visible<br/>with head raised were included<br/>in this grade.</u> |
| Grade II             | - | easily visible with head in normal<br>position;   |
| Grade III            | - | visible at a distance;  |
| Grade IV             | - | monstrous goiters.  |

For epidemiologic purposes, glands were considered abnormal when Grade I or  
 larger. These glands were recorded as diffuse or nodular. A series of trials  
 were needed for the responsible team leaders to come to agreement about grade  
 and type (diffuse or nodular). The five teams administered the iodized oil  
 to the Tocachi population at the same time as the epidemiologic survey. Ninety  
 per cent (960) of the Tocachi villagers were injected. The other 10 per cent  
 refused the injection. There were no cases of local reaction to the iodine,  
 except for one of transitory erythema.

For evaluation of cretinism, the fundamental fact taken into account  
 was the mental deficiency of the subject. The mental deficiency should be  
 obvious in the opinion of the surveyor, and confirmed by the manner in which  
 the subject lived in relation to the rest of the community. The subject would  
 be considered by his family incapable of conducting the normal activities of  
 the average inhabitants of the village (agricultural tasks, small crafts, etc.).  
 This criterion was employed because many of the inhabitants of these communi-  
 ties were characterized by a certain degree of simplicity in comparison to  
 residents of an urban area.

Examination of selected children included a PA x-ray of the left hand,  
 as well as 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 in) with a Bucky field-  
 portable x-ray unit. Anthropometric measurements were also made in all these  
 children.

Duplicate samples of water were taken, as well as samples of the crude sea-salt which is consumed in both villages. Samples of soil were also taken. Samples of first morning urine before breakfast were obtained. Half of these samples were sent to Boston Medical Laboratories (Boston, Massachusetts) in order to determine the stable iodine content. The other samples were examined in Quito. The samples of urine were used to determine iodine and creatinine according to the method of Bosnes and Taussky (4).

Blood samples were also taken for TI, PBI,  $T_4I$ , BEI, and BII determinations according to the methods of Benotti and Benotti (1, 3) and of Murphy (30). Resin uptake of  $^{131}I$ -labeled triiodothyronine was according to Mitchell et al. (29).

Volunteers from both villages were brought to Quito. The  $^{131}I$  thyroid uptake, conversion ratio,  $PBI^{131}I$  per cent per liter, salivary iodide clearance, saliva/plasma ratio, and saliva/PBI ratio tests were done after a dose of 50 microcuries of  $^{131}I$ .

Shortly after the completion of the injection program a physician and a midwife were assigned fulltime to Tocachi and La Esperanza. 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 on goiter prevalence and incidence were conducted at 6, 12, 20, and 25 months after the injection program. Thyroid functional studies and determinations of iodine and creatinine in urine were done at the same times.

After 25 months of iodination in April 1968, exactly the same studies were made as in March 1966. These included nutritional surveys, x-ray studies, etc. Most of these were made on the same subjects. In April 1968 we also conducted intelligence performance tests, using the Goodenough Method modified in recent years by Harris (23), on school-age children.

#### RESULTS AND DISCUSSION

Both in Tocachi and La Esperanza the socioeconomic situation is precarious (Table 1).<sup>\*</sup> This was noted by Luis León (27), who wrote, 28 years ago, that these villages "tend toward degeneration and extinction." At present the situation has changed but little. Both in Tocachi and La Esperanza there is a high percentage of infant mortality, a high incidence of illegitimacy, a low level of literacy, little exposure to culture outside the villages, and great poverty reflected by the small percentage of artisans and the low income. Chronic iodine deficiency is severe in both villages (Table 1). Prevalence of goiter and associated defects is high (Table 2).

<sup>\*</sup> All tables appear at the end of this article.

The mentally defective with mental deficiency and II, with mental deficiency motor abnormalities include types are believed to be cretinism in both villages in Mulia Valley in western Ecuador severe and the incidence in Tocachi, La Esperanza, distinct from that associated with hypothyroidism and dwarfism.

Numerous reports on endemic goiter have been reconsidered here. Studies in cretins from both Tocachi and La Esperanza are important facts. Thyroid function in both villages, and their culture. Thus there was no cretinism or in untreated congenital muscle bulk, or delayed reproductive development after birth despite the subjects are able to compensate through a deafmute, mentally defective. Otherwise the person may develop thyroid even in adult life.

Nutritional surveys following facts: caloric intake, vitamin A, especially of a type is fundamentally based upon. There has been no noteworthy change.

The height of adults was not significantly different noticeably ( $P < 0.04$  for difference attributable to a better diet).

A fall in the prevalence in men and women, was regular administration. After the and women, the decrease in goiter in women and men in the population decreased (Figure 3).

The prevalence of disease conducted six months after 5): nodular goiter noticeable the following surveys, and. At the survey on the 25th month diffuse goiter ratio increased population increased (20) (Figure 4).

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The mentally defective persons were divided into two types: Type I, with mental deficiency and severe impairment in hearing and speech; and Type II, with mental deficiency, impaired hearing and speech, short stature, and motor abnormalities including spastic paresis of the lower extremities. Both types are believed to be examples of endemic cretinism. The syndrome of cretinism in both villages is much like the endemic cretinism occurring in the Mulia Valley in western New Guinea (8). In Mulia iodine deficiency is equally severe and the incidence of cretinism is strikingly similar to that in Tocachi. In Tocachi, La Esperanza, and in Mulia, the clinical syndrome of cretinism is distinct from that associated with endemic goiter in the Belgian Congo, where hypothyroidism and dwarfing typically occur (12).

Numerous reports on the clinical features of cretinism in relation to endemic goiter have been reviewed by Choufoer (8) and need not be extensively reconsidered here. Studies on thyroid function and skeletal muscle structure in cretins from both Tocachi and La Esperanza (19, 35) have outlined two important facts. Thyroid function was similar in cretins and "normal" subjects in both villages, and there was no evident disorder in skeletal muscle structure. Thus there was no evidence of skeletal muscle involvement as in myxedema or in untreated congenital hypothyroidism, such as myotonia, increased muscle bulk, or delayed relaxation of stretch reflexes. We believe that intrauterine hypothyroidism leads to the neural abnormalities, and that these persist after birth despite the subsequent course of thyroid function. If the thyroid is able to compensate through any mechanism to prevent continued hypothyroidism, a deafmute, mentally defective individual of normal proportions may result. Otherwise the person may develop as a typical dwarfed cretin, who may be hypothyroid even in adult life.

Nutritional surveys done in March 1966 and in June 1968 outlined the following facts: caloric consumption was low, as were protein, fat, and vitamin A, especially of animal origin. The daily diet in these communities is fundamentally based upon barley, corn, and potatoes and other tubers. There has been no noteworthy improvement in diet during these two years (Table 3).

The height of adult subjects from Tocachi and those from La Esperanza was not significantly different (Table 4). Mean values for weight differed noticeably ( $P < 0.04$  for males and  $< 0.03$  for females). This is presumably attributable to a better caloric intake in La Esperanza.

A fall in the prevalence of goiter, both in the total population and in men and women, was regular and consistent for 20 months after Ethiodol administration. After the 20th month, also in the total population and in men and women, the decrease stopped and prevalence began to rise. The ratio of goiter in women and men increased while the prevalence of goiter in the total population decreased (Figure 4, Tables 5, 7, 9, 11, 14).

The prevalence of diffuse and nodular goiter, at the time of the survey conducted six months after iodization, presented the following picture (Figure 5): nodular goiter noticeably increased, while diffuse goiter decreased. In the following surveys, and up to the 20th month, nodularity steadily decreased. At the survey on the 25th month nodularity started a new increase. The nodular-diffuse goiter ratio increased, while the prevalence of goiter in the total population increased (20) (Tables 5, 7, 9, 11, 13).



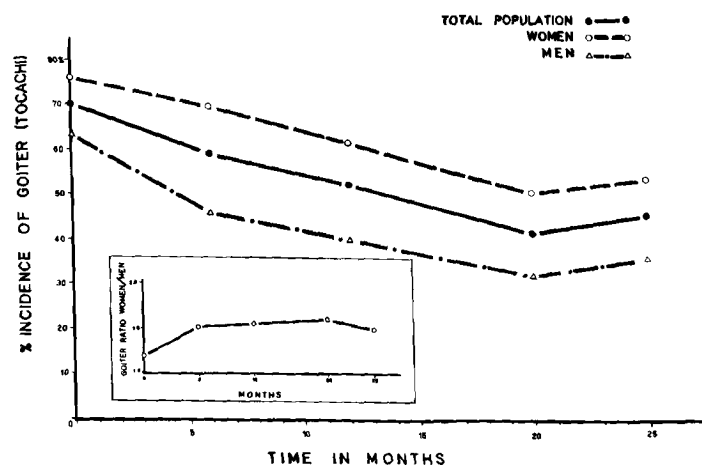


Figure 4. Total goiter prevalence, and prevalence in men and women from Tocachi, at the time of iodized oil administration and in the surveys at 6, 12, 20, and 25 months after administration. Female-male goiter ratio for the same periods is shown in the frame (Tables 5, 7, 9, 11, 13).

Figure 5. Prevalence of nodular and diffuse goiter for the total treated population from Tocachi at the time of iodized oil administration and in the surveys at 6, 12, 20, and 25 months after administration. Nodular/diffuse goiter ratio for the same periods is shown in the frame (Tables 5, 7, 9, 11, 13).

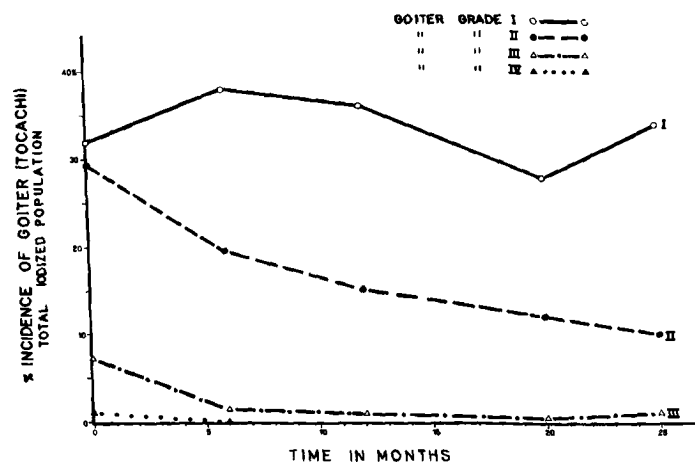
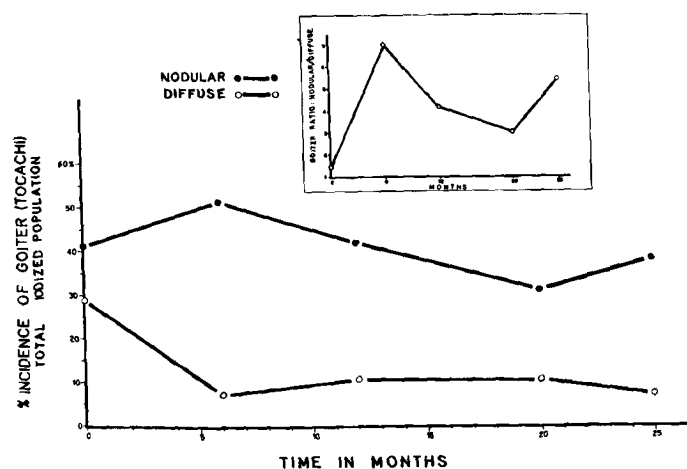


Figure 6. Goiter prevalence according to size for the total injected population from Tocachi at the time of iodized oil administration and in the surveys at 6, 12, 20, and 25 months after administration (Tables 5, 7, 9, 11, 13).

As to goiter size, it was distinct decrease of the decrease continued into the decrease in size of I in the incidence of Grade I goiters also tended to diminish survey at 20 months, however tended to increase (Figure 4).

A linear study of was made (Tables 15, 16, size reduction of large g Grade III goiter (Figure I, and then these became month. From the 20th month became Ob thyroids, most Grade III goiters became which has been evident at lution of nodular goiters happens to nodular goiter goiters became nodular Grade I progressively same time nodular Grade II month a significant number thyroids became Ob, and so way the sharp increase of tration of Ethiodol, and a in the total population at increase of nodular goiter involution of hyperplastic

Regarding the effect 8, 10, 12, 14), the reduction was seen during the first 40 years of age. Regarding the total population. thyroid in children born in Tocachi children of La Esperanza up of the April 1968 survey, prevalence in La Esperanza from there has been a significant

Six months after iodine clearly depressed. A rest control surveys, including (Table 24, Figure 9). The in all control surveys (Table

The deposit oil was tically within normal limit during the first months the iodide into  $T_4$  and  $T_3$ . PBI This indicates that PBI detection when iodized oil is used who studied the effects of

Figure 4. Total goiter prevalence, and prevalence in men and women from Tocachi, at the time of iodized oil administration and in the surveys at 6, 12, 20, and 25 months after administration. Female-male goiter ratio for same periods is shown in the line (Tables 5, 7, 9, 11, 13).

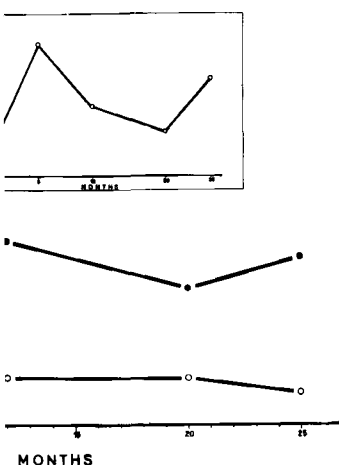


Figure 6. Goiter prevalence according to size for the total injected population in Tocachi at the time of iodized oil administration and in the surveys at 6, 12, 20, and 25 months after administration (Tables 5, 7, 9, 11, 13).

As to goiter size, it was evident that administration of Ethiodol produced a distinct decrease of the incidence of Grade II goiters and larger, and this decrease continued into the survey at 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 survey at 20 months, however, this type of goiter (but not those of larger size) tended to increase (Figure 6, Tables 5, 7, 9, 11, 13).

A linear study of the evolution of different grades and types of glands was made (Tables 15, 16, 17, 18, 19, 20, 21). There was a steady and progressive reduction of large goiters until the 20th month after iodization. Thus a Grade III goiter (Figure 7, Table 21), for instance, first became Grade II or I, and then these became Ob and Oa thyroids, as time passed, up to the 20th month. From the 20th month a considerable number of Grade I and II goiters became Ob thyroids, most of the Grade II goiters became Grade I, and the few Grade III goiters became Grade II. This has been the epidemiological picture which has been evident at the 25th month after iodization. As to linear evolution of nodular goiters (Figure 8, Table 20), we took as an example what happens to nodular goiter Grade II. More than half of the Grade II nodular goiters became nodular Grade I during the first six months. A good number of nodular Grade I progressively evolved and became Ob or Oa thyroids. At the same time nodular Grade II goiters became nodular Grade I. After the 20th month a significant number of nodular Grade II goiters became Nodular I, Oa thyroids became Ob, and some of these became Grade I. We must explain in this way the sharp increase of Grade I goiter prevalence 25 months after administration of Ethiodol, and also the beginning of an increase of goiter prevalence in the total population at that time. It seems unquestionable that the sharp increase of nodular goiter found six months after iodization is a result of involution of hyperplastic thyroid tissue resulting from the action of Ethiodol.

Regarding the effect of Ethiodol on goiter prevalence by age (Tables 6, 8, 10, 12, 14), the reduction 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 per cent for the total population. There was not a single instance of a palpable thyroid in children born in Tocachi to iodized mothers. Eighteen per cent of the children of La Esperanza up to 2 years of age, who were examined at the time of the April 1968 survey, presented palpable glands. As to the goiter prevalence in La Esperanza from March 1966 to April 1968, results indicate that there has been a significant increase (Tables 22, 23).

Six months after iodization, uptake of  $^{131}\text{I}$  by the thyroid proved to be clearly depressed. A restoration toward normality was observed in successive control surveys, including the control conducted 25 months after injection (Table 24, Figure 9). The  $\text{PB}^{131}\text{I}$  was low in a considerable number of cases in all control surveys (Table 25).

The deposit oil was not extractable with butanol. BEI has remained practically within normal limits 25 months after iodization (Table 26). Thus even during the first months the glands retained a normal capacity for transforming iodide into  $\text{T}_4$  and  $\text{T}_3$ . PBI's were high until two years after iodization. This indicates that PBI determinations are not a valid index of thyroid function when iodized oil is used. Similar results have been reported by Carter, who studied the effects of oral Lipiodol on PBI concentrations (7).

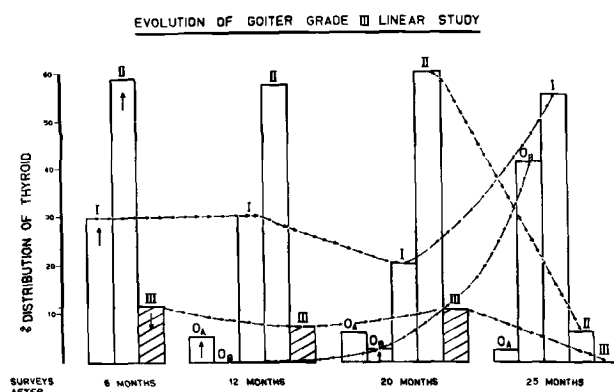


Figure 7. Goiter Grade III evolution, linear study. Surveys made in Tocachi at 6, 12, 20, and 25 months after iodized oil administration (Table 21). The number of subjects who presented Grade III goiter during the survey done just before injection was 70.

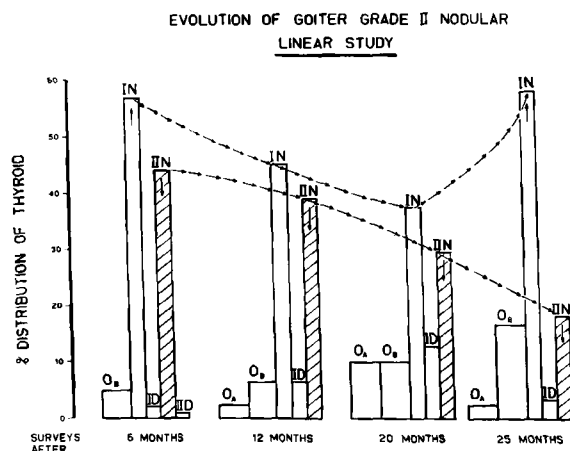
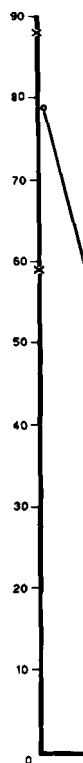


Figure 8. Evolution of Grade II nodular goiter, linear study. Surveys made in Tocachi at 6, 12, 20, and 25 months after iodized oil administration (Table 20). The number of subjects who presented Grade II nodular goiter during the survey done just before injection was 200.

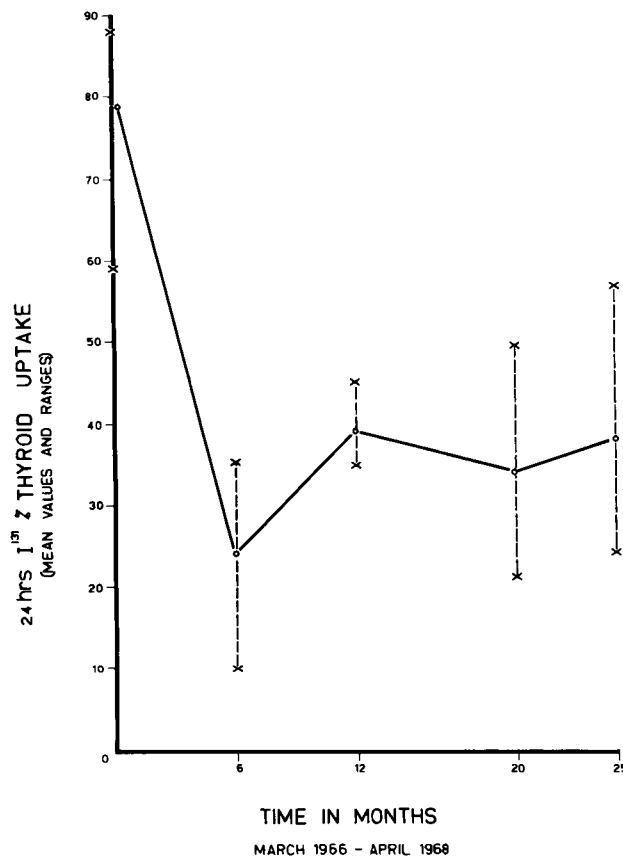
24 hrs  $I^{131}$  THYROID UPTAKE  
(MEAN VALUES AND RANGES)



Six months after iodine administration, the uptake was statistically different between La Esperanza (Tocachi: number of subjects; S.D. = 43. La Esperanza: S.D. = 32.  $t = 0.36$ ). The hypometabolism in either village was not significant.

The urinary excretory pattern was exponential. The equation was  $Y = 35.0 - 0.126 \cdot t$ . Since the adults who had received 2 mg of iodine would be virtually accomplished, it implies that an Ethiodol dose of no more than thirty-five mg would be sufficient.

Three subjects from the village of La Esperanza were examined in April 1968. Their thyroid function curves were superimposable on the curve of the village of La Esperanza. The program was started.



MARCH 1966 - APRIL 1968

Figure 9. Mean values and ranges for the 24-hour  $^{131}\text{I}$  % thyroid uptake, in Tocachi volunteers examined just before the injection of Ethiodol, and after 6, 12, 20, and 25 months.

Six months after iodization the Achilles reflex relaxation time was not statistically different between the inhabitants from Tocachi and those from La Esperanza (Tocachi: number of subjects = 195; mean value = 292 milliseconds; S.D. = 43. La Esperanza: number of subjects = 195; mean value = 293; S.D. = 32.  $t = 0.36$ ). There were almost no subjects with values suggesting hypometabolism in either village.

The urinary excretion of iodine (UEI) (Table 27, Figure 10) followed an exponential pattern. The excretion pattern could be expressed by  $\text{UEI}_t = \text{UEI}_0 \cdot e^{-0.126 \cdot t}$ . Since the subjects on whom we did UEI determinations 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 an Ethiodol dose equal to half of that used would be eliminated in no more than thirty-five months.

Three subjects from Tocachi who refused injection in March 1966 were examined in April 1968. Their  $^{131}\text{I}$  and  $^{127}\text{I}$  tests and urinary iodine excretion were superimposable on those found in the same village before the prophylaxis program was started.

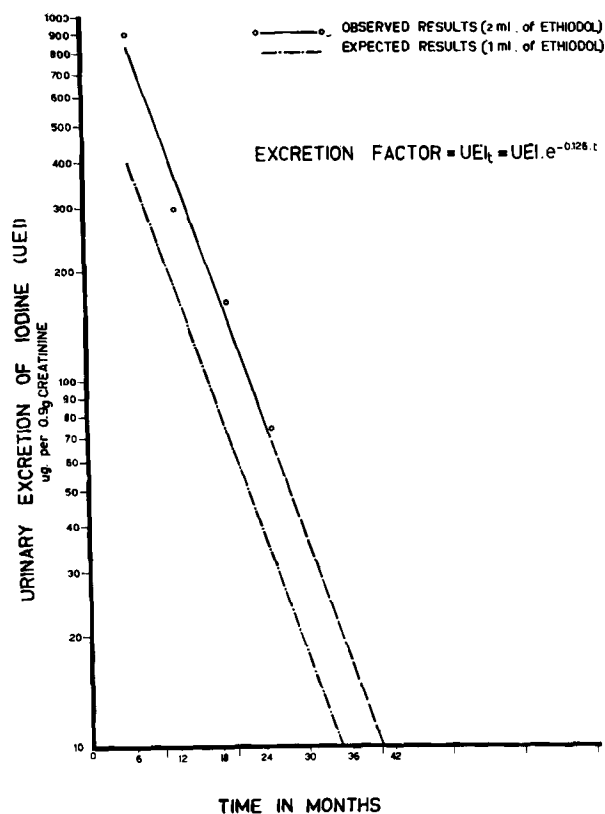


Figure 10. Evolution of urinary excretion of iodine ( $\mu\text{g}$  per 0.9 g creatinine). Mean values at 6, 12, 20, and 25 months after iodization. The UEI mean value in Tocachi was  $10.4 \mu\text{g}$  daily before injection.

In the survey six months after administration of Ethiodol, there were a few subjects in Tocachi who presented a clinical picture suggesting hyperthyroidism. They were taken back to Quito for hospitalization and careful examination. The disease was confirmed in three women, all elderly and with large nodular goiters (Table 28). The laboratory tests useful for their diagnosis were the BMR, the BEI and  $T_3$ - $^{131}\text{I}$  resin uptake, since the other tests were exactly the same as for other iodized subjects who were not suspected of having hyperthyroidism. It is interesting to note that the suppression test with KSCN in these three patients performed according to the method of Sánchez-Martin (33) was the same as described by him for normal subjects, and also by Fierro-Benítez and Garcés (15) for subjects with endemic goiter without autonomous nodules.

Tapazol administration at a dose of 45 mg a day for two or three months was enough to change the picture in two (cases 1 and 2) of the three women. One of them was ready for an incidental gastrectomy three months from the beginning of treatment.

The third woman presented a clinical picture of hyperthyroidism. Among laboratory tests done from those of the other iodized subjects at the same time were the BMR, the BEI and  $T_3$ - $^{131}\text{I}$  resin uptake. These were high. All these subjects. In April 1968 the third woman presented hyperthyroidism in spite of Tapazol administration (irregularly). Laboratory tests showed: 24 hr = 38 per cent; 96 hr = 38 per cent; 24 hr  $\text{PB}^{131}\text{I}$  per cent dose = 38 per cent. She was hospitalized and became euthyroid after six weeks.

Intramuscular injection of Ethiodol produced no local or general reactions by technical personnel and subjects.

Goiter in an isolated form was found in 36 per cent reduction two months after iodization. It has been small in the age group.

Reduction of goiter size during the period between the 20th and 25th month after iodization. The prevalence of goiter began to decrease in size, and the number of Grade I goiters. At the 25th month after the iodization, the prevalence of large goiters was 10 per cent.

The increased incidence of nodules was observed at the 6th month survey. These nodules as a result of iodization of the thyroid tissue.

Administration of iodine led to the appearance of goiter in some subjects. Administration of iodized oil led to normal thyroid size.

Urinary excretion of iodine follows an exponential pattern after administration of Ethiodol for adults, the figures until 40 months after iodization. The increased excretion was observed.

Among 960 subjects followed up, more than 45 years old, the laboratory tests useful for diagnosis were the BMR, the BEI and  $T_3$ - $^{131}\text{I}$  resin uptake. Tapazol was effective in the treatment of hyperthyroidism required hospitalization.

The third woman presented hyperthyroidism one year after injection. Among laboratory tests done in March 1967, the results that were different from those of the other iodized subjects from Tocachi who had the same tests at the same time were the BEI, serum thyroxine, and resin uptake of  $^{131}\text{I-T}_3$ . These were high. All these tests were within normal limits for other iodized subjects. In April 1968 this third woman continued to present clinical hyperthyroidism in spite of Tapazol administration at a dose of 75 mg per day (taken irregularly). Laboratory data were:  $^{131}\text{I}$  thyroid uptake: 8 hr = 30 per cent; 24 hr = 38 per cent; 96 hr = 24 per cent; 24 hr conversion ratio = 56 per cent; 24 hr  $\text{PB}^{131}\text{I}$  per cent dose per liter = 0.24; BEI = 9.0  $\mu\text{g}$  per cent; BII = 4  $\mu\text{g}$  per cent. She was hospitalized by the end of April 1968 and became clinically euthyroid after six weeks of daily administration of 75 mg of Tapazol.

#### SUMMARY

Intramuscular injections of iodized oil (Ethiodol) have produced no local or general reactions of iodine intolerance. They may be administered by technical personnel under medical supervision.

Goiter in an isolated rural district of the Ecuadorean Andes has had a 36 per cent reduction two years after administration of iodized oil. Reduction has been small in the age group over 40 years.

Reduction of goiter incidence was regular and progressive until the period between the 20th and the 25th months after iodization, after which time prevalence of goiter began to increase. This was primarily an increase in the number of Grade I goiters. Larger goiters at the same period of time continued to decrease in size, and Grade I goiters did not increase in size. At the 25th month after the injection program there was a sharp reduction in the prevalence of large goiters.

The increased incidence of small nodular goiters, which was so noticeable at the 6th month survey, should be attributed to a better delineation of these nodules as a result of involution of previously hyperplastic thyroid tissue.

Administration of iodized oil to mothers before delivery has prevented the appearance of goiter in their children, at least for the first two years. Administration of iodized oil has produced a restoration of thyroid function to normal.

Urinary excretion of iodine following administration of iodized oil follows an exponential pattern. At doses used in the present program (2 ml of Ethiodol for adults), the urinary excretion of iodine would be over basal figures until 40 months after injection. If the dose would be reduced to 1 ml, the increased excretion would remain until 35 months after injection.

Among 960 subjects injected, three developed hyperthyroidism. They were women more than 45 years old with large nodular goiters. Laboratory tests useful for diagnosis were: BMR, BEI,  $\text{T}_4$ , and resin uptake of  $^{131}\text{I-T}_3$ . Tapazol was effective in curing the disease. One of the three hyperthyroid required hospitalization.

The present study indicates that the use of intramuscularly injected iodized oil is a useful means for combating endemic goiter and cretinism in rural areas where the endemic is severe. The method is cheap, long-acting, relatively free of side effects, and can be easily applied through modest local health services.

Using 1 ml of Ethiodol as a dose, results should be similar to those reported in this paper. Accordingly, we recommend that 1 ml of Ethiodol be used for adults in future programs, and proportionally smaller doses for children. The entire population of the goitrous area from 0 to 45 years of age of both sexes should be injected. There is no need to exclude persons with nodular goiter, but they may be given a smaller dose.

#### ACKNOWLEDGMENTS

Our gratitude is due Dr. John B. Stanbury, who made this program in Ecuador possible. We also wish to thank Dr. John Kevany, Dr. Andreis Querido, and Dr. Joseph Benotti for their help, cooperation, and training. The project has received generous help from Lederle Laboratories, the Teen Club of Chestnut Hill, Massachusetts, Caritas (Section of Ecuador), Life Laboratories (Ecuador), and the Andean Mission of Ecuador.

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Table 1. Ethnic and socioeconomic aspects of Tocachi and La Esperanza and data on iodine content of salt, water, soil, and urine.

	TOCACHI	LA ESPERANZA
Population	1,100	2,500
Altitude (meters above sea level)	2,952	2,883
% half-breeds	59.43	45.24
% Indians	38.80	50.08
% subjects born in the village	97.00	91.00
% infant mortality	43.00	29.00
% natural abortion	2.80	4.20
% unwed mothers	26.00	14.00
% illiterate subjects	31.00	34.00
% subjects who have visited the coast region	5.00	9.00
% artisans	5.00	5.00
Annual income per person (U.S. dollars)	90	85
<u>Iodine content of salt, water, soil, and urine</u>		
Iodine in salt ( $\mu\text{g/g}$ )	0.24	0.24
Iodine in water ( $\mu\text{g/l}$ )	1.00	0.85
Iodine in soil ( $\mu\text{g/kg}$ )	7.00	23.00
$\text{I}^{127}$ urinary excretion ( $\mu\text{g}$ per 0.9 g creatinine)	10.4	17.7

Table 2. Prevalence

General goiter
Nodular goiter
Diffuse goiter
ENDEMIC CRETINISM
Mental deficiency
impairment in h
ENDEMIC CRETINISM
Mental deficiency
impairment in h
and short stature
abnormalities
DEAFMUTISM
Severe impairment
and speech
DEAFNESS
Severe impairment
MUTISM
Severe deficit i
MOTOR ABNORMALITIES
OTHER CONGENITAL M

za and data on iodine content

TOCACHI	LA ESPERANZA
1,100	2,500
2,952	2,883
59.43	45.24
38.80	50.08
97.00	91.00
43.00	29.00
2.80	4.20
26.00	14.00
31.00	34.00
5.00	9.00
5.00	5.00
90	85
<u>and urine</u>	
0.24	0.24
1.00	0.85
7.00	23.00
10.4	17.7

Table 2. Prevalence of goiter and of neural and motor abnormalities, per cent 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 TYPE I: Mental deficiency and severe impairment in hearing and speech	7.4	5.5
ENDEMIC CRETINISM TYPE II: Mental deficiency and severe impairment in hearing and speech and short stature and motor abnormalities	0.8	0.5
DEAFMUTISM Severe impairment in hearing and speech	4.5	2.5
DEAFNESS Severe impairment in hearing	1.6	0.0
MUTISM Severe deficit in speech	0.4	0.4
MOTOR ABNORMALITIES	1.0	0.8
OTHER CONGENITAL MALFORMATIONS	0.4	1.2

Table 3. Average consumption of calories and nutritive elements per person per day. Tocachi and La Esperanza, March 1966 and June 1968. Children who were less than one year old were not taken into account (Ecuadorian National Institute of Nutrition).

	TOCACHI		LA ESPERANZA	
	March 1966	June 1968	March 1966	June 1968
Calories	1,577.64	1,604.49	1,699.58	1,860.00
Total protein (g)	38.66	39.15	39.03	48.31
Animal protein (g)	5.85	2.77	4.06	4.48
Vegetable protein (g)	32.81	36.38	34.97	43.83
Total fat (g)	22.32	25.17	26.30	24.16
Animal fat (g)	13.56	2.21	11.05	0.31
Vegetable fat (g)	8.76	22.96	15.25	23.85
Carbohydrate (g)	280.54	312.30	327.79	362.40
Calcium (g)	0.20	0.16	0.22	0.29
Iron (mg)	20.45	19.72	23.47	32.60
Total vitamin A (I.U.)	588.65	823.71	1,340.76	1,000.00
Animal vitamin A (I.U.)	114.81	40.79	75.82	152.00
Vegetable vitamin A (I.U.)	473.84	782.92	1,264.94	848.00
Thiamine (mg)	0.92	1.30	1.18	1.43
Niacin (mg)	17.86	27.68	25.09	29.32
Riboflavin (mg)	0.50	0.55	0.54	0.83
Vitamin C (mg)	56.32	119.94	93.81	108.61

Table 4. Height and weight of the subjects from 19 to 50 years old. Tocachi and La Esperanza, May 1966.

		Number	Mean value	Standard deviation	Probability
HEIGHT (cm)	MEN	Tocachi	113	152	8.3
		La Esperanza	80	156	6.7
	WOMEN	Tocachi	206	142	6.7
		La Esperanza	220	145	6.4
WEIGHT (kg)	MEN	Tocachi	113	53.4	6.8
		La Esperanza	80	57.0	7.0
	WOMEN	Tocachi	213	45.6	7.0
		La Esperanza	217	50.0	6.6

Table 5. Prevalence and distribution of goiter by type and size in the survey conducted just before injection. Total subjects surveyed: 960. Tocachi, March 1966.

		DIFFUSE GOITER								NODULAR GOITER				TOTAL	
		Oa	Ob	Oa+Ob	DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N	Total N	Total N
MALE	No.	137	35	172	100	37	1	138	60	72	22	5	159	297	297
	%	29.2	7.4	36.6	21.3	7.8	0.2	29.4	12.7	15.3	4.6	1.0	33.9	63.3	63.3
FEMALE	No.	89	29	118	91	44	2	137	57	128	45	6	236	373	373
	%	18.1	5.9	24.0	18.5	8.9	0.4	27.9	11.6	26.0	9.1	1.2	50.3	75.9	75.9
M + F		226	64	290	191	81	3	275	117	200	67	11	395	670	670

Person per day. Tocachi and  
less than one year old  
(e of Nutrition).

LA ESPERANZA	
March 1966	June 1968
1,699.58	1,860.00
39.03	48.31
4.06	4.48
34.97	43.83
26.30	24.16
11.05	0.31
15.25	23.85
327.79	362.40
0.22	0.29
23.47	32.60
1,340.76	1,000.00
75.82	152.00
1,264.94	848.00
1.18	1.43
25.09	29.32
0.54	0.83
93.81	108.61

Tocachi and La Esperanza.

Standard deviation	Probability
8.3	0.7
6.7	
6.7	0.6
6.4	
6.8	0.04
7.0	
7.0	0.03
6.6	

Table 5. Prevalence and distribution of goiter by type and size in the survey conducted just before injection.  
Total subjects surveyed: 960. Tocachi, March 1966.

		DIFFUSE GOITER							NODULAR GOITER					TOTAL
		Oa	Ob	Oa+Ob	DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N	GOITER
MALE	No.	137	35	172	100	37	1	138	60	72	22	5	159	297
	%	29.2	7.4	36.6	21.3	7.8	0.2	29.4	12.7	15.3	4.6	1.0	33.9	63.3
FEMALE	No.	89	29	118	91	44	2	137	57	128	45	6	236	373
	%	18.1	5.9	24.0	18.5	8.9	0.4	27.9	11.6	26.0	9.1	1.2	50.3	75.9
M + F	No.	226	64	290	191	81	3	275	117	200	67	11	395	670
	%	23.5	6.6	30.2	19.8	8.4	0.3	28.6	12.1	20.8	6.0	1.1	41.1	69.7

Table 6. Prevalence and distribution of goiter by age in the survey conducted just before injection.  
Total subjects surveyed: 960. Tocachi, March 1966.

		DIFFUSE GOITER							NODULAR GOITER					TOTAL
AGE PERIOD YEARS	NUMBER	Oa	Ob	Oa+Ob	DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N	GOITER
0-5	178	No.	98	18	116	45	15	60		2			2	54
		%	55.0	10.1	65.1	25.2	8.4	33.7		1.1			1.1	34.9
6-12	160	No.	37	12	49	68	30	98	5	8			13	111
		%	23.1	7.5	30.6	42.5	18.7	61.2	3.1	5.0			8.1	69.3
13-18	85	No.	11	8	19	23	7	30	9	27			36	66
		%	12.9	9.4	22.3	27.0	8.2	35.2	10.5	31.7			42.3	77.6
19-40	292	No.	54	12	66	40	13	56	60	82	24	4	170	226
		%	18.4	4.1	22.6	13.6	4.4	19.1	20.5	28.0	8.2	1.3	58.2	77.3
41-+	245	No.	26	14	40	15	16	31	43	81	43	7	174	205
		%	10.6	5.7	16.3	6.1	6.5	12.5	17.5	33.0	17.5	2.8	71.0	83.6

Table 7. Prevalence and distribution of goiter by type and size in the survey conducted six months after injection.  
Total subjects surveyed: 490. Tocachi, September 1966.

		DIFFUSE GOITER							NODULAR GOITER					TOTAL
		Oa	Ob	Oa+Ob	DI	DII	DIID	Total D	NI	NII	NIID	NIV	Total N	GOITER
MALE	No.	54	63	117	8	2		10	68	20	1		89	99
	%	25.0	29.1	54.1	3.7	0.9		4.6	31.4	9.2	0.4		41.2	45.8
FEMALE	No.	46	38	84	21	5		26	88	70	6		164	190
	%	16.7	13.8	30.6	7.6	1.8		9.4	32.1	25.5	2.1		59.8	69.3
M + F	No.	100	101	201	29	7		36	156	90	7		253	289
	%	20.4	20.6	41.0	5.9	1.4		7.3	31.8	18.3	1.4		51.6	58.9

Table 8. Prevalence and distribution of goiter by age in the survey conducted six months after injection.  
Total subjects surveyed: 490. Tocachi, September 1966.

AGE PERIOD		DIFFUSE GOITER							NODULAR GOITER					TOTAL
YEARS	NUMBER	Oa	Ob	Oa+Ob	DI	DII	DIID	Total D	NI	NII	NIID	NIV	Total N	GOITER
0-5	135	No. 79 % 58.5	37 27.4	116 85.9	6 4.4	1 0.7		7 5.1	11 8.1	1 0.7			12 18.8	19 14.0
6-12	76	No. 6 % 7.8	27 35.5	33 43.4	13 17.1	2 2.6		15 19.7	22 28.9	6 7.8			28 36.8	43 56.5
13-18	45	No. 2 % 4.4	14 31.1	16 35.5	4 8.8			4 8.8	18 40.0	7 15.5			25 55.5	29 55.1
19-40	129	No. 8 % 6.2	18 13.9	26 20.1	6 4.6	4 3.1		10 7.7	66 51.1	26 20.1	1 0.7		93 72.0	103 79.8
41-+	105	No. 5 % 4.7	5 4.7	10 9.5					39 37.1	50 47.6	6 5.7		95 90.4	95 90.4

Table 9. Prevalence and distribution of goiter by type and size in the survey conducted 12 months after injection.  
Total subjects surveyed: 584. Tocachi, March 1967.

		DIFFUSE GOITER							NODULAR GOITER					TOTAL
		Oa	Ob	Oa+Ob	DI	DII	DIID	Total D	NI	NII	NIID	NIV	Total N	GOITER
MALE	No.	88	63	151	21	2		23	56	18	3		77	100
	%	35.0	25.0	60.1	8.3	0.7		9.1	22.3	7.1	1.1		30.6	39.8
FEMALE	No.	71	56	127	36	2		38	98	67	3		168	206
	%	21.3	16.8	38.1	10.8	0.6		11.4	29.4	20.1	0.9		50.4	61.8

6-12	76	No. %	2 4.4	14 31.1	16 35.5	4 8.8			4 8.8	18 40.0	7 15.5		25 55.5	29 55.1
13-18	45	No. %	2 4.4	14 31.1	16 35.5	4 8.8			4 8.8	18 40.0	7 15.5		25 55.5	29 55.1
19-40	129	No. %	8 6.2	18 13.9	26 20.1	6 4.6	4 3.1		10 7.7	66 51.1	26 20.1	1 0.7	93 72.0	103 79.8
41-+	105	No. %	5 4.7	5 4.7	10 9.5					39 37.1	50 47.6	6 5.7	95 90.4	95 90.4

Table 9. Prevalence and distribution of goiter by type and size in the survey conducted 12 months after injection.  
Total subjects surveyed: 584. Tocachi, March 1967.

		DIFFUSE GOITER								NODULAR GOITER					TOTAL
		Oa	Ob	Oa+Ob	DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N	GOITER	
MALE	No.	88	63	151	21	2		23	56	18	3		77	100	
	%	35.0	25.0	60.1	8.3	0.7		9.1	22.3	7.1	1.1		30.6	39.8	
FEMALE	No.	71	56	127	36	2		38	98	67	3		168	206	
	%	21.3	16.8	38.1	10.8	0.6		11.4	29.4	20.1	0.9		50.4	61.8	
M + F	No.	159	119	278	57	4		61	154	85	6		245	306	
	%	27.2	20.3	47.6	9.7	0.6		10.4	26.3	14.5	1.0		41.9	52.3	

Table 10. Prevalence and distribution of goiter by age in the survey conducted 12 months after injection.  
Total subjects surveyed: 584. Tocachi, March 1967.

AGE PERIOD YEARS	NUMBER		DIFFUSE GOITER							NODULAR GOITER					TOTAL
			Oa	Ob	Oa+Ob	DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N	GOITER
0-5	127	No. %	94 74.0	22 17.3	106 91.3	6 4.7			6 4.7	5 3.9				5 3.9	11 8.6
6-12	115	No. %	22 19.1	41 35.6	63 54.7	29 25.2			29 25.2	22 19.1	1 0.8			23 20.0	52 45.2
13-18	58	No. %	8 13.7	19 32.7	27 46.5	11 18.9	1 1.7		12 20.6	16 27.5	3 5.1			19 32.7	31 53.4
19-40	141	No. %	20 14.1	28 19.8	48 34.0	8 5.6	3 2.1		11 7.8	51 36.1	29 20.5	2 1.4		82 58.1	93 65.9
41-+	143	No. %	15 10.4	9 6.2	24 16.7	3 2.0			3 2.0	60 41.9	52 36.3	4 2.7		116 81.1	119 83.2

Table 11. Prevalence and distribution of goiter by type and size in the survey conducted 20 months after injection.  
Total subjects surveyed: 560. Tocachi, November 1967.

		DIFFUSE GOITER						NODULAR GOITER					TOTAL	
		Oa	Ob	Oa+Ob	DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N	GOITER
MALE	No.	118	51	169	15	1		16	45	16	2		63	79
	%	47.5	20.5	68.5	6.0	0.4		6.4	18.1	6.4	0.8		25.4	14.1
FEMALE	No.	99	50	149	37	5		42	59	46	6		111	153
	%	32.7	16.5	49.3	12.2	1.6		13.9	19.5	15.2	1.9		36.7	27.3
M + F	No.	217	101	318	52	6		58	104	62	8		174	232
	%	38.7	18.0	56.7	9.2	1.0		10.3	18.5	11.0	1.4		31.0	41.4

Table 12. Prevalence and distribution of goiter by age in the survey conducted 20 months after injection.  
Total subjects surveyed: 560. Tocachi, November 1967.

AGE PERIOD YEARS		NUMBER	DIFFUSE GOITER						NODULAR GOITER					TOTAL	
			Oa	Ob	Oa+Ob	DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N	GOITER
0-5	156	No. %	121 77.5	12 7.6	133 85.2	7 4.4			7 4.4	8 5.1	2 1.2			10 6.4	17 10.8
6-12	95	No. %	18 18.9	34 35.7	52 54.7	23 24.2	4 4.2		27 28.4	14 14.7	2 2.1			16 16.8	43 45.2
13-18	43	No. %	10 23.2	17 39.5	27 62.7	8 18.6			8 18.6	8 18.6				8 18.6	16 37.2
19-40	134	No. %	39 29.1	24 17.9	63 47.0	11 8.2	2 1.4		13 9.7	32 23.8	25 18.6	1 0.7		58 43.2	71 52.9
41-+	138	No. %	29 21.0	14 10.1	43 31.1	3 2.1			3 2.1	42 30.4	43 31.1	7 5.0		92 66.6	95 68.8

Table 13. Prevalence and distribution of goiter by type and size in the survey conducted 25 months after injection.  
Total subjects surveyed: 758. Tocachi, April 1968.

					DIFFUSE GOITER				NODULAR GOITER				TOTAL	
					DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N	GOITER
		Oa	Ob	Oa+Ob										
MALE	No.	129	100	229	14			14	94	18	2		114	128
	%	36.1	28.0	64.1	3.9			3.9	26.3	5.0	0.5		31.9	35.8
FEMALE	No.	96	90	186	39	1		40	111	58	6		175	215
	%	23.9	22.4	46.3	9.7	0.2		9.9	17.6	14.4	1.4		43.6	53.6

6-12	95	No. %	18 18.9	34 35.7	52 54.7	23 24.2	4 4.2	27 28.4	14 14.7	2 2.1		16 16.8	43 45.2
13-18	43	No. %	10 23.2	17 39.5	27 62.7	8 18.6		8 18.6	8 18.6			8 18.6	16 37.2
19-40	134	No. %	39 29.1	24 17.9	63 47.0	11 8.2	2 1.4	13 9.7	32 23.8	25 18.6	1 0.7	58 43.2	71 52.9
41-+	138	No. %	29 21.0	14 10.1	43 31.1	3 2.1		3 2.1	42 30.4	43 31.1	7 5.0	92 66.6	95 68.8

Table 13. Prevalence and distribution of goiter by type and size in the survey conducted 25 months after injection.  
Total subjects surveyed: 758. Tocachi, April 1968.

		DIFFUSE GOITER							NODULAR GOITER					TOTAL
		Oa	Ob	Oa+Ob	DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N	
MALE	No. %	129 36.1	100 28.0	229 64.1	14 3.9			14 3.9	94 26.3	18 5.0	2 0.5		114 31.9	128 35.8
FEMALE	No. %	96 23.9	90 22.4	186 46.3	39 9.7	1 0.2		40 9.9	111 17.6	58 14.4	6 1.4		175 43.6	215 53.6
M + F	No. %	225 29.7	190 25.1	415 54.8	53 7.0	1 0.1		54 7.1	205 27.1	76 10.0	8 1.0		289 38.2	343 45.3

Table 14. Prevalence and distribution of goiter by age in the survey conducted 25 months after injection.  
Total subjects surveyed: 758. Tocachi, April 1968.

AGE PERIOD YEARS	NUMBER		DIFFUSE GOITER							NODULAR GOITER					TOTAL
			Oa	Ob	Oa+Ob	DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N	
0-5	166	No. %	130 78.3	21 12.6	115 90.9	11 6.6			11 6.6	1 0.6	3 1.8			4 2.4	15 9.0
6-12	139	No. %	20 14.3	87 62.5	107 76.9	25 17.9	1 0.7		26 18.7	5 3.5	1 0.7			6 4.3	32 23.1
13-18	64	No. %	14 21.8	32 50.0	46 71.8	11 17.1	17.1		11 17.1	7 10.9				7 10.9	18 28.2
19-40	192	No. %	31 16.1	45 23.4	76 39.5	5 2.6			5 2.6	88 45.8	19 9.8	4 2.0		111 57.8	116 60.5
41-+	197	No. %	30 15.2	5 2.5	35 17.7	1 0.5			1 0.5	104 52.7	53 26.9	4 2.0		161 81.7	162 82.3



Table 15. Evolution of thyroids of grade Oa, linear study. Number of subjects of this group surveyed in March 1966: 226.

THYROID		T O C A C H I											
		SURVEY AFTER 6 MONTHS			SURVEY AFTER 12 MONTHS			SURVEY AFTER 20 MONTHS			SURVEY AFTER 25 MONTHS		
		MALE No. 59	FEMALE No. 40	M+F No. 99	MALE No. 71	FEMALE No. 42	M+F No. 113	MALE No. 59	FEMALE No. 34	M+F No. 93	MALE No. 88	FEMALE No. 54	M+F No. 142
Oa	No. %	34 57.6	22 55.0	56 56.5	48 67.6	24 57.1	72 63.7	44 74.5	23 67.6	67 72.0	55 62.5	22 40.7	77 54.2
Ob	No. %	12 20.3	8 20.0	20 22.2	16 22.5	11 26.1	27 23.8	13 22.0	8 23.5	21 22.5	21 23.8	21 38.8	42 29.5
IN	No. %	8 13.5	5 12.5	13 13.1	5 7.0	3 7.1	8 7.0	2 3.3	2 5.8	4 4.3	9 10.2	3 5.5	12 8.4
ID	No. %	3 5.0	4 10.0	7 7.0	1 1.4	4 9.5	5 4.4	- -	1 2.9	1 1.0	1 1.1	6 11.1	7 4.9
IIN	No. %	2 3.3	- -	2 2.0	- -	- -	- -				2 2.2	2 3.7	4 2.8
IID	No. %	- -	1 2.5	1 1.0	1 1.4	- -	1 0.8						

Table 16. Evolution of thyroids Ob, linear study. Number of subjects of this group surveyed in March 1966: 64.

		T O C A C H I											
		SURVEY AFTER 6 MONTHS			SURVEY AFTER 12 MONTHS			SURVEY AFTER 20 MONTHS			SURVEY AFTER 25 MONTHS		
		MALE No. 59	FEMALE No. 40	M+F No. 99	MALE No. 71	FEMALE No. 42	M+F No. 113	MALE No. 59	FEMALE No. 34	M+F No. 93	MALE No. 88	FEMALE No. 54	M+F No. 142

IIN	No. %	2 3.3	-	2 2.0	-	-	-	2.2	3.7	2.8
IID	No. %	-	1 2.5	1 1.0	1 1.4	-	1 0.8			

Table 16. Evolution of thyroids Ob, linear study. Number of subjects of this group surveyed in March 1966: 64.

THYROID	T O C A C H I											
	SURVEY AFTER 6 MONTHS			SURVEY AFTER 12 MONTHS			SURVEY AFTER 20 MONTHS			SURVEY AFTER 25 MONTHS		
	MALE No. 17	FEMALE No. 13	M+F No. 30	MALE No. 20	FEMALE No. 16	M+F No. 36	MALE No. 20	FEMALE No. 14	M+F No. 34	MALE No. 27	FEMALE No. 18	M+F No. 45
Oa	No. 3 % 17.6	2 15.3	5 16.6	6 30.0	2 12.5	8 22.2	7 35.0	6 42.8	13 38.2	13 48.1	3 16.6	16 35.5
Ob	No. 9 % 52.9	7 53.8	16 53.6	7 35.0	11 68.7	18 50.0	9 45.0	4 28.5	13 38.2	8 29.6	9 50.0	17 37.7
IN	No. 5 % 29.4	1 7.6	6 20.0	4 20.0	3 18.7	7 19.4	3 15.0	3 21.4	6 17.6	4 14.8	2 11.1	6 13.3
ID	No. - % -	2 15.3	2 6.6	2 10.0	-	2 5.5	1 5.0	1 7.1	2 5.8	2 7.4	4 22.2	6 13.3
IIN	No. %			1 5.0	-	1 2.7						
IID	No. - % -	1 7.6	1 3.3									

Table 17. Evolution of goiters diffuse I, linear study. Number of subjects of this group surveyed in March 1966: 191.

THYROID		T O C A C H I											
		SURVEY AFTER 6 MONTHS			SURVEY AFTER 12 MONTHS			SURVEY AFTER 20 MONTHS			SURVEY AFTER 25 MONTHS		
		MALE No. 58	FEMALE No. 48	M+F No. 106	MALE No. 50	FEMALE No. 64	M+F No. 114	MALE No. 55	FEMALE No. 51	M+F No. 106	MALE No. 73	FEMALE No. 64	M+F No. 137
Oa	No. %	7 12.0	8 16.6	15 14.1	10 20.0	13 20.3	23 20.1	20 36.3	16 31.3	36 33.9	14 19.1	14 21.8	28 20.4
Ob	No. %	27 46.5	14 29.1	41 38.6	21 42.0	19 29.6	40 35.0	16 29.0	17 33.3	33 31.1	42 57.5	26 40.6	68 49.6
IN	No. %	17 29.3	15 31.2	32 30.1	10 20.0	15 23.4	25 21.9	7 12.7	7 13.7	14 13.2	9 12.3	9 14.0	18 13.1
ID	No. %	5 8.6	6 12.5	11 10.3	8 16.0	16 25.0	24 21.0	10 18.1	10 19.6	20 18.8	8 10.9	13 20.3	21 15.3
IIN	No. %	2 3.4	3 6.2	5 4.7	1 2.0	- -	1 0.8	2 3.6	1 1.9	3 2.8	- -	1 1.5	1 0.7
IID	No. %	- -	2 4.1	2 1.8	- -	1 1.5	1 0.8				- -	1 1.5	1 0.7

Table 18. Evolution of goiters nodular I, linear study. Number of subjects of this group surveyed in March 1966: 117.

		T O C A C H I											
		SURVEY AFTER 6 MONTHS			SURVEY AFTER 12 MONTHS			SURVEY AFTER 20 MONTHS			SURVEY AFTER 25 MONTHS		

IIN	No.	2	3	5	1	-	1	3	1	2	-	1	0
	%	3.4	6.2	4.7	2.0	-	0.8	3.6	1.9	2.8	-	1.5	0.7
IID	No.	-	2	2	-	1	1	-	-	-	-	1	1
	%	-	4.1	1.8	-	1.5	0.8	-	-	-	-	1.5	0.7

Table 18. Evolution of goiters nodular I, linear study. Number of subjects of this group surveyed in March 1966: 117.

T O C A C H I													
THYROID		SURVEY AFTER 6 MONTHS			SURVEY AFTER 12 MONTHS			SURVEY AFTER 20 MONTHS			SURVEY AFTER 25 MONTHS		
		MALE	FEMALE	M+F	MALE	FEMALE	M+F	MALE	FEMALE	M+F	MALE	FEMALE	M+F
		No. 22	No. 34	No. 56	No. 35	No. 35	No. 70	No. 33	No. 28	No. 61	No. 41	No. 35	No. 76
Oa	No. %		1 2.9	1 1.7	6 17.1	1 2.8	7 10.0	10 30.3	6 21.4	16 26.2	5 12.1	3 8.5	8 10.5
Ob	No. %	2 9.0	5 14.7	7 12.5	14 40	8 22.8	22 31.4	7 21.2	5 17.8	12 19.6	6 14.6	6 17.1	12 15.7
IN	No. %	14 63.6	16 47.0	30 53.5	14 40.0	18 51.4	32 45.7	15 45.4	8 28.5	23 37.7	27 65.8	20 57.1	47 61.8
ID	No. %	2 9.0	3 8.8	5 8.9	- -	5 14.2	5 7.1	- -	5 17.8	5 8.1	1 2.4	1 2.8	2 2.6
IIN	No. %	4 18.0	9 26.4	13 23.2	1 2.8	3 8.5	4 5.7	1 3.0	4 14.2	5 8.1	2 4.8	5 14.2	7 9.2
IID													

Table 19. Evolution of goiters diffuse II, linear study. Number of subjects of this group surveyed in March 1966: 81.

THYROID		T O C A C H I											
		SURVEY AFTER 6 MONTHS			SURVEY AFTER 12 MONTHS			SURVEY AFTER 20 MONTHS			SURVEY AFTER 25 MONTHS		
		MALE No. 19	FEMALE No. 24	M+F No. 43	MALE No. 27	FEMALE No. 30	M+F No. 57	MALE No. 23	FEMALE No. 27	M+F No. 50	MALE No. 30	FEMALE No. 32	M+F No. 62
Oa	No. %	- -	2 8.3	2 4.6	1 3.7	2 6.6	3 5.2	5 21.7	4 14.8	9 18.0	3 10.0	3 9.3	6 9.6
Ob	No. %	8 42.1	2 8.3	10 23.2	7 25.9	3 10.0	10 17.5	4 17.3	4 14.8	8 16.0	15 50.0	7 21.8	22 35.4
IN	No. %	6 31.5	11 45.8	17 39.5	10 37.0	10 33.3	20 35.0	7 30.4	3 11.1	10 20.0	- -	- -	- -
ID	No. %	1 5.4	3 12.5	4 9.3	8 29.6	8 26.6	16 28.0	3 13.0	7 25.9	10 20.0	4 13.3	8 25.0	12 19.3
IIN	No. %	2 10.8	6 25.0	8 18.6	1 3.7	6 20.0	7 12.2	3 13.0	5 18.5	8 16.0	7 23.3	9 28.1	16 25.8
IID	No. %	2 10.8	- -	2 4.6	- -	1 3.3	1 1.7	1 4.3	4 14.8	5 10.0	1 3.3	5 15.6	6 9.6

Table 20. Evolution of goiters nodular II, linear study. Number of subjects of this group surveyed in March 1966: 200.

		T O C A C H I			
		SURVEY AFTER 6 MONTHS	SURVEY AFTER 12 MONTHS	SURVEY AFTER 20 MONTHS	SURVEY AFTER 25 MONTHS

IIN	No. %	2 10.8	0 25.0	0 18.6	1 3.7	0 20.0	7 12.2	9 13.0	9 18.5	0 16.0	7 23.3	9 28.1	10 25.8
IID	No. %	2 10.8	- -	2 4.6	- -	1 3.3	1 1.7	1 4.3	4 14.8	5 10.0	1 3.3	5 15.6	6 9.6

Table 20. Evolution of goiters nodular II, linear study. Number of subjects of this group surveyed in March 1966: 200.

THYROID		T O C A C H I											
		SURVEY AFTER 6 MONTHS			SURVEY AFTER 12 MONTHS			SURVEY AFTER 20 MONTHS			SURVEY AFTER 25 MONTHS		
		MALE No. 24	FEMALE No. 73	M+F No. 97	MALE No. 34	FEMALE No. 91	M+F No. 126	MALE No. 27	FEMALE No. 78	M+F No. 105	MALE No. 48	FEMALE No. 101	M+F No. 149
Oa	No. %	- -	- -	- -	2 5.8	1 1.0	3 2.3	5 18.5	6 7.6	11 10.4	2 4.1	2 1.9	4 2.6
Ob	No. %	4 16.6	1 1.3	5 5.1	3 8.8	5 5.4	8 6.3	4 14.8	6 7.6	10 10.4	8 16.6	16 15.8	24 16.1
IN	No. %	12 50.0	34 46.5	46 57.7	17 50.0	39 42.8	56 44.4	12 44.4	28 35.8	40 38.0	29 60.4	58 57.4	87 58.3
ID	No. %	- -	2 2.6	2 2.0	3 8.8	5 5.4	8 6.3	1 3.7	12 15.3	13 12.3	1 2.0	4 3.9	5 3.3
IIN	No. %	8 33.3	35 47.9	43 44.3	9 26.4	40 43.9	49 38.8	5 18.5	26 33.3	31 29.5	7 14.5	20 19.8	27 18.1
IID	No. %	- -	1 1.3	1 1.0									

Table 21. Evolution of goiters nodular III, linear study. Number of subjects of this group surveyed in March 1966: 67.

THYROID		T O C A C H I											
		SURVEY AFTER 6 MONTHS			SURVEY AFTER 12 MONTHS			SURVEY AFTER 20 MONTHS			SURVEY AFTER 25 MONTHS		
		MALE No. 6	FEMALE No. 27	M+F No. 33	MALE No. 10	FEMALE No. 27	M+F No. 37	MALE No. 6	FEMALE No. 27	M+F No. 33	MALE No. 12	FEMALE No. 34	M+F No. 46
Oa	No. %				1 10.0	1 3.7	2 5.4	1 16.6	1 3.7	2 6.0	- -	1 2.9	1 2.1
Ob	No. %												
IN	No. %	2 33.3	8 29.6	10 30.3	2 20.0	7 25.9	9 24.3	- -	6 22.2	6 18.1	8 66.6	9 26.4	17 36.9
ID	No. %				- -	2 7.4	2 5.4	- -	1 3.7	1 3.0			
IIN	No. %	4 66.6	15 55.4	19 57.5	5 50.0	16 59.2	21 56.7	5 83.3	15 55.5	20 60.6	4 33.3	21 61.7	25 54.3
IIIN	No. %	- -	4 14.8	4 12.1	2 20.0	1 3.7	3 8.1	- -	4 14.8	4 12.0	- -	3 8.8	3 6.5

Table 22. Prevalence and distribution of goiter by type and size. La Esperanza, March 1966.

		DIFFUSE GOITER							NODULAR GOITER				TOTAL GOITER
		Oa	Ob	Oa+Ob	DI	DII	DIII	Total D	NI	NII	NIII	NIV	Total N
MALE	No. %	218 50.3	34 7.8	252 58.1	106 24.4	23 5.3	1 0.2	130 30.0	32 7.3	20 4.6	9 2.0		61 14.0
FEMALE	No. %	179 33.5	34 6.3	213 39.9	107 20.0	42 7.8	5 0.9	154 28.8	59 11.0	77 14.4	27 5.0	3 0.5	166 31.1
													320 60.0

IIN	No. %	4 66.6	15 55.4	19 57.5	5 50.0	16 59.2	21 56.7	5 83.3	15 55.5	20 60.6	4 33.3	21 61.7	25 54.3
IIIN	No. %	- -	4 14.8	4 12.1	2 20.0	1 3.7	3 8.1	- -	4 14.8	4 12.0	- -	3 8.8	3 6.5

Section VII

Table 22. Prevalence and distribution of goiter by type and size. La Esperanza, March 1966.

		Oa	Ob	Oa+Ob	DIFFUSE GOITER				NODULAR GOITER				Total N	TOTAL GOITER
					DI	DII	DIII	Total D	NI	NII	NIII	NIV		
MALE	No.	218	34	252	106	23	1	130	32	20	9		61	191
	%	50.3	7.8	58.1	24.4	5.3	0.2	30.0	7.3	4.6	2.0		14.0	44.0
FEMALE	No.	179	34	213	107	42	5	154	59	77	27	3	166	320
	%	33.5	6.3	39.9	20.0	7.8	0.9	28.8	11.0	14.4	5.0	0.5	31.1	60.0
M + F	No.	397	68	465	203	65	6	284	91	97	36	3	227	511
	%	41.0	7.0	48.1	22.0	6.7	0.6	29.3	9.4	10.0	3.7	0.3	23.4	52.8

Table 23. Prevalence and distribution of goiter by type and size. La Esperanza, April 1968.

		Oa	Ob	Oa+Ob	DIFFUSE GOITER				NODULAR GOITER				Total N	TOTAL GOITER
					DI	DII	DIII	Total D	NI	NII	NIII	NIV		
MALE	No.	116	162	278	98	15		113	143	44	9		196	309
	%	19.7	27.6	47.4	16.7	2.5		19.2	24.4	7.5	1.5		33.4	52.7
FEMALE	No.	77	122	199	107	31	2	140	137	141	25	1	304	444
	%	11.9	18.9	30.9	16.6	4.8	0.3	21.7	21.3	21.9	3.8	0.1	47.2	69.0
M + F	No.	193	284	477	205	46	2	253	280	185	34	1	500	753
	%	15.7	23.1	38.8	16.6	3.7	0.1	20.5	22.7	15.0	2.7	0.08	40.6	61.2

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Table 24. Evolution of  $^{131}\text{I}$  thyroid uptake in iodized subjects from Tocachi.

	2 hr. Mean value range	24 hr. Mean value range	96 hr. Mean value range
Before iodization No. 18	60 45-70	79 59-88	75 61-86
After 6 months No. 10	10 7-18	23 10-38	22 8-38
After 12 months No. 7	14 9-18	39 35-45	38 33-45
After 20 months No. 7	12 8-17	34 21-49	31 17-45
After 25 months No. 10	12 6-18	38 24-56	34 20-53
Non-iodized subjects (1 April 1968) No. 3	43 38-48	72 70-74	61 54-68

Table 25. Evolution of  $^{131}\text{I}$  thyroid function in iodized subjects from Tocachi.

	Conversion ratio per cent, 24 hr. Mean value range	PB $^{131}\text{I}$ per cent 24 hr. Mean value range
Before iodization	86 55-92	0.29 0.10-0.34
After 6 months	6 2-15	0.019 0.008-0.04
After 12 months	14 8-21	0.04 0.02-0.07
After 20 months	31 15-51	0.21 0.06-0.42
After 25 months	36 11-57	0.14 0.02-0.24

Table 26. E

Before iodization No. 18
After 6 months No. 10
After 12 months No. 14
After 20 months No. 5
After 25 months No. 14

Table 27. Evolutio

Before iodization No. 27
After 6 months No. 10
After 12 months No. 35
After 20 months No. 13
After 25 months No. 43
Non-iodized subjects (April 1968) No. 18

ts from Tocachi.

96 hr. Mean value range
75 61-86
22 8-38
38 33-45
31 17-45
34 20-53
61 54-68

ts from Tocachi.

<sup>31</sup> I per cent 24 hr. Mean value range
0.29 0.10-0.34
0.019 0.008-0.04
0.04 0.02-0.07
0.21 0.06-0.42
0.14 0.02-0.24

Table 26. Evolution of <sup>127</sup>I blood tests in iodized subjects from Tocachi.

	TI µg% Mean value range	PBI µg% Mean value range	BEI µg% Mean value range	BII µg% Mean value range
Before iodization No. 18	2.84 1.2-5.6	2.76 1.2-5.0	2.08 0.8-5.0	0.60 0.4-0.8
After 6 months No. 10	20 9- 20	20 8- 20	4.40 2.0-7.0	10.00 6.0-15.4
After 12 months No. 14	11.16 8.0-15.2	11.14 7.8-14.4	5.85 4.6-6.8	5.62 2.2-10.2
After 20 months No. 5	9.13 7.3-10.8	8.01 7.1-9.5	5.50 4.1-6.5	2.20 0.9-3.2
After 25 months No. 14	7.72 2.0-12.2	7.15 1.5-11.0	5.69 1.4-7.4	1.57 0.4-4.5

Table 27. Evolution of urinary excretion of iodine in iodized subjects from Tocachi.

	UEI µg/100 ml.		CREATININE mg/100 ml.		UEI µg per 0.9 g creatinine	
	Mean value	Range	Mean value	Range	Mean value	Range
Before iodization No. 27	0.37	0.2-0.8	32.8	21-69	10.4	7.4-25.2
After 6 months No. 10	32.50	9.2-10.3	31.8	19-59	920.0	482-1,575
After 12 months No. 35	9.90	2.4-16.0	31.0	13-44	292.6	142-415
After 20 months No. 13	5.45	1.3-10.2	30.6	15-50	160.4	80-173
After 25 months No. 43	2.89	0.5-8.9	33.2	18-58	78.4	30-135
Non-iodized subjects (April 1968) No. 18	0.53	0.2-1.4	32.8	17-54	14.5	11.5-24.7

Table 28. Data obtained in the thyrotoxic women from Tocachi  
(after six months of administration of iodized oil).

	Patient No. 1	Patient No. 2	Patient No. 3
Age	45	67	60
Goiter March 1966	N-II	N-III	N-II
Goiter October 1966	N-I	N-III	N-I
BMR, per cent	+24	+53	+82
Cholesterol mg per 100 ml	212	190	178
$^{131}\text{I}$ thyroid uptake			
8 hours	16	23	24
24 hours	22	32	33
96 hours	20	31	30
PB $^{131}\text{I}$ per liter at 24 hours	0.02	0.008	0.09
KSCN Suppression test - per cent dose	1	4	0
BEI, $\mu\text{g}$ per cent	7.8	12.0	8.0
BII, $\mu\text{g}$ per cent	14.0	10.5	13.5
$\text{T}_3$ - $^{131}\text{I}$ resin uptake	40	50	52

## IODIZED OIL IN THE DEFECTS

### II. EFFE SOMATIC

Ignacio  
Eduardo  
Carlos D

A program of prophylactic intramuscular administration of iodized oil to the children of Tocachi and La Esperanza has been initiated. The program is designed to emphasize that the incidence of cretinism is due to goiter, incidence of cretinism is due to goiter, and both have a common factor, and both have a common factor. Tocachi were given iodized oil subjects.

All children born during the following times: 0-15 days, 16-30 days, 31-60 days, 61-90 days, 91-120 days, 121-150 days, 151-180 days, 181-210 days, 211-240 days, 241-270 days, 271-300 days, 301-330 days, 331-360 days, 361-390 days, 391-420 days, 421-450 days, 451-480 days, 481-510 days, 511-540 days, 541-570 days, 571-600 days, 601-630 days, 631-660 days, 661-690 days, 691-720 days, 721-750 days, 751-780 days, 781-810 days, 811-840 days, 841-870 days, 871-900 days, 901-930 days, 931-960 days, 961-990 days, 991-1020 days, 1021-1050 days, 1051-1080 days, 1081-1110 days, 1111-1140 days, 1141-1170 days, 1171-1200 days, 1201-1230 days, 1231-1260 days, 1261-1290 days, 1291-1320 days, 1321-1350 days, 1351-1380 days, 1381-1410 days, 1411-1440 days, 1441-1470 days, 1471-1500 days, 1501-1530 days, 1531-1560 days, 1561-1590 days, 1591-1620 days, 1621-1650 days, 1651-1680 days, 1681-1710 days, 1711-1740 days, 1741-1770 days, 1771-1800 days, 1801-1830 days, 1831-1860 days, 1861-1890 days, 1891-1920 days, 1921-1950 days, 1951-1980 days, 1981-2010 days, 2011-2040 days, 2041-2070 days, 2071-2100 days, 2101-2130 days, 2131-2160 days, 2161-2190 days, 2191-2220 days, 2221-2250 days, 2251-2280 days, 2281-2310 days, 2311-2340 days, 2341-2370 days, 2371-2400 days, 2401-2430 days, 2431-2460 days, 2461-2490 days, 2491-2520 days, 2521-2550 days, 2551-2580 days, 2581-2610 days, 2611-2640 days, 2641-2670 days, 2671-2700 days, 2701-2730 days, 2731-2760 days, 2761-2790 days, 2791-2820 days, 2821-2850 days, 2851-2880 days, 2881-2910 days, 2911-2940 days, 2941-2970 days, 2971-3000 days, 3001-3030 days, 3031-3060 days, 3061-3090 days, 3091-3120 days, 3121-3150 days, 3151-3180 days, 3181-3210 days, 3211-3240 days, 3241-3270 days, 3271-3300 days, 3301-3330 days, 3331-3360 days, 3361-3390 days, 3391-3420 days, 3421-3450 days, 3451-3480 days, 3481-3510 days, 3511-3540 days, 3541-3570 days, 3571-3600 days, 3601-3630 days, 3631-3660 days, 3661-3690 days, 3691-3720 days, 3721-3750 days, 3751-3780 days, 3781-3810 days, 3811-3840 days, 3841-3870 days, 3871-3900 days, 3901-3930 days, 3931-3960 days, 3961-3990 days, 3991-4020 days, 4021-4050 days, 4051-4080 days, 4081-4110 days, 4111-4140 days, 4141-4170 days, 4171-4200 days, 4201-4230 days, 4231-4260 days, 4261-4290 days, 4291-4320 days, 4321-4350 days, 4351-4380 days, 4381-4410 days, 4411-4440 days, 4441-4470 days, 4471-4500 days, 4501-4530 days, 4531-4560 days, 4561-4590 days, 4591-4620 days, 4621-4650 days, 4651-4680 days, 4681-4710 days, 4711-4740 days, 4741-4770 days, 4771-4800 days, 4801-4830 days, 4831-4860 days, 4861-4890 days, 4891-4920 days, 4921-4950 days, 4951-4980 days, 4981-5010 days, 5011-5040 days, 5041-5070 days, 5071-5100 days, 5101-5130 days, 5131-5160 days, 5161-5190 days, 5191-5220 days, 5221-5250 days, 5251-5280 days, 5281-5310 days, 5311-5340 days, 5341-5370 days, 5371-5400 days, 5401-5430 days, 5431-5460 days, 5461-5490 days, 5491-5520 days, 5521-5550 days, 5551-5580 days, 5581-5610 days, 5611-5640 days, 5641-5670 days, 5671-5700 days, 5701-5730 days, 5731-5760 days, 5761-5790 days, 5791-5820 days, 5821-5850 days, 5851-5880 days, 5881-5910 days, 5911-5940 days, 5941-5970 days, 5971-6000 days, 6001-6030 days, 6031-6060 days, 6061-6090 days, 6091-6120 days, 6121-6150 days, 6151-6180 days, 6181-6210 days, 6211-6240 days, 6241-6270 days, 6271-6300 days, 6301-6330 days, 6331-6360 days, 6361-6390 days, 6391-6420 days, 6421-6450 days, 6451-6480 days, 6481-6510 days, 6511-6540 days, 6541-6570 days, 6571-6600 days, 6601-6630 days, 6631-6660 days, 6661-6690 days, 6691-6720 days, 6721-6750 days, 6751-6780 days, 6781-6810 days, 6811-6840 days, 6841-6870 days, 6871-6900 days, 6901-6930 days, 6931-6960 days, 6961-6990 days, 6991-7020 days, 7021-7050 days, 7051-7080 days, 7081-7110 days, 7111-7140 days, 7141-7170 days, 7171-7200 days, 7201-7230 days, 7231-7260 days, 7261-7290 days, 7291-7320 days, 7321-7350 days, 7351-7380 days, 7381-7410 days, 7411-7440 days, 7441-7470 days, 7471-7500 days, 7501-7530 days, 7531-7560 days, 7561-7590 days, 7591-7620 days, 7621-7650 days, 7651-7680 days, 7681-7710 days, 7711-7740 days, 7741-7770 days, 7771-7800 days, 7801-7830 days, 7831-7860 days, 7861-7890 days, 7891-7920 days, 7921-7950 days, 7951-7980 days, 7981-8010 days, 8011-8040 days, 8041-8070 days, 8071-8100 days, 8101-8130 days, 8131-8160 days, 8161-8190 days, 8191-8220 days, 8221-8250 days, 8251-8280 days, 8281-8310 days, 8311-8340 days, 8341-8370 days, 8371-8400 days, 8401-8430 days, 8431-8460 days, 8461-8490 days, 8491-8520 days, 8521-8550 days, 8551-8580 days, 8581-8610 days, 8611-8640 days, 8641-8670 days, 8671-8700 days, 8701-8730 days, 8731-8760 days, 8761-8790 days, 8791-8820 days, 8821-8850 days, 8851-8880 days, 8881-8910 days, 8911-8940 days, 8941-8970 days, 8971-9000 days, 9001-9030 days, 9031-9060 days, 9061-9090 days, 9091-9120 days, 9121-9150 days, 9151-9180 days, 9181-9210 days, 9211-9240 days, 9241-9270 days, 9271-9300 days, 9301-9330 days, 9331-9360 days, 9361-9390 days, 9391-9420 days, 9421-9450 days, 9451-9480 days, 9481-9510 days, 9511-9540 days, 9541-9570 days, 9571-9600 days, 9601-9630 days, 9631-9660 days, 9661-9690 days, 9691-9720 days, 9721-9750 days, 9751-9780 days, 9781-9810 days, 9811-9840 days, 9841-9870 days, 9871-9900 days, 9901-9930 days, 9931-9960 days, 9961-9990 days, 9991-10020 days, 10021-10050 days, 10051-10080 days, 10081-10110 days, 10111-10140 days, 10141-10170 days, 10171-10200 days, 10201-10230 days, 10231-10260 days, 10261-10290 days, 10291-10320 days, 10321-10350 days, 10351-10380 days, 10381-10410 days, 10411-10440 days, 10441-10470 days, 10471-10500 days, 10501-10530 days, 10531-10560 days, 10561-10590 days, 10591-10620 days, 10621-10650 days, 10651-10680 days, 10681-10710 days, 10711-10740 days, 10741-10770 days, 10771-10800 days, 10801-10830 days, 10831-10860 days, 10861-10890 days, 10891-10920 days, 10921-10950 days, 10951-10980 days, 10981-11010 days, 11011-11040 days, 11041-11070 days, 11071-11100 days, 11101-11130 days, 11131-11160 days, 11161-11190 days, 11191-11220 days, 11221-11250 days, 11251-11280 days, 11281-11310 days, 11311-11340 days, 11341-11370 days, 11371-11400 days, 11401-11430 days, 11431-11460 days, 11461-11490 days, 11491-11520 days, 11521-11550 days, 11551-11580 days, 11581-11610 days, 11611-11640 days, 11641-11670 days, 11671-11700 days, 11701-11730 days, 11731-11760 days, 11761-11790 days, 11791-11820 days, 11821-11850 days, 11851-11880 days, 11881-11910 days, 11911-11940 days, 11941-11970 days, 11971-12000 days, 12001-12030 days, 12031-12060 days, 12061-12090 days, 12091-12120 days, 12121-12150 days, 12151-12180 days, 12181-12210 days, 12211-12240 days, 12241-12270 days, 12271-12300 days, 12301-12330 days, 12331-12360 days, 12361-12390 days, 12391-12420 days, 12421-12450 days, 12451-12480 days, 12481-12510 days, 12511-12540 days, 12541-12570 days, 12571-12600 days, 12601-12630 days, 12631-12660 days, 12661-12690 days, 12691-12720 days, 12721-12750 days, 12751-12780 days, 12781-12810 days, 12811-12840 days, 12841-12870 days, 12871-12900 days, 12901-12930 days, 12931-12960 days, 12961-12990 days, 12991-13020 days, 13021-13050 days, 13051-13080 days, 13081-13110 days, 13111-13140 days, 13141-13170 days, 13171-13200 days, 13201-13230 days, 13231-13260 days, 13261-13290 days, 13291-13320 days, 13321-13350 days, 13351-13380 days, 13381-13410 days, 13411-13440 days, 13441-13470 days, 13471-13500 days, 13501-13530 days, 13531-13560 days, 13561-13590 days, 13591-13620 days, 13621-13650 days, 13651-13680 days, 13681-13710 days, 13711-13740 days, 13741-13770 days, 13771-13800 days, 13801-13830 days, 13831-13860 days, 13861-13890 days, 13891-13920 days, 13921-13950 days, 13951-13980 days, 13981-14010 days, 14011-14040 days, 14041-14070 days, 14071-14100 days, 14101-14130 days, 14131-14160 days, 14161-14190 days, 14191-14220 days, 14221-14250 days, 14251-14280 days, 14281-14310 days, 14311-14340 days, 14341-14370 days, 14371-14400 days, 14401-14430 days, 14431-14460 days, 14461-14490 days, 14491-14520 days, 14521-14550 days, 14551-14580 days, 14581-14610 days, 14611-14640 days, 14641-14670 days, 14671-14700 days, 14701-14730 days, 14731-14760 days, 14761-14790 days, 14791-14820 days, 14821-14850 days, 14851-14880 days, 14881-14910 days, 14911-14940 days, 14941-14970 days, 14971-15000 days, 15001-15030 days, 15031-15060 days, 15061-15090 days, 15091-15120 days, 15121-15150 days, 15151-15180 days, 15181-15210 days, 15211-15240 days, 15241-15270 days, 15271-15300 days, 15301-15330 days, 15331-15360 days, 15361-15390 days, 15391-15420 days, 15421-15450 days, 15451-15480 days, 15481-15510 days, 15511-15540 days, 15541-15570 days, 15571-15600 days, 15601-15630 days, 15631-15660 days, 15661-15690 days, 15691-15720 days, 15721-15750 days, 15751-15780 days, 15781-15810 days, 15811-15840 days, 15841-15870 days, 15871-15900 days, 15901-15930 days, 15931-15960 days, 15961-15990 days, 15991-16020 days, 16021-16050 days, 16051-16080 days, 16081-16110 days, 16111-16140 days, 16141-16170 days, 16171-16200 days, 16201-16230 days, 16231-16260 days, 16261-16290 days, 16291-16320 days, 16321-16350 days, 16351-16380 days, 16381-16410 days, 16411-16440 days, 16441-16470 days, 16471-16500 days, 16501-16530 days, 16531-16560 days, 16561-16590 days, 16591-16620 days, 16621-16650 days, 16651-16680 days, 16681-16710 days, 16711-16740 days, 16741-16770 days, 16771-16800 days, 16801-16830 days, 16831-16860 days, 16861-16890 days, 16891-16920 days, 16921-16950 days, 16951-16980 days, 16981-17010 days, 17011-17040 days, 17041-17070 days, 17071-17100 days, 17101-17130 days, 17131-17160 days, 17161-17190 days, 17191-17220 days, 17221-17250 days, 17251-17280 days, 17281-17310 days, 17311-17340 days, 17341-17370 days, 17371-17400 days, 17401-17430 days, 17431-17460 days, 17461-17490 days, 17491-17520 days, 17521-17550 days, 17551-17580 days, 17581-17610 days, 17611-17640 days, 17641-17670 days, 17671-17700 days, 17701-17730 days, 17731-17760 days, 17761-17790 days, 17791-17820 days, 17821-17850 days, 17851-17880 days, 17881-17910 days, 17911-17940 days, 17941-17970 days, 17971-18000 days, 18001-18030 days, 18031-18060 days, 18061-18090 days, 18091-18120 days, 18121-18150 days, 18151-18180 days, 18181-18210 days, 18211-18240 days, 18241-18270 days, 18271-18300 days, 18301-18330 days, 18331-18360 days, 18361-18390 days, 18391-18420 days, 18421-18450 days, 18451-18480 days, 18481-18510 days, 18511-18540 days, 18541-18570 days, 18571-18600 days, 18601-18630 days, 18631-18660 days, 18661-18690 days, 18691-18720 days, 18721-18750 days, 18751-18780 days, 18781-18810 days, 18811-18840 days, 18841-18870 days, 18871-18900 days, 18901-18930 days, 18931-18960 days, 18961-18990 days, 18991-19020 days, 19021-19050 days, 19051-19080 days, 19081-19110 days, 19111-19140 days, 19141-19170 days, 19171-19200 days, 19201-19230 days, 19231-19260 days, 19261-19290 days, 19291-19320 days, 19321-19350 days, 19351-19380 days, 19381-19410 days, 19411-19440 days, 19441-19470 days, 19471-19500 days, 19501-19530 days, 19531-19560 days, 19561-19590 days, 19591-19620 days, 19621-19650 days, 19651-19680 days, 19681-19710 days, 19711-19740 days, 19741-19770 days, 19771-19800 days, 19801-19830 days, 19831-19860 days, 19861-19890 days, 19891-19920 days, 19921-19950 days, 19951-19980 days, 19981-20010 days, 20011-20040 days, 20041-20070 days, 20071-20100 days, 20101-20130 days, 20131-20160 days, 20161-20190 days, 20191-20220 days, 20221-20250 days, 20251-20280 days, 20281-20310 days, 20311-20340 days, 20341-20370 days, 20371-20400 days, 20401-20430 days, 20431-20460 days, 20461-20490 days, 20491-20520 days, 20521-20550 days, 20551-20580 days, 20581-20610 days, 20611-20640 days, 20641-20670 days, 20671-20700 days, 20701-20730 days, 20731-20760 days, 20761-20790 days, 20791-20820 days, 20821-20850 days, 20851-20880 days, 20881-20910 days, 20911-20940 days, 20941-20970 days, 20971-21000 days, 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