EFFICACY OF LOW ORAL DOSES OF IODIZED OIL IN THE CONTROL OF IODINE DEFICIENCY IN ZAIRE

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Abstract *Background.* About one billion people worldwide are at risk for iodine deficiency. Despite existing programs of prophylaxis, the prevention of iodine deficiency is still a challenge throughout the developing world. We studied the efficacy of low doses of iodized oil in an area of severe iodine deficiency in Zaire.

Methods. Seventy-five subjects with visible goiter were randomly assigned to receive a single oral dose of placebo or either 0.1 or 0.25 ml of iodized oil, corresponding to 0, 47, and 118 mg of iodine, respectively. The mean ages of the subjects in the three groups were 23, 22, and 22 years, respectively, and the ratios of males to females were 0.25, 0.32, and 0.19. Efficacy was assessed by evaluating goiter size and measuring urinary iodine and serum thyroid hormone concentrations for 12 months.

Results. Goiter size decreased in most of the subjects who received either dose of iodized oil. Their urinary iodine concentrations were normal for six to nine months and their serum thyroxine and thyrotropin concentrations were nearly all normal throughout the study period. There were no side effects, even in subjects whose serum thyroxine concentrations had initially been low. In the placebo group, neither goiter size nor any of the biochemical values changed.

Conclusions. The oral administration of a single small dose of iodized oil is capable of correcting iodine deficiency for about a year. This method of supplementation is likely to be more effective, efficient, and acceptable than the administration of either intramuscular or large oral doses of iodized oil. (N Engl J Med 1992;326:236-41.)

EFFECTIVE control of iodine deficiency by iodine supplementation is still a challenge in developing countries.[1] Provision of iodized salt is often unsuccessful because of unfavorable climatic or economic conditions, a shortage of iodized salt in local markets, and the use of noniodized local salt. Single intramuscular injections of iodized oil (0.5 to 2.0 ml) provide adequate amounts of iodine for two to three years,[2] but injections have serious disadvantages, including the potential to serve as a vector for communicable diseases and the high cost of mass campaigns. The oral administration of iodized oil (1 to 2 ml) has recently been advocated as an alternative, but experience with this method is limited.[3-5]

Regardless of the route of administration, large doses of iodine have harmful effects, especially in subjects with iodine deficiency, who are extremely sensitive to acute or chronic iodine excess.[6] In such subjects, iodine can cause transient inhibition of intrathyroidal hormone biosynthesis,[6] a transient increase in serum thyrotropin (thyroid-stimulating hormone) concentrations,[7] the production of thyroid autoantibodies,[8] thyroid-tissue necrosis (in animals),[9,10] exacerbation of goiter,[11] failure to reduce goiter size,[12] and thyrotoxicosis.[13] These effects may be more frequent and severe after oral administration of iodine than after intramuscular administration, because the iodized oil is rapidly deiodinated in the digestive tract.[14]

For these reasons, there is an urgent need for more effective and safer methods of iodine supplementation. We report here the results of a controlled trial with low oral doses (0.1 and 0.25 ml) of iodized oil conducted in a severely iodine-deficient area in Zaire in which goiter is endemic.

METHODS

Study Area

Iodine deficiency in the Kivu region of Zaire was first described in the 1960s.[15,16] This endemia is a major health problem in an area whose population density is very high (75 to 400 people per square kilometer) and whose inhabitants are poor and inadequately nourished.[17] Our study examined the Bulenga peninsula, an area on the northwestern shore of Lake Kivu facing Idjwi Island. It is part of the health district of Kirotshe and has a population of 18,109 (according to the medical census of 1986).

In 1987 a preliminary survey on the peninsula revealed a prevalence of goiter close to 50 percent. The median urinary iodine concentration was approximately 0.16 μmol per liter. The mean (±SD) urinary thiocyanate concentration (171±150 μmol per liter) was low, indicating that large amounts of goitrogenic foodstuffs were not being consumed. Beyond this survey, no study of iodine deficiency had been conducted in the area.

Study Design

To estimate the severity of iodine deficiency, we carried out a survey of 2083 subjects identified after random cluster sampling of 100 households in each of the seven villages on the peninsula (Table 1). The prevalence of goiter was assessed by clinical examination,[18] and obvious clinical manifestations of thyroid dysfunction were recorded. Urine specimens were collected from a systematic (1 in 10) subsample of 197 subjects to assess the degree of iodine deficiency.

We then selected for this trial subjects who were older than 15 years, were clinically euthyroid, and had visible goiters. Pregnant women were excluded. From among the eligible subjects, 75 were enrolled in the randomized, single-blind, placebo-controlled trial. Informed consent was obtained from each of them. The subjects were randomly assigned to one of three groups and entered the trial on the same day. The subjects in group A received a single oral dose of vegetable oil and the subjects in groups B and C received single oral doses of 0.1 and 0.25 ml, respectively, of iodized oil (Ultrafluid Lipiodol, Guerbet, Aulnay-sous-bois, France; 475 mg of iodine per

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Table 1. Prevalence of Goiter According to Age and Sex in 2083 People on the Bulenga Peninsula.*

Age (yr)	Men					Women				
	no. (%)	Goiter grade				no. (%)	Goiter grade			
		0	1	2	3		0	1	2	3
		no.					no.			
0–4	306 (30.9)	220	83	3	0	268 (24.5)	198	70	0	0
5–14	239 (24.1)	72	155	12	0	265 (24.3)	64	180	21	0
15–29	116 (11.7)	61	50	5	0	241 (22.1)	38	133	65	5
30–44	183 (18.5)	92	73	16	2	188 (17.2)	38	81	60	9
≥45	147 (14.8)	119	25	3	0	130 (11.9)	46	52	27	5
Total	991 (100)	564	386	39	2	1092 (100)	384	516	173	19

*Thyroid size was estimated according to the classification of the World Health Organization[18]: 0 indicates no goiter, 1 palpable but not visible goiter, 2 visible goiter, and 3 very large goiter.

milliliter). These doses corresponded to 47 and 118 mg of iodine, respectively. Iodine cross-contamination between subjects was carefully avoided. The mean ages in groups A, B, and C were 23, 22, and 22 years, respectively, and the ratios of males to females were 0.25, 0.32, and 0.19 (Table 2).

We estimated thyroid size before and 3 and 12 months after treatment by tracing the outline of the thyroid surface, after careful palpation, on a piece of thin paper applied to the neck. The outline was then measured with a planimeter.[19] The weighted mean of duplicate surface measurements was used for further analysis. The reproducibility of measurements of the outline by two independent investigators was excellent ($r = 0.99$).

Single urine samples (untimed) were obtained before treatment and 5 days and 1, 2, 3, 4, 5, 6, 9, and 12 months after treatment. In six additional subjects treated with 0.25 ml of iodized oil, urine samples were collected daily for four days after treatment. Urinary iodine concentrations were measured with a fully automated Technicon AutoAnalyzer (Technicon, Tarrytown, N.Y.); the smallest detectable concentration was 0.04 μmol per liter.[20,21] Since differences in the daily excretion of creatinine in Kivu can lead to erroneous values for iodine excretion when the iodine:creatinine ratio is used, we expressed the results only as iodine concentrations.[21-23]

Blood samples were obtained immediately before treatment and 5 days and 3, 6, 9, and 12 months after treatment. The serum was separated immediately and stored at −20°C for subsequent analysis. Serum triiodothyronine, thyroxine, and thyroxine-binding globulin levels and the free-thyroxine index (calculated as the ratio of thyroxine to thyroxine-binding globulin) were determined by radioimmunoassay.[24] Thyroglobulin antibodies and thyroid microsomal antibodies were also measured by radioimmunoassay (Techland, Liege, Belgium), and thyrotropin by an immunoradiometric assay (Henning, Berlin, Germany). All measurements were performed in duplicate. Laboratory reference values (for Belgian subjects) were as follows: urinary iodine, 0.04 to 1.20 μmol per liter; triiodothyronine, 1.4 to 3.2 nmol per liter; thyroxine, 50 to 150 nmol per liter; thyroxine-binding globulin, 11 to 21 mg per liter; free-thyroxine index, 10 to 27 pmol per liter; and thyrotropin, 0.4 to 4.0 mU per liter.

Statistical Analysis

For normally distributed measures (serum triiodothyronine and thyroxine), the results were analyzed by Student's t-test. For measures not normally distributed (serum thyrotropin and urinary iodine), the results were analyzed by the Wilcoxon test and Mann–Whitney test. Tables and figures show either mean values (serum triiodothyronine and thyroxine) or median values and 95 percent confidence intervals (serum thyrotropin and urinary iodine).[25] Some comparisons were also made with the chi-square test. All P values were adjusted for multiple comparisons (Bonferroni correction).

Results

Epidemiologic Study

The mean prevalence of goiter in Bulenga was 54 percent (Table 1), whereas that of visible goiter was 11 percent and that of nodular goiter 8 percent. The differences between the age and sex strata were significant ($P<0.001$). The prevalence of goiter in women of childbearing age (15 to 44 years) was 82 percent. The pattern of prevalence according to sex, age, and grade of goiter was typical of Central Africa.[26]

Urinary iodine concentrations ranged from 0.04 to 1.18 μmol per liter (median, 0.14 μmol per liter) (Fig. 1). The distribution of individual values was homogeneous but markedly skewed to the left; two thirds of the subjects had values ≤0.16 μmol per liter, corresponding to severe iodine deficiency.[23] There were no significant differences according to age, sex, or grade of goiter. Among the 2083 subjects, 6 (0.3 percent) had unequivocal clinical manifestations of cretinism.

Table 2 shows the base-line clinical and demographic characteristics of the three study groups. The mean values for age; sex; serum triiodothyronine, thyroxine, and thyrotropin concentrations; and urinary iodine concentrations were similar in the three groups.

The intake of iodine in the 75 study subjects was similar to that in the 197 subjects surveyed initially. The urinary iodine concentrations in the 75 study subjects ranged from 0.05 to 1.15 μmol per liter before treatment, with a median value of 0.14 μmol per liter.

Urinary Iodine Concentrations after Treatment

There was a prolonged increase in urinary iodine concentrations after the oral administration of iodine. Figure 2 shows the longitudinal changes in median urinary iodine concentrations in the three groups. In

Table 2. Base-Line Demographic and Clinical Characteristics of the Study Groups.*

Characteristic	Group A (N = 25)	Group B (N = 25)	Group C (N = 25)
Mean (±SD) age (yr)†	23±5	22±5	22±6
Sex ratio (M:F)‡	0.25	0.32	0.19
Subjects with grade 2 goiter (no.)	25	25	25
Mean (±SD) serum triiodothyronine (nmol/liter)§	3.3±0.6	3.2±0.6	3.2±0.5
Mean (±SD) serum thyroxine (nmol/liter)§	66±27	62±27	57±26
Median serum thyrotropin (mU/liter)¶	2.9 (2.0–3.8)	2.4 (1.6–3.8)	2.7 (1.4–5.6)
Median urinary iodine (μmol/liter)¶	0.17 (0.11–0.21)	0.19 (0.09–0.21)	0.16 (0.11–0.21)

*Values in parentheses are 95 percent confidence intervals.
†There was no statistical difference between the groups by the Kruskal–Wallis test.
‡There was no statistical difference between the groups by the chi-square test.
§There was no statistical difference between the groups by Student's t-test.
¶There was no statistical difference between the groups by the Mann–Whitney test.

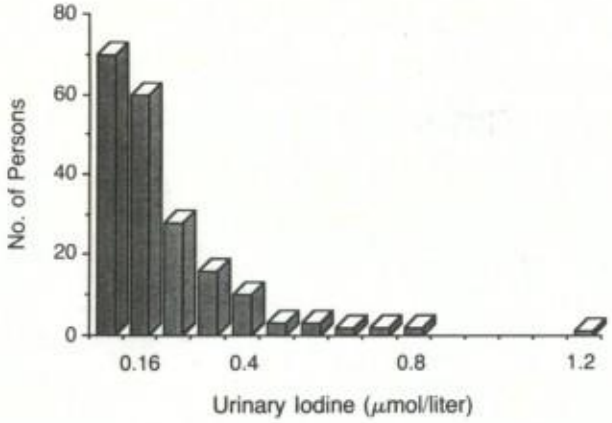

Figure 1. Distribution of Urinary Iodine Concentrations in a Representative Sample of 197 Inhabitants of the Bulenga Peninsula.

Sixty-six percent of those sampled had urinary iodine concentrations of ≤0.16 μmol per liter, 93.4 percent had concentrations of ≤0.39 μmol per liter, and 99.5 percent had concentrations of ≤0.79 μmol per liter.

groups B and C, the median concentrations were greatly increased five days after treatment, after which they slowly declined to near the base-line levels. The values in group C were only slightly higher than those in group B. The median values were greater than 0.39 μmol per liter in group B for three months and in group C for as long as six months. We considered 0.39 μmol per liter to be a target value since it represents the median value in Belgium, where the daily intake of iodine is just sufficient.[27] At 12 months, the median values in groups B and C were 0.20 and 0.24 μmol per liter, respectively. In the six additional subjects who received 0.25 ml of iodized oil, in whom urine samples were collected daily for four days, the median urinary iodine concentration fell abruptly from 262 μmol per liter on day 1 to 4.9 μmol per liter on day 4.

Goiter Size after Treatment

The mean thyroid-surface outline three months after treatment was 4 percent larger than before treatment in group A, and 36 percent smaller in groups B and C. Twelve months after treatment, the mean outline was 9 percent smaller than before treatment in group A, 44 percent smaller in group B, and 52 percent smaller in group C.

Biochemical Measures after Treatment

The mean serum thyroxine concentration before treatment was marginally low in all three study groups (66, 62, and 57 nmol per liter in groups A, B, and C, respectively). There was a significant ($P<0.01$) increase in serum thyroxine in groups B and C after 3 months, and the values were similar after 6 and 12 months (Fig. 3). In contrast, the mean serum thyroxine concentration did not change significantly in group A. The serum free-thyroxine index followed a similar pattern. The serum thyrotropin concentrations, which were about 3 mU per liter in the three groups before treatment, decreased significantly ($P<0.01$) in groups B and C three months after treatment. The lower values were maintained for as long as one year (Fig. 4). Table 3 shows the number of subjects in each group who had serum thyrotropin concentrations of more than 4 mU per liter at different times after treatment.

Figure 5 shows the changes in serum thyroxine and thyrotropin concentrations in all the subjects in groups B and C who had serum thyroxine concentrations in the hypothyroid range (<50 nmol per liter) before treatment. All but one of these subjects had normal thyroxine and normal thyrotropin concentrations three months after treatment. None had a decrease in thyroxine or an increase in thyrotropin characteristic of iodine-induced hypothyroidism.

Four subjects, two in group B and two in group C, had low serum thyrotropin concentrations (<0.02 mU per liter) three months after treatment. Among these subjects, only one (from group C) had above-normal serum concentrations of thyroxine (211 nmol per liter) and triiodothyronine (8.4 nmol per liter) at three months. The values in this subject were lower six months after treatment and normal at one year.

The mean serum triiodothyronine concentrations before treatment were 3.3±0.6, 3.2±0.7, and 3.2±0.5 nmol per liter in groups A,

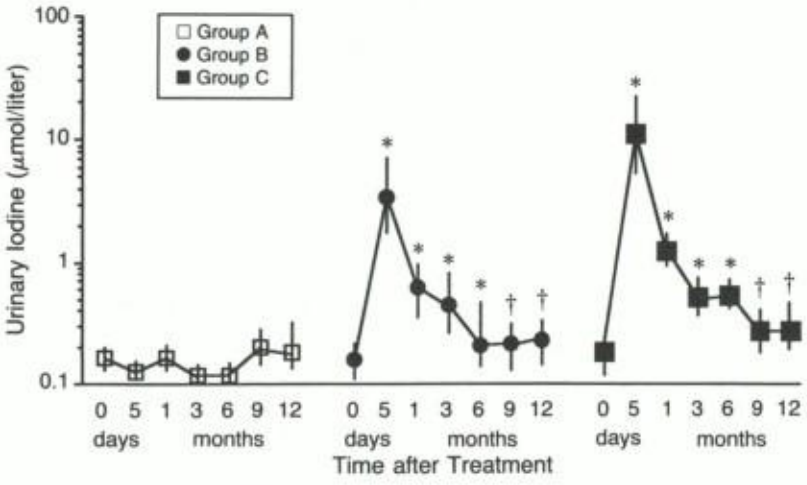

Figure 2. Longitudinal Changes in Median Urinary Iodine Concentrations in the Study Groups after Treatment.

Asterisks denote $P<0.01$ and daggers $P<0.05$ for the comparison with base-line values by the Wilcoxon test. Bars indicate 95 percent confidence intervals.

B, and C, respectively. They did not change significantly after treatment in any group. Finally, all serum samples were negative for antithyroglobulin and antithyroid microsomal antibodies at all times.

Discussion

Severe iodine deficiency in this region of Zaire, which is characterized by a very high prevalence of goiter and a very low urinary iodine concentration (<0.16 μmol per liter) in 66 percent of the inhabitants, constitutes a major public health problem. This trial demonstrates that the oral administration of one small dose of iodized oil (0.1 or 0.25 ml) can correct severe iodine deficiency for about one year. The efficacy of the intervention was demonstrated by the normalization of serum thyroxine and thyrotropin concentrations and the reduction in goiter size in the study subjects who received iodized oil. The low doses of iodine maintained iodine metabolism within the physiologic range and were not accompanied by the very large iodine overload that results from the use of

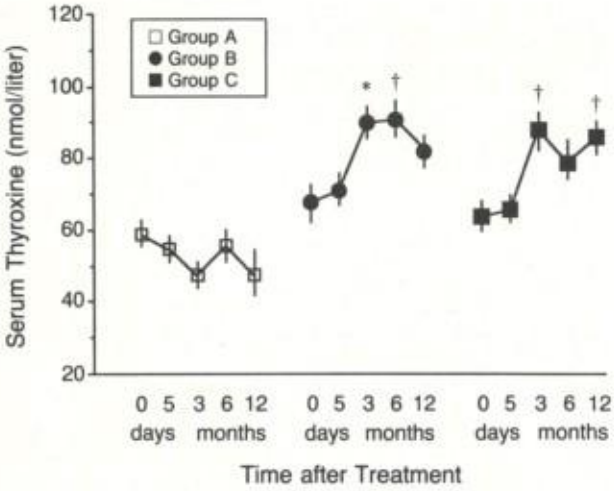

Figure 3. Longitudinal Changes in Mean (±SE) Serum Thyroxine Concentrations in the Study Groups after Treatment.

The asterisk denotes P<0.01 and the daggers P<0.05 for the comparison with base-line values by Student's t-test.

larger doses of iodized oil. Although there was moderate overload during the first three to five days after the administration of the iodized oil, we found no evidence of inhibition of thyroid function by iodine at any time during the follow-up period. This finding is in agreement with the evidence that there is rapid degradation of a large part of the iodized oil in the digestive tract,[14] which permits us to postulate that huge amounts of iodine are released when larger doses of iodized oil are administered.

Our results contrast favorably with those reported after the oral administration of larger doses of iodized oil to subjects with iodine deficiency. For instance, in the Ubangi region of Zaire, 4 of 14 subjects treated

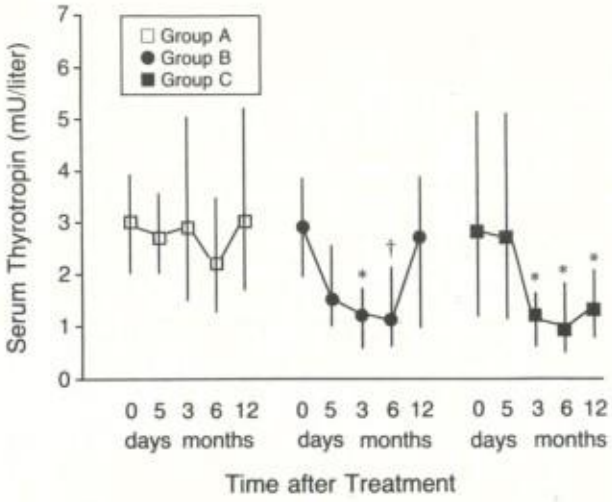

Figure 4. Longitudinal Changes in Median Serum Thyrotropin Concentrations in the Study Groups after Treatment.

Asterisks denote P<0.01 and the dagger P<0.05 for the comparison with base-line values by the Wilcoxon test. Bars indicate 95 percent confidence intervals.

with 1.5 ml of oral iodized oil had an increase in serum thyrotropin and a decrease in serum thyroxine five days after treatment,[7] and in Sudan serum thyroxine concentrations decreased significantly one month after the oral administration of 1 ml of iodized oil.[3] Iodine-induced abnormalities could also account for the failure of goiters to decrease in size after the oral administration of 1 or 2 ml of iodized oil in Spain and Zaire.[5,12]

It is noteworthy that serum thyroxine concentrations were normal 9 and 12 months after the oral administration of iodized oil despite the return of urinary iodine concentrations to low levels. We suggest that the replenishment of thyroid iodine stores by the low oral dose was sufficient to maintain adequate secretion of thyroid hormones for a few months after urinary iodine concentrations had fallen to nearly pretreatment values. A similar observation has been reported after the intramuscular injection of iodized oil.[28]

One of our subjects had transient biochemical thyrotoxicosis. Although some degree of thyrotoxicosis cannot be avoided in a few patients, especially those

Table 3. Study Subjects with Serum Thyrotropin Concentrations >4 mU per Liter after Treatment.

Time after Treatment	Group A	Group B	Group C
	number of subjects		
Base line	7	7	9
3 mo	8	1	1
6 mo	6	1	3
12 mo	7	1	2

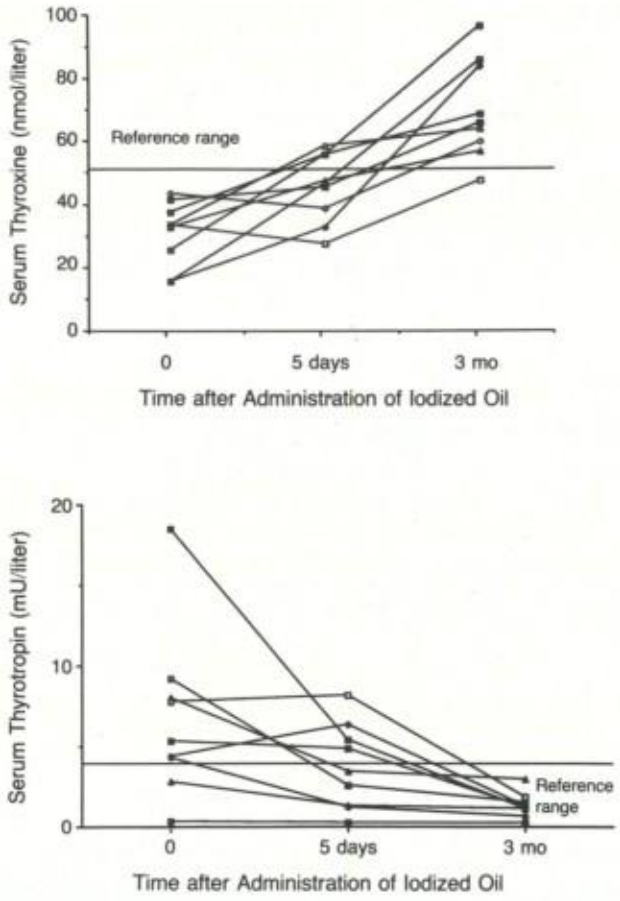

Figure 5. Variations in Serum Thyroxine and Thyrotropin Concentrations after the Administration of Iodized Oil in the Eight Subjects with Thyroxine Levels of <50 nmol per Liter before Treatment.

The reference range for thyroxine is above the horizontal line, and the reference range for thyrotropin is below the horizontal line.

with large nodular goiters, whatever the method of iodine supplementation, doses of iodized oil that increase thyroid iodine stores only moderately would be expected to minimize the severity and the duration of iodine-induced thyrotoxicosis. The fact that circulating thyroid autoantibodies are not induced is an additional benefit of low doses of iodized oil.

Assessing goiter size by mapping the thyroid proved to be a useful procedure, especially since ultrasonography was not available. Considering the large size and nodularity of the goiters, the obvious reduction in the size of the goiters in groups B and C was unexpected. This beneficial effect could strengthen the compliance of the target population, because the obvious discomfort of thyroid enlargement is perceived more easily than the insidious complications of hypothyroidism.

Several lines of evidence — ease of administration, normalization of urinary iodine concentrations, increase in serum thyroxine concentrations, decrease in goiter size, and absence of side effects — indicate that the oral administration of low doses of iodized oil (0.1 or 0.25 ml) is a practical, safe, and effective means of correcting severe iodine deficiency for an entire year. Although we did not study a large number of subjects, we thought the evidence was strong enough to warrant treating the whole population of the Bulenga peninsula with such doses of iodized oil. That treatment and its evaluation are in progress.

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