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# Supplementary Iodine Fails to Reverse Hypothyroidism in Adolescents and Adults with Endemic Cretinism*

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**ABSTRACT.** The efficacy of supplemental iodine in correcting hypothyroidism in adults and older children with endemic myxedematous cretinism is not known. To investigate this issue we administered im iodized oil (1.5 mL) to 28 hypothyroid endemic cretins (TSH, >5 mIU/L) from western China, aged 14–52 yr (mean = 29 SD = 11 yr). Clinical examination, intelligence testing (Hiskey Nebraska Test of Learning Aptitude and the Griffiths Mental Development Scales), and thyroid function tests were performed before and 6 months after iodine supplementation.

We found that signs of thyroid hormone deficiency, dwarfism, and delayed sexual maturity persisted after iodine supplementation. Further, mental disability and other clinical features of neurological damage were not altered by treatment. The mean serum concentration of total $T_4$ before treatment was 75 nmol/L (SD = 40) and fell after iodized oil administration to 56 nmol/L (SD = 29; $P < 0.001$). Mean serum levels of TSH before and after iodine showed a paradoxical fall [85 mIU/L (SD = 102) and 46 mIU/L (SD = 46), respectively]. Serum TSH levels decreased into the normal range (<5 mIU/L) in only 1 of 28 patients (4%).

We conclude that iodine supplementation does not reverse thyroid hormone deficiency or its sequelae in adolescents and adults with endemic myxedematous cretinism. Iodized oil in this age group of patients with endemic cretinism does not appear to be beneficial and should be used with caution. (*J Clin Endocrinol Metab* **70:** 336, 1990)

ENDEMIC cretinism remains a major public health problem in many countries despite the introduction of iodine prophylaxis programs (1). Although thyroid function is usually normal in endemic cretins with predominant neurological findings (neurological cretins), severe hypothyroidism is a characteristic feature of endemic cretins from Zaire, Nepal, and Western China (2). These myxedematous cretins are characterized by signs of thyroid hormone deficiency, dwarfism, delayed puberty, and a pattern of neurological deficits identical to that found in euthyroid cretins (2). In these endemias where myxedematous cretinism predominates, large numbers of cretins remain untreated, and consequently, protracted hypothyroidism results in further physical disability and decreased life expectancy for these patients (3).

The most appropriate therapy for these hypothyroid cretins has not been established, but iodine supplementation, given parenterally as iodized oil, has been advocated as a means of correcting thyroid hormone deficiency (4, 5). Iodized oil is a safe and achievable public health measure in remote developing parts of the world where delivery of health services on a regular basis is difficult. Using this approach, Vanderpas and colleagues (5) found that iodized oil reversed hypothyroidism in young myxedematous cretins (<4 yr of age), but was only partially successful in older children (4–14 yr) (5). This age dependency of response implied a progressive loss of thyroid hormone reserve of myxedematous cretins with increasing age. The aim of the present study was to evaluate the efficacy and safety of iodine supplementation in an older cohort of myxedematous cretins, given that these patients are more at risk from the effects of prolonged hypothyroidism and are the commonest age group encountered in most endemias (2). The study was undertaken in Qinghai Province, western China, where we have recently described a predominantly myxedematous endemia (2). Our results indicate that iodized oil in

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this age group is not efficacious and, in some cases, may exacerbate thyroid hormone deficiency.

## Materials and Methods

### *Patients*

Sixty-nine patients who satisfied the clinical diagnostic criteria of endemic cretinism were surveyed from Qinghai Province, western China. The background and epidemiology of this endemia have been previously reported, as have the clinical, radiological, audiometric, psychometric, and biochemical features of these patients (2). Iodized salt prophylaxis was introduced in 1978, but the results of neonatal screening suggest that this program was unsuccessful. On the basis of serum TSH levels patients were divided into euthyroid (n = 32; TSH, ≤5 mIU/L) and hypothyroid (n = 37; TSH, >5 mIU/L) groups.

### *Protocol*

All hypothyroid patients were given 1.5 ml im iodized oil (Lipiodol) containing 720 mg resorbable iodine and were reassessed after 6 months. From the original survey, 28 (age range, 14–52 yr) and 24 (age range, 7–42 yr) patients from the hypothyroid and euthyroid groups, respectively, returned for follow-up. The clinical features of these patients are shown in Table 1. Euthyroid patients served as test-retest controls for evaluation of intelligence and neurological findings. The nature, outcome, possible risks, and benefits of the study were explained to patients and/or their parents (guardians) in the local language. The protocol was approved by the Ethics Committee of Westmead Hospital, and all patients participated on an informed voluntary basis.

### *Clinical variables*

Each patient was examined independently by an endocrinologist and neurologist using a detailed checklist. Clinical thyroid status was assessed, and goiter was graded according to the 1986 Pan American Health Organization classification (6). Sexual development was scored using Tanner scales for pubertal development. A detailed neurological examination was undertaken in all patients. Clinical findings were videotaped for discussion and analysis by the team.

TABLE 1. Clinical variables in euthyroid and hypothyroid patients with endemic cretinism

| | Euthyroid cretins (n = 24) | Hypothyroid cretins (n = 28) | *P* |
|---|---|---|---|
| Sex | 11 M, 13 F | 14 M, 14 F | NS[a] |
| Age (yr) | 22 (10) | 29 (11) | 0.02[b] |
| Thyroid vol (mL)[c] | 16.9 (16.0) | 5.7 (4.9) | 0.001[b] |
| Ht (cm) | 137 (16.7) | 134 (15.3) | NS |
| Radiological bone delay (yr)[d] | 2.2 (2.6) | 5.9 (7.1) | 0.02[b] |
| Neurological signs | Present | Present | NS[a] |

Results are the mean ± SD.

[a] By $\chi^2$ test, $P < 0.05$.

[b] By unpaired $t$ test, $P < 0.05$.

[c] Calculated from thyroid ultrasound.

[d] Radiological bone delay is calculated by subtracting radiological bone age from chronological age in those patients with unfused epiphyses.

### *Psychometric testing*

Cognitive function was assessed using the Griffiths Mental Development Scales (7) and the Hiskey-Nebraska Test of Learning Aptitude (8). The Griffiths Mental Development Scales provide a psychodiagnostic approach toward the collection of information about the development of infants in the first 2 yr of life and were later extended to cover the age range from birth to 8 yr (7). The scales cover significant sequences of development or avenues of learning and include gross and fine motor development, the constructive application of fine motor skills, responsive listening, speech, and social skills development. The Griffiths Scales examine locomotor, personal-social, hearing and speech, eye and hand coordination skills, and the integration of these in a more general performance scale.

The Hiskey-Nebraska Test of Learning Aptitude was designed to assess the intellectual capacity in children from 3–16 yr of age, using pantomime and practice exercises to communicate instructions (8). Intrinsically interesting items are used to establish rapport, and the test has the advantage of also being useful with children of normal hearing. The scale has 12 subsets: bead patterns, memory for color, picture identification, picture associations, paper folding, visual attention span, block patterns, drawing completion, memory for digits, puzzle blocks, picture analogies, and spatial reasoning. Drawing completion was not appropriate for the Chinese culture, and this item was dropped from the scale.

### *Biochemical evaluation*

Serum TSH was measured by commercial immunoradiometric assay kit (Biomedical Systems Ltd., Sydney, Australia). The interassay coefficient of variation (CV) of this assay is 3.4% at TSH levels greater than 40 mIU/L. Serum $T_3$ and $T_4$ (CV, 6.2% at serum $T_3$ level of 1.5 nmol/L; CV, 6.2% at $T_4$ level of 51.5 nmol/L) were measured by RIA (Biomedical Systems Ltd., Sydney, Australia). Serum free $T_4$ ($FT_4$) concentrations were determined by a sensitive two-step RIA kit (Clinical Assays, Cambridge, MA). The interassay coefficients of variation of this assay are 6.4% and 10.5% at $FT_4$ levels of 2.2 and 8.9 pmol/L, respectively. Serum samples were shipped frozen to Australia and analyzed within 1 month of collection. Serum was available from 23 of the 28 hypothyroid cretins before and after iodine supplementation and was tested within the same assay to reduce interassay variation.

Urinary iodine was measured using a modification of the method described by Garry *et al.* (9), which avoids acid digestion by dialyzing urine. The iodine content of the dialysate was measured by an automated colorimetric method based on the catalytic action of iodine on the oxidation of arsenious ions by ceric ions (Technicon Autoanalyzer II System, Technicon, Tarrytown, NY) (9). Urine for iodine estimation was obtained during the period of hospitalization and, therefore, reflects iodine intake while the patient was hospitalized at the Institute of Endemic Diseases rather than iodine intake in the patients' homes.

*Thyroid autoantibodies*

Antithyroglobulin and antimicrosomal antibodies were determined by a commercial hemagglutination assay (Wellcome, Breckenham, United Kingdom) before and after iodine supplementation.

*Statistical analysis*

Differences between mean values for quantitative variables were evaluated with Student's paired $t$ test. Distributions of frequencies were compared by $\chi^2$ test with Yate's continuity correction. Simple linear regression analysis was used for analyzing the effects of pretreatment variables on intervention outcome. Spearman's rank correlation procedure was used for analysis of biochemical data after intervention with iodized oil. Arithmetic means are expressed as the mean ± 1 SD. All $P$ values resulted from two-tailed tests, and values below 0.05 were considered significant.

## Results

*Thyroid function*

Figures 1 and 2 show individual values for serum TSH, $T_4$, $FT_4$, and $T_3$ before therapy and 6 months after treatment with iodized oil in 28 hypothyroid patients with endemic cretinism. The mean level of serum TSH decreased from 85 mIU/L [SD = 102; 95% confidence interval (CI), 45.2–124] to 46 mIU/L (SD = 46; 95% CI, 28.3–64.3; by paired $t$ test, $P = 0.001$; Table 2). However, serum TSH levels decreased into the normal range (TSH, <5 mIU/L) in only one patient (from 5.7 to 0.8 mIU/L). The change in serum TSH levels after iodine (ΔTSH) showed a negative correlation with pretreatment serum TSH levels ($r = -0.5$; $P = 0.01$). That is, the greatest fall in serum TSH levels occurred in patients with higher initial values of serum TSH (Fig. 1).

Despite a fall in serum TSH levels, mean serum levels of $T_4$ and $FT_4$ in hypothyroid endemic cretins did not rise, but decreased from 75 nmol/L (SD = 40; 95% CI, 60.2–91.5) and 12.0 pmol/L (SD = 7.2; 95% CI, 9.1–14.8) to 56 nmol/L (SD = 29; 95% CI, 44.5–67.0; by paired $t$ test, $P = 0.001$) and 9.3 pmol/L (SD = 7.5; 95% CI, 5.8–12.7; by paired $t$ test, $P = 0.015$), respectively. Changes in serum $T_4$ levels after iodine ($\Delta T_4$) correlated negatively with pretreatment serum $T_4$ levels ($r = -0.56$; $P = 0.002$). That is, the decremental effect of iodine on serum $T_4$ levels was greatest in those patients with mild hypothyroidism (Fig. 1). Although 4 of 28 (14%) patients showed a rise in serum $T_4$ levels after iodine treatment, this increase was minor and did not restore thyroid hormone levels into the normal range. No cases of clinical or biochemical thyrotoxicosis were observed after iodine supplementation.

One of the adaptative mechanisms of the thyroid gland to iodine deficiency is preferential secretion of total $T_3$ (10). After iodine supplementation, mean serum $T_3$ levels decreased (Tables 2 and 3), particularly in those patients with severe hypothyroidism.

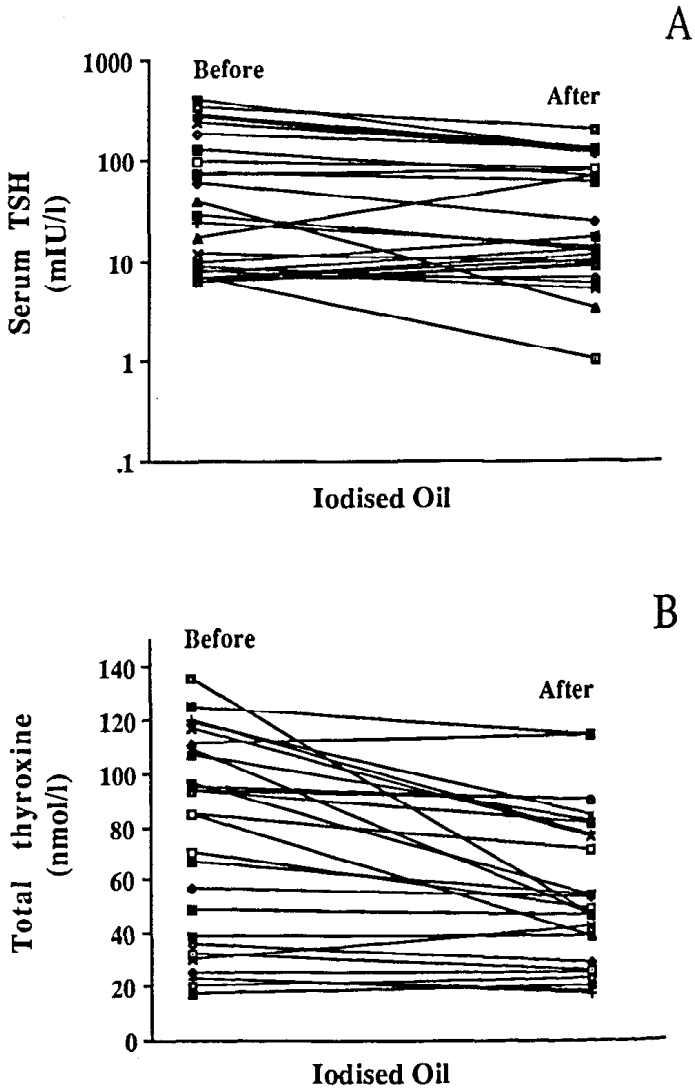


FIG. 1. Individual serum TSH (A) and serum $T_4$ (B) levels of hypothyroid cretins before and 6 months after im iodized oil treatment. In A serum TSH levels are plotted on a log scale.

Changes in thyroid function tests observed after iodized oil treatment showed no relation to age of the patient (age *vs.*% Δ serum TSH: $r = 0.085$; $P = 0.67$; age *vs.*% Δ serum $T_4$: $r = 0.13$; $P = 0.5$) or thyroid size (thyroid volume *vs.*% Δ serum TSH: $r = 0.3$; $P = 0.14$; thyroid volume *vs.* % Δ serum $T_4$; $r = 0.2$; $P = 0.3$).

The influence of changes in serum $T_4$, $FT_4$, and $T_3$ levels after iodized oil treatment on serum TSH levels was analyzed. A negative correlation between $\Delta T_4$ and ΔTSH ($\rho = -0.623$; $P < 0.05$) and between $\Delta FT_4$ and ΔTSH ($\rho = -0.236$; $P > 0.05$) was found. In other words, patients with severe hypothyroidism exhibited a lesser fall in serum $T_4$ levels after iodized oil treatment. A positive correlation between $\Delta T_3$ and ΔTSH was observed ($\rho = 0.34$; $P = 0.09$), indicating that falling TSH

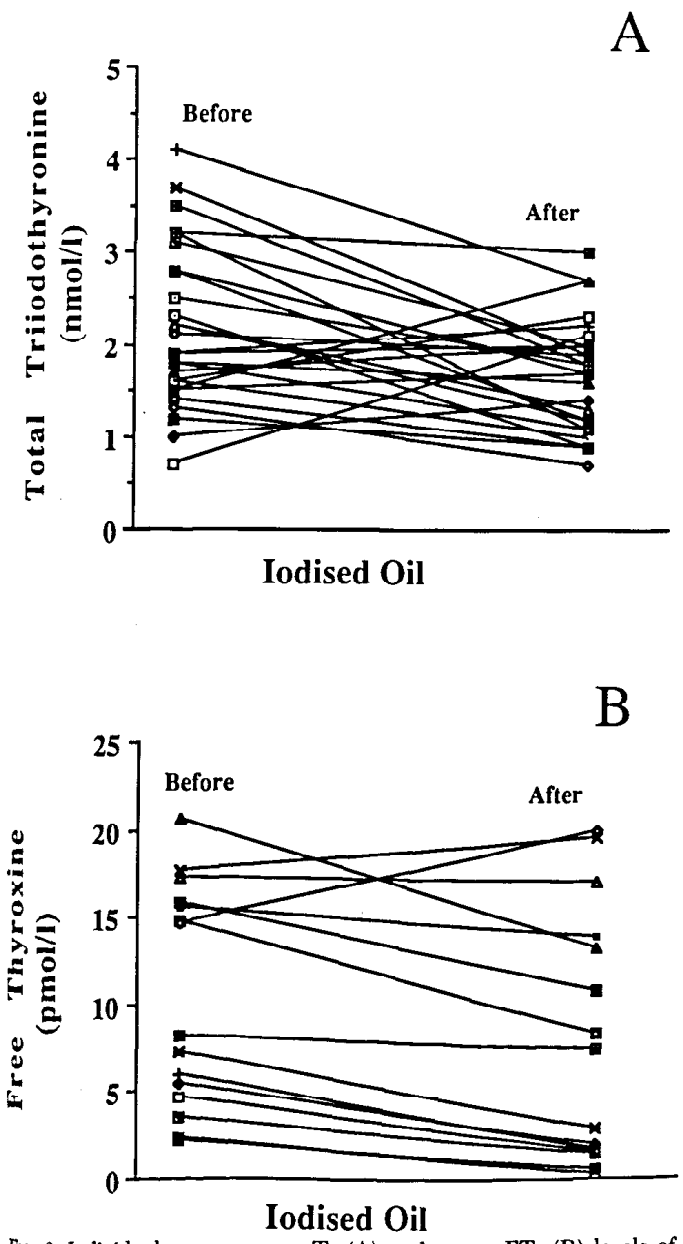


FIG. 2. Individual serum serum $T_3$ (A) and serum $FT_4$ (B) levels of hypothyroid cretins before and 6 months after im iodized oil treatment.

TABLE 2. Biochemical parameters in hypothyroid patients with endemic cretinism before and after iodized oil treatment

| | Before iodized oil | After iodized oil | $P^a$ |
|---|---|---|---|
| $TT_4$ (nmol/L)[b] | 75 (40) | 56 (29) | 0.001 |
| $FT_4$ (pmol/L)[c] | 12.0 (7.2) | 9.3 (7.5) | 0.015 |
| $TT_3$ (nmol/L)[d] | 2.2 (0.9) | 1.7 (0.6) | 0.006 |
| TSH (mIU/L)[e] | 85 (102) | 46 (46) | 0.001 |
| Urinary iodine (μg/g creatinine) | 117 (45) | 348 (146) | <0.001 |

Results are the mean ± SD.
[a] By paired *t* test.
[b] Normal, 70–160 nmol/L.
[c] Normal, 11–25.1 pmol/L.
[d] Normal, 1.2–2.8 nmol/L.
[e] Normal, 0.1–6.0 mIU/L.

levels may have been due to falling $T_3$ levels.

The data were reanalyzed to search for differences in response to iodized oil between patients with mild hypothyroidism (serum TSH, >5 and ≤60 mIU/L; n = 16) and severe hypothyroidism (serum TSH, >60 mIU/L; n = 12). The latter group is comparable to those patients studied by Vanderpas *et al.* (5). The major effect of iodized oil on thyroid function tests was evident in endemic cretins with severe hypothyroidism (Table 3). Contrary to the patients studied by Vanderpas *et al.* (5), no improvement in thyroid function was observed.

In euthyroid patients with endemic cretinism, no significant differences were found between mean levels of serum TSH, $T_4$, $FT_4$, and $T_3$ from the original survey to the second survey 6 months later.

*Urinary iodine*

Urine for iodine estimation was obtained during the period of hospitalization, and results, therefore, reflect iodine intake while the patient was hospitalized (Table 2). Urinary iodine levels rose significantly after iodine supplementation.

*Clinical variables*

Signs of thyroid hormone deficiency (myxedema, facial puffiness, alopecia, carotenemia, and delayed ankle jerks) were equally as frequent in the treated group before and 6 months after iodized oil treatment (Table 4). Goiter stage estimated clinically did not change; in particular, thyroid tissue was impalpable in severely thyroid hormone-deficient patients. The mean growth velocity in hypothyroid patients (with unfused epiphysises on radiology; 0.6 cm/yr) remained significantly depressed compared to that in euthyroid patients with endemic cretinism (3.6 cm/yr; $P < 0.05$).

Although an increasing trend in IQ was found in euthyroid and hypothyroid patients with endemic cretinism, this trend was not significant; mean IQ levels in hypothyroid cretins, before and 6 months after therapy were 31.2 (SD = 13.0) and 34.4 (SD = 15.4; by paired *t* test, $P > 0.05$), respectively. In euthyroid cretins, mean IQ levels were 27.3 (SD = 10.2) and 29.5 (SD = 8.5; by paired *t* test, $P > 0.05$] at the first and second surveys, respectively. The test-retest correlation between the first and second assessments in all patients was 0.93, a good indicator of the reliability of the tests.

Neurological signs were present to an equal extent in both euthyroid and hypothyroid patients with endemic cretinism before treatment (2), and no changes were found after treatment with iodized oil.

TABLE 3. Thyroid function test results in hypothyroid and severely hypothyroid endemic cretins before and after treatment with iodized oil

| | Hypothyroid cretins (n = 16)[a] | | | Severely hypothyroid cretins (n = 12)[b] | | |
|---|---|---|---|---|---|---|
| | Iodized oil | | $P^c$ | Iodized oil | | $P^c$ |
| | Before | After | | Before | After | |
| Serum TSH (mIU/L) | 13.1 ± 12.6 | 11.3 ± 13.2 | 0.7 | 180 ± 88 | 93 ± 30 | 0.001 |
| Serum $TT_4$ (nmol/L) | 102 ± 23 | 73 ± 24 | 0.002 | 40 ± 29 | 34 ± 17 | 0.2 |
| Serum $FT_4$ (pmol/L) | 17 ± 5 | 14.8 ± 4.8 | 0.06 | 5.7 ± 3.0 | 1.9 ± 1.9 | 0.003 |
| Serum $T_3$ (nmol/L) | 2.5 ± 1.0 | 2.0 ± 0.5 | 0.1 | 2.0 ± 0.7 | 1.2 ± 0.4 | 0.002 |

Results are the mean ± SD. $TT_4$, Total $T_4$.
[a] Serum TSH, >5 and ≤60 mIU/L.
[b] Serum TSH, >60 mIU/L.
[c] By paired *t* test.

TABLE 4. Clinical features of hypothyroid cretins before and after iodized oil treatment

| | Before (%) | After (%) |
|---|---|---|
| Altered level of consciousness | 4 | 4 |
| Galactorrhea | 8 | 8 |
| Clinical myxedema | 36 | 31 |
| Loss of the outer third of the eyebrow | 73 | 80 |
| Prolonged ankle reflex relaxation | 36 | 36 |

All signs were assessed clinically. n = 28.

### *Thyroid autoantibodies*

Antimicrosomal and antithyroglobulin antibodies were not detected in any patient (euthyroid or hypothyroid), either from the original survey or after treatment with iodized oil.

## Discussion

In this report we examined the effects of supplemental iodine on thyroid function in adolescents and adults with myxedematous endemic cretinism. We found no beneficial effects of im iodized oil on clinical or biochemical parameters of thyroid hormone deficiency, neurological damage, or intellectual disability. Moreover, in severely hypothyroid patients there was a worsening of biochemical hypothyroidism after iodized oil treatment, as shown by decreased serum concentrations of free and total $T_4$.

The reversibility of thyroid dysfunction with supplemental iodine in patients with myxedematous cretinism appears to be age dependent. Our data complement and extend the findings of Vanderpas *et al.* (5), who treated children with endemic myxedematous from Zaire. In the Zairian study, all children less than 4 yr of age were rendered euthyroid 5 months after iodized oil injections, but a partial response was observed in older children (aged 4–14 yr), in whom only 43% became euthyroid after treatment (5). In the present study all endemic cretins were older than 14 yr and exhibited a variable degree of thyroid hormone deficiency before treatment. Clinical and biochemical features of severe hypothyroidism, identical to those described by Vanderpas *et al.* (5), were present in just under half of the treated cases. Nevertheless, in our study no improvement in serum $T_4$ levels was observed in patients with mild or severe hypothyroidism after parenteral iodized oil treatment. These findings together with data of Vanderpas *et al.* (5) may be partly explained by a progressive degenerative process of the thyroid (particularly in severely hypothyroid cretins) which results in the loss of thyroid hormone reserve and an inability to respond to iodine supplementation.

This degenerative process results in thyroid atrophy, a well recognized clinical and pathological feature of patients with myxedematous cretinism (2, 11). At postmortem, the thyroid gland of these patients is fibrosed and sclerotic, with occasional lymphocytic cell infiltration (12). We have recently confirmed the finding of thyroid atrophy in myxedematous cretins by the use of portable, real time ultrasound (2). The etiopathogenesis of thyroid destruction in these cretins is not clear, but exhaustion atrophy (13), thiocyanate toxicity (14), and concomitant selenium deficiency (15) have been suggested as possible causes. An alternative explanation for thyroid atrophy may be autoimmune degeneration of the thyroid gland, as found in patients with sporadic congenital hypothyroidism (16). Whatever the cause and the pathophysiological mechanism responsible for thyroid destruction in myxedematous cretins, it appears that this process is not operative at birth, but becomes an important factor with increasing age.

Although urinary iodine levels were not low in our patients before treatment, reflecting iodine intake within the Institute, these cretins were iodine deficient, as indicated by results of neonatal blood spot screening collected from their home villages. Preliminary neonatal blood spot screening results (collected between July and October 1988) in 1334 neonates from Qinghai Province show that iodine deficiency continues to impose a substantial health burden on this population. In these areas,

46% of neonates had blood spot TSH levels above 10 mIU/L, and 1.2% of neonates had TSH levels greater than 30 mIU/L (our unpublished data).

In the present study serum TSH levels fell in the majority of patients after iodized oil treatment despite decreased or unchanged serum levels of $T_4$. The explanation of this phenomenon is not apparent, but may relate to interassay variation or may reflect altered peripheral levels of $T_3$, since the level of iodine intake greatly influences serum $T_3$ levels (10). Serum $T_3$ levels rise as part of the thyroid gland's adaptative response to iodine deficiency (10). After iodine supplementation, serum $T_3$ levels in our study decreased, which may have altered feedback regulation of TSH at the pituitary level. Alternatively, as described with amiodarone, iodized oil may directly feed back on the pituitary and suppress serum TSH levels (17). The glycoprotein structure of the TSH molecule is altered in states of hypothyroidism (18). It is not known whether iodine status influences this glycoprotein structure, which may alter the immunoreactivity, but not the bioactivity, of the TSH molecule.

The public health implications of the present study are important in terms of both the feasibility of delivery of effective treatment protocols and the correct treatment of the individual. In most endemias, as in Qinghai Province, young patients with endemic myxedematous cretinism are now rare due to successful iodine prophylaxis programs. The largest number of hypothyroid cretins who require treatment are either older children or adults, who were invariably born before the introduction of iodine prophylaxis. In these older patients supraphysiological doses of iodine, in the form of iodized oil, are ineffective and potentially harmful. Similar detrimental effects of excess iodine have been described in other states of hypothyroidism (19). $T_4$ replacement, currently under investigation, is the treatment of choice for these endemic cretins.

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