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# The Prevention and Control of Iodine Deficiency Disorders

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# Contents


Preface vii

List of participants ix

Introduction. Message from Director General, World Health Organization
*H. Mahler* 1
Message from Executive Director, UNICEF
*J.P. Grant* 3

**Section I. Overview**

An overview of the prevention and control of iodine deficiency disorders
*B.S. Hetzel* 7

**Section II. The iodine deficiency disorders**

The iodine deficiency disorders: Introduction and general aspects
*J.B. Stanbury* 35
Neurological involvement in iodine deficiency disorders
*R. DeLong* 49
Developmental disorders associated with severe iodine deficiency
*N. Bleichrodt, I. Garcia, C. Rubio, G. Morreale de Escobar and F. Escobar del Rey* 65
Neonatal chemical hypothyroidism in iodine-deficient environments
*N. Kochupillai and C.S. Pandav* 85
Use of ultrasonography for goiter assessment in IDD: Studies in Tanzania
*W. Wachter, C.R. Pickardt, R. Gutekunst, K. Horn, A. Konig, F.P. Kavishe and P.C. Scriba* 95

## Section III. The status of iodine technology


Control of iodine deficiency disorders by iodination of salt: Strategy for developing countries
*M.G. Venkatesh Mannar* 111

Iodized oil in the treatment and prophylaxis of IDD
*J.T. Dunn* 127

Alternatives to salt and oil for iodine supplementation
*J.T. Dunn* 135


## Section IV. IDD control programs at the national level


Introduction
*B.S. Hetzel* 141

Reports from ICCIDD committees:

Assessment and communication for IDD control programs
*C.H. Thilly, N. Chawla, G.A. Clugston, F.P. Kavishe, E. DeMaeyer and R. Manoff* 143

The planning and management or IDD control programs
*C.S. Pandav, R.C. Carriere, N. Kochupillai, T. Ma and L.M. Nath* 149

The monitoring and evaluation of IDD control programs
*G. Medeiros-Neto, R. Djokomoeljanto, M. Benmiloud, M.C. DeBlanco, M. Irie, T.Z. Lu and C.R. Pickardt* 157

Special aspects of IDD control programs:

Communication. Social marketing: New tool to combat iodine deficiency disorders
*R.K. Manoff* 165

Reaching the hundredth monkey: Problems and opportunities in communiation for IDD control
*N. Chawla* 177

Assessment and planning for IDD control programs
*C.H. Thilly, P. Bourdoux, B. Swennen, N. Bebe, D. Due and A.M. Ermans* 181

Economic dimensions of iodine deficiency disorders
*H.M. Levin* 195

The national IDD control program in Peru: Implementation of a model
*E.A. Pretell* 209

Monitoring and evaluation of an IDD control program in Nepal
*S. Acharya* 213

## Section V. Regional reviews of IDD control: Present status and future prospects


Iodine deficiency disorders in Africa
*O.L. Ekpechi* 219
Iodine deficiency disorders in the Americas
*E.A. Pretell and J.T. Dunn* 237
Iodine deficiency disorders in Europe
*R. Gutekunst and P.C. Scriba* 249
Iodine deficiency disorders in the Middle East
*M. Benmiloud* 265
Iodine deficiency disorders in South East Asia
*G.A. Clugston, E.M. Dulberg, C.S. Pandav and R.L. Tilden* 273
Iodine deficiency disorders in the Western Pacific Region
*T. Ma and T.Z. Lu* 309


## Section VI. Implications for the future


The iodine deficiency disorders: Research needs
*J.B. Stanbury* 319
IDD control: Lessons for the future
*D.P. Haxton* 325
Toward a global strategy for the prevention and control of iodine deficiency disorders
*B.S. Hetzel* 329


## Appendices


Appendix 1. The 39th World Health Assembly (Geneva, May 1986) resolution on the prevention and control of iodine deficiency disorders 339
Appendix 2. International Council for the control of iodine deficiency disorders 341
Appendix 3. Names and addresses of Office Bearers, Executive Committee Members, and Regional Coordinators of ICCIDD 342

Author Index 345

Subject Index 347

*The Prevention and Control of Iodine Deficiency Disorders*
*B.S. Hetzel, J.T. Dunn and J.B. Stanbury, eds.*



# USE OF ULTRASONOGRAPHY FOR GOITER ASSESSMENT IN IDD: STUDIES IN TANZANIA

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## ABSTRACT

A follow-up study of iodine deficiency, goiter prevalence, and hypothyroidism was performed in the southern highlands of Tanzania using ultrasound equipment to calculate the volumes of the thyroid. The data indicate that thyroid palpation overestimated the volume of the gland, at least in children. Both in children and in adults thyroglobulin levels were elevated. The thyroglobulin release in children was more closely related to TSH levels, whereas in adults increased thyroglobulin was related to goiter size and pathological echo patterns. In school children exposed to severe iodine deficiency, hypothyroidism as detected by TSH levels of more than 5μU/ml was more prevalent than increased thyroid volume, whereas in adults the goiter prevalence was as expected. This finding underlines the demand for a reliable program of prophylactic iodine supplementation for children and young adults in this and similar iodine deficient areas.

## INTRODUCTION

The southern Tanzanian highland is a region of severe iodine deficiency (1,2), with an iodine supply of less than 25 μg per day, resulting in endemic goiter, hypothyroidism, and endemic cretinism (3). A follow-up of a limited iodine supplementation project, which had been established earlier as a pilot program, was performed in 1985, in order to evaluate the benefit of iodized oil injections on hypothyroidism and goiter in children and young adults.

Ultrasound volumetry of the thyroid was used for the first time in a field study such as this. It provided the opportunity to use objective criteria for the evaluation of goiter prevalence and size, especially with respect to the effect of iodine supplementation, and to correlate these with laboratory parameters such as serum levels of thyroid hormones, TSH, and thyroglobulin.

## METHODS AND STUDY POPULATION

**Iodine excretion**

Casual urines were collected from 167 school children in two villages of the highlands and two villages near the main road. Iodine concentration was measured by a modification of the ceric arsenious acid wet ash method (4). The creatinine concentration was determined by a routine method. Since there was no significant difference in the iodine excretion among the four villages, the data are presented together. They are compared with those of 75 well-nourished Swedish children 13 years of age (5).

**Thyroid volumes and echographical patterns.** Thyroid volumes were determined by ultrasound (Sonoline 1300, Siemens, Erlangen FRG; Transducer 4 MHz). Length, width, and thickness of both lobes were measured separately and the volumes were calculated by multiplication of these parameters using the model of a rotation ellipsoid, based on the following formula (6):

$$a \cdot b \cdot c \cdot \pi/6 = \text{volume (ml)}$$
$$a = \text{length};\ b = \text{width};\ c = \text{thickness}$$

The correction factor of 0.479, which substituted for $\pi/6$, was verified in a study comparing the echographic determination of post mortem volumes and true volumes of the two thyroid lobes determined by water submersion after autopsy (6). The mean error of the method is 16% when the thyroid volume is below 100 ml. This method was applied to 309 school children (6-17 years of age) and 63 adults. Using this method we found the normal thyroid volume of well-nourished Swedish school children 13 years of age (n = 224), who were never exposed to iodine deficiency (7), to be $4.2 \pm 1.7$ ml (8), and $10.1 \pm 4.9$ ml in healthy Swedish adults (n = 303). Based on these data the upper limit of normal thyroid volume is 10 ml in children and 20 ml in adults when echographical volumetry has been used; moderate enlargement is diagnosed for children in the range of 10-20 ml and for adults in the range of 20-30 ml. Normal echo patterns were assumed when echogeneity of thyroid tissue was homogenous and more dense when compared to the neck muscles.

**Abnormal echo pattern.** This included nodules with increased and decreased echogeneity and diffusely or irregularly reduced echogeneity of the whole organ tissue, independent of the thyroid size, as found with hyperplastic lesions and reduced colloid content.

**Thyroid function.** This was investigated by determination of thyrotropin (TSH) levels as published earlier (2). For confirmation of the results thyroxine and thyroxine binding globulin were determined (2).

**Thyroglobulin.** Thyroglobulin levels were measured in 286 children and 63 adults by a conventional double antibody radioimmunoassay (9). The reliability of each value was documented by investigation of the recovery of 100 ng/ml thyroglobulin standard added to the respective serum. In Table IV and in the text, median and ranges of thyroglobulin levels are given. For the statistical evaluation, mean values and standard deviations were used.

**Thyroid autoantibodies.** A commercial test system was used (Wellcome, Burgwedel, FRG).

**Statistics.** Correlation analysis was performed by the Fisher test. Significances of differences were investigated by the unpaired Student test.

## RESULTS

### Iodine deficiency

Mean iodine excretion was 39 $\mu$g iodine/g creatinine in 167 school children (Table I). The extremely high standard deviations (Table I) were due to the highly variable creatinine excretion (Table II). The mean creatinine excretion was significantly lower ($p < 0.01$) than that of the Swedish children. Therefore, the ratio of iodine to creatinine is an unreliable parameter for comparing nutritional iodine intake of Tanzanian and Swedish school children. This becomes obvious from the systematic comparison of urinary concentrations of iodine and creatinine in the casual urine samples of Tanzanian and Swedish children, which revealed significantly reduced ($p < 0.01$) excretion of both iodine and creatinine in the Tanzanian children (Table II).

### Goiter prevalence

Thyroid volumes in 309 school children and 62 adults, as determined by ultrasound, appear in Figures 1 and 2, respectively. Normal thyroid volumes were found in 49% of 51 children with previous iodine supplementation, and in 59% of 258 without iodine. Only 17.6% and 18.2% of the children had thyroid volumes of more than 20 ml. There was no significant decrease in goiter prevalence of children who had received iodine supplementation 1-2 years previously. From the limited number of 62 adults, 50% had thyroid volumes of more than 20 ml. In contrast to the children, the prevalence of goiter was significantly higher in the 23 adults without previous iodine prophylaxis (61%) than in those 39 with it (20.5%). In school children there was no correlation of thyroid volumes either with urinary iodine excretion or with TSH levels (see below).

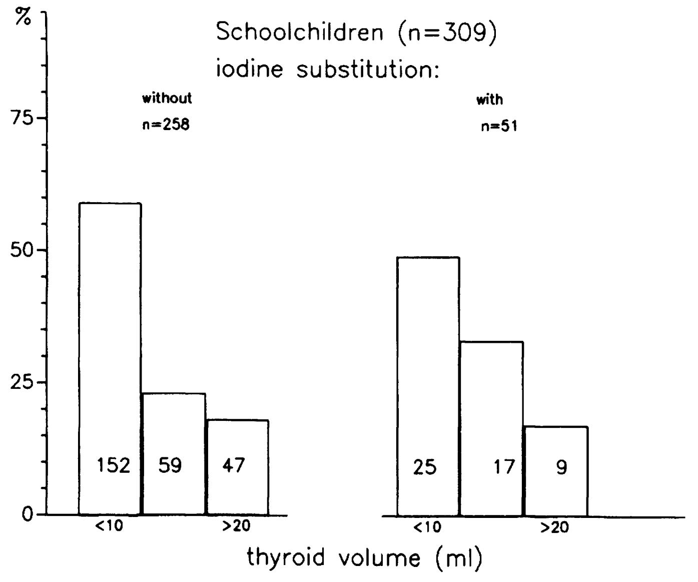


Figure 1. Thyroid volumes as measured by ultrasound equipment in children without (n=258) and with (n=51) previous iodine substitution. For evaluation of goiter size see Methods.

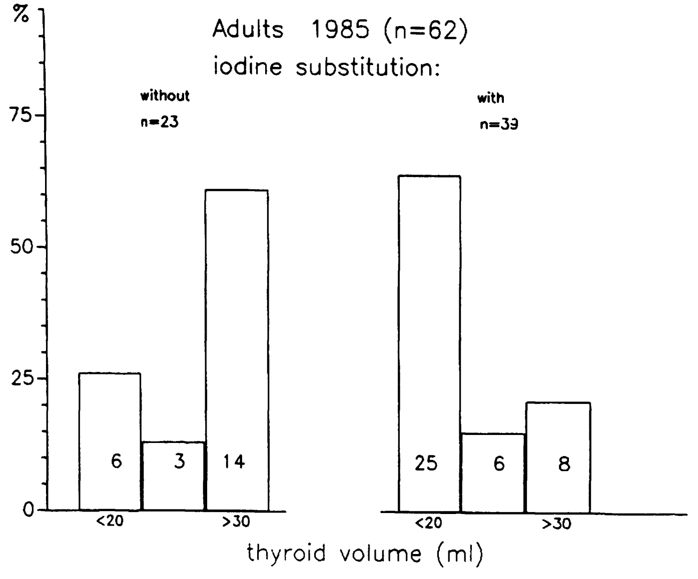


Figure 2. Thyroid volumes as measured by ultrasound equipment in adults without (n=23) and with (n=39) previous iodine substitution. For evaluation of goiter size see Methods.

**Thyroid volume and continuous iodine supplementation by potassium iodide tablets**

One hundred school children each received potassium iodide tablets containing 100 $\mu$g iodide each every school day (Fig. 3). After nearly two years, 23 had a thyroid volume of more than 10 ml. The younger ones (n = 59; 9-10 years of age), who had received the tablets from the time they began school, had thyroid volumes below 10 ml, with four exceptions. Twenty-seven children in the age group of 12-13 years, who began receiving the tablets shortly after entrance to school, had normal thyroid volumes, with two exceptions, whereas the older children (n = 17; 15-17 years of age), who had not received iodine tablets before the age of 13-15 years, had thyroid enlargements between 10 and 30 mls, with one exception.

**TABLE I. IODINE EXCRETION IN TANZANIAN SCHOOL CHILDREN**

| Year of survey | n | iodine excretion ($\mu$g I/g creatinine) (mean $\pm$ SD) |
|---|---|---|
| 1979 | 23 | 18.0 $\pm$ 9.3 |
| 1985 | 167 | 39.0 $\pm$ 18.4 |

**TABLE II. COMPARISON OF IODINE AND CREATININE EXCRETION IN 167 TANZANIAN (T) AND 75 SWEDISH (S) SCHOOL CHILDREN**

| | | Median | Range |
|---|---|---|---|
| Creatinine (mg/dl) | T | 51 | 0.4 - 257 |
| | S | 120 | 32 - 420 |
| Iodine ($\mu$g/dl) | T | 2.6 | 0.1 - 25 |
| | S | 22.3 | 4.5 - 52 |

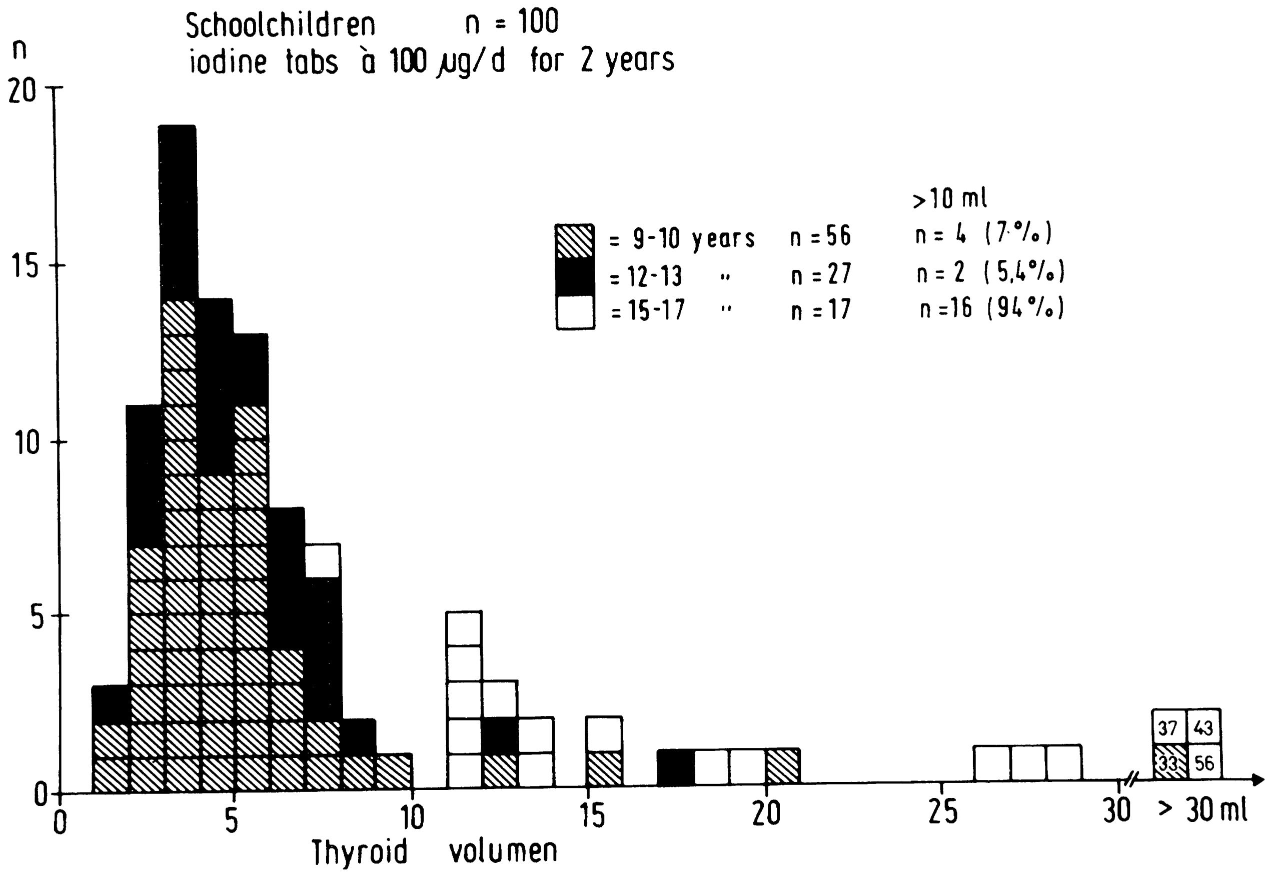


Figure 3. Distribution of thyroid volumes in 100 children during continuous iodine supply by potassium iodide tablets.

**Prevalence of hypothyroidism**

Figures 4 and 5 summarize 3 different investigations of basal TSH levels in school children from the southern highlands of Tanzania in 1979, 1982, and 1985. Figure 4 depicts the results in children without previous iodine prophylaxis and Figure 5 those in children with it. The prevalence of elevated TSH levels was 61% in 1979 and 1985, when 62 and 238 school children were investigated (Fig. 4), whereas it was 32% in 1982 when 560 children without iodine prophylaxis were investigated.

The main difference between the investigations in 1979/85 and that in 1982 was the location of the 1982 study in mountainous, remote villages lying at an altitude of 2000 meters and more, whereas the study of 1982 included 291 children from 2 villages at an altitude of approximately 1400 m near the main road from Dar-es-Salaam, where the nutritional supply, including important foods, was better when compared to that of the more remote villages.

In comparison to the untreated (Fig. 5), the prevalence of elevated TSH levels was significantly reduced to 2%, 7%, and 9% respectively with a relative increase in borderline cases after iodine application 1-2 years before.

In the 1985 study, 48% of the children without iodine prophylaxis had an unequivocally decreased $T_4$/TBG ratio below 1.8 (arbitrary unit; normal range 1.8-5.7), in contrast to only 5.5% of children who had received previous iodine. Thus at least 48% of the children were hypothyroid by this criterion.

**Ultrasound pattern and thyroid volume.** Echo patterns are available in 284 children, whose thyroid volumes were normal in 157, borderline in 67, and increased in 60. Fourteen children with normal volumes and eight who were borderline, and 31 of 60 children with goiters, had pathological echo patterns such as nodularity, diffusely and irregularly reduced echogeneity of thyroid tissue (Table III).

Comparison of TSH levels and these echo findings (Table III) revealed no correlation of echo patterns and elevated TSH levels, since 132 out of 174 hypothyroid children (76%) had normal ultrasound findings.

An analogous study included 76 adults, 31 of whom (41%) had normal echo patterns. These had normal or borderline thyroid volumes. Sixteen out of 47 adults with pathological echo patterns had normal or borderline increased thyroid volumes, whereas all 29 adults with clear cut thyroid enlargement had additional pathological echo findings.

Thirty-seven adults had normal and 18 had borderline elevated TSH levels. Echo patterns were normal in 21 (57%) and 6 (33%) of them respectively, whereas 17 out of 21 individuals (81%) with TSHs above 5 mU/l had pathological echo findings. Thus, with increasing thyroid volume, pathological echo findings increased in children as well as in adults, whereas a relationship between echo findings and hypothyroidism is obvious only in adults.

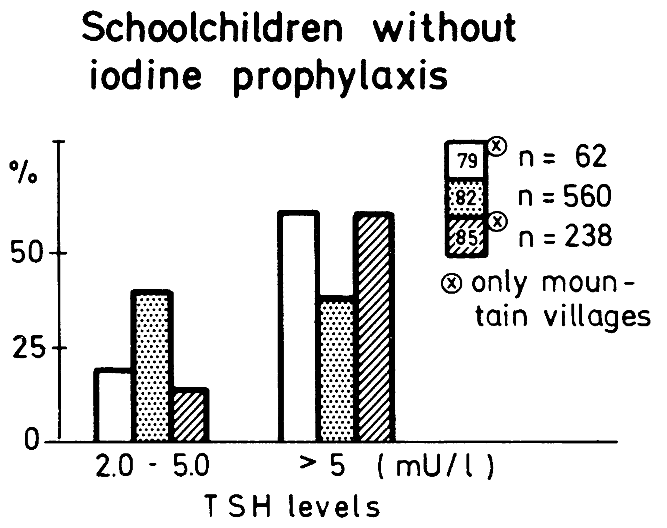


Figure 4. Prevalence of hypothyroidism in school children without iodine prophylaxis. TSH levels > 5 mU/l indicate hypothyroidism. TSH levels in the range 2-5 mU/l are assumed to represent borderline thyroid hormone deficiency (14). White column, 1979 results; stippled column, 1982 results, including 2 villages near the main road at lower altitude of approx. 1400 meters (n=291); hatched column, 1985 investigation.

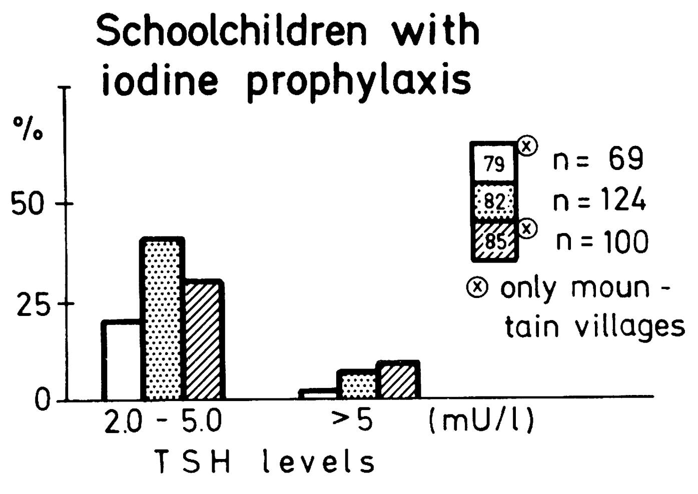


Figure 5. TSH levels in school children 1-2 years after iodine prophylaxis. For explanation see Fig. 4.

**TABLE III. COMPARISON BETWEEN ULTRASOUND PATTERN, THYROID VOLUME, AND THYROTROPIN LEVELS IN SCHOOL CHILDREN AND ADULTS**

| | Thyroid volume | | | Thyrotropin level | | |
|---|---|---|---|---|---|---|
| | normal | borderline | increased | normal | borderline | elevated |
| Children (n = 284) | | | | | | |
| Echo | | | | | | |
| Normal | 143(91)* | 59(88) | 29(48) | 36(90) | 63(90) | 132(76) |
| Pathologic | 14(9) | 8(12) | 31(52) | 4(10) | 7(10) | 42(24) |
| Total | 157(100) | 67(100) | 60(100) | 40(100) | 70(100) | 174(100) |
| Adults (n = 76) | | | | | | |
| Echo | | | | | | |
| Normal | 26(74) | 5(42) | -- | 21(57) | 6(33) | 4(19) |
| Pathologic | 9(26) | 7(58) | 29(100) | 16(43) | 12(67) | 17(81) |
| Total | 35(100) | 12(100) | 29(100) | 37(100) | 18(100) | 21(100) |

* Number in parentheses indicates percent of total.

**Thyroglobulin levels.** Thyroglobulin (TG) levels of 275 school children and 63 adults were investigated with respect to the ultrasound findings. Only 20% of the school children had a normal TG level (below 60 ng/ml) whereas the median TG levels in school children with normal and with pathological echo patterns were elevated (Table IV). The difference between these two groups was not significant.

In adults with normal echo patterns, the median TG was 17 ng/ml (Table IV), being significantly lower ($p < 0.01$) than in children with normal echo findings. The prevalence of elevated TG increased with pathological findings. The difference between TG levels in the group with normal ultrasound patterns and those with nodularity was highly significant ($p < 0.01$).

TABLE IV. COMPARISON OF ULTRASOUND PATTERN AND THYROGLOBULIN LEVELS IN SCHOOL CHILDREN AND ADULTS

| Echogeneity | School children (n = 275) | | | Adults (n = 63) | | |
|---|---|---|---|---|---|---|
| | | TG (ng/ml) | | | TG (ng/ml) | |
| | n | median | range | n | median | range |
| normal | 219 | 324 | 10-3622 | 25 | 17 | 10-316 |
| reduced | 34 | 726 | 10-3270 | 5 | 150 | 10-722 |
| complex | 2 | 19 | 3894 | 2 | 179 | 1962 |
| nodular | 20 | 652 | 10-2877 | 31 | 1039 | 10-5000 |

TABLE V. THYROID AUTOANTIBODIES IN UNTREATED AND LIPIDOL-TREATED CHILDREN AND ADULTS

| | n | MAB | | TgAB | |
|---|---|---|---|---|---|
| | | pos | neg | pos | neg |
| Untreated children | 253 | 3 | 250 | 6 | 247 |
| Untreated goitrous adults | 14 | 0 | 14 | 0 | 14 |
| Treated children | 193 | 1 | 192 | 2 | 191 |
| Treated women | 53 | 0 | 53 | 0 | 53 |
| Total | 513 | 4 | 509 | 8 | 505 |

MAB = microsomal antibodies; TgAB = thyroglobulin antibodies

After logarithmic transformation of all parameters investigated, there was no significant correlation between the urinary iodine excretion and TG, but there was a significant correlation between thyroid volume and TG as well as between TSH and TG levels. When children and adults were grouped according to previous iodine supplementation, the correlation between thyroid volume and TG remained significant only in the group with previous iodine application ($n = 37$; $p = 0.02$), whereas the correlation of TSH and TG remained highly significant independent of previous iodine application ($p < 0.01$ for both) in children. In adults, the correlation of TSH with TG was no longer significant, in contrast to the correlation of thyroid volume with TG levels ($p < 0.01$).

**Thyroid autoantibodies.** We investigated 67 young female adults and 346 school children with and without previous iodized oil injections, as well as 100 children during continuous potassium iodide application (Table V), with respect to a possible increase of focal thyroiditis detectable by thyroid autoantibodies. Among 267 untreated individuals, three had positive microsomal antibodies and six had positive TgAB-titers. Out of 246 treated individuals one had microsomal antibodies and two had positive titers of TgAB. All these titers were in the range of 1:400 to 1:1600.

## DISCUSSION

In the highlands of Tanzania malnutrition is prevalent, but exact data on its types and degrees are lacking. Thus, the ratio of iodine over creatinine is an unreliable index of nutritional iodine intake in this population, because this ratio is artifactually high with a wide range of variation. This observation is in agreement with those of Escobar del Rey (10) and Bourdoux et al. (11). However, iodine deficiency could be ascertained by a comparison of iodine excretion in casual urine samples of Tanzanian children with those of Swedish children who have sufficient nutritional iodine intake (7). Low median iodine excretion of 2.6 $\mu$g/dl (range 0.1-25 $\mu$g/dl) is comparable with that in Zaire (11), an area with a high prevalence of endemic cretinism and a mean iodine concentration of 2.4-4.6 $\mu$g/dl in casual samples. Thus, it is obvious that there is a persistent severe iodine deficiency (3) in the southern highlands of Tanzania.

The investigation of school children before iodine supplementation also confirms the persistently high prevalence (60%) of elevated TSH levels in this area from 1979-1985. There is some evidence of a lower prevalence of hypothyroidism in the villages near the main road at an altitude of approximately 1400 meters, as demonstrated by the significantly lower prevalence of elevated TSH levels when only 48% of the children under investigation lived in the mountainous area, despite the fact that there was no significant difference in iodine excretion.

The comparison of TSH levels in schoolchildren before and after iodized oil injection showed a significant decline in clearly elevated TSH levels in response to iodine supplementation in all three studies (1,2). These data document the beneficial effect of iodized oil with respect to hypothyroidism in school children.

The beneficial effect of iodine substitution to pregnant females for newborns and infants was shown in an earlier study (2). The mothers had normal TSH levels up to 3 years after supplementation. Their children were euthyroid as long as they were breastfed, whereas 16% of the children ages 2-3 years developed hypothyroidism when exposed to the iodine deficiency of the region after breastfeeding stopped. Thus, the degree of iodine deficiency and of hypothyroidism in this area would justify repetitive iodine supplementation by iodized oil injection in the defined target populations such as children and young adult females, especially early in pregnancy (1). On the other hand, the limited study of continuous iodine supplementation by potassium iodide tablets also promises success if the tablets are available and the compliance of teachers and children is sufficient.

The use of ultrasound equipment to evaluate the prevalence of endemic goiter in a field study in a developing country is presented here for the first time, to our knowledge. When echography is used, the thyroid volume in a healthy population never exposed to iodine deficiency is below 10 ml in children 13 years of age, with no significant differences between boys and girls. In adults, thyroid volume is below 20 ml. We accepted echographical volumetry as the most reliable method to determine thyroid size, from the epidemiological investigations of Gutekunst and coworkers in Sweden and Germany (5,8). Based on these data, the cut-off points presented here were chosen and a range of above 10 ml was introduced for borderline cases. Despite these low cut-off points, the study reveals a prevalence of only 17-20% of unequivocally enlarged thyroids (with a volume of more than 20 ml) and a prevalence of normal thyroid volume in 50-60% of the children. Since prevalence of goiter in this area has been found to be 90% in school children twice before (1,2) by palpation by the same investigators, this study clearly shows that goiter size is grossly overestimated by palpation, at least in thin young children, some of whom suffer from malnutrition. These data show clearly that, in children, hypothyroidism (as indicated by TSH values above 5 $\mu$U/ml) prevails over goiter size as a consequence of iodine deficiency.

Another unexpected finding was the lack of difference in thyroid volumes of children with and without previous iodine supplementation despite a significantly decreased prevalence of hypothryoidism after iodine supplementation (Fig. 1 versus Figs. 4 and 5). These data also indicate that in severe iodine deficiency, biochemical hypothyroidism is more prominent in children than is goiter. In contrast, in adults iodine substitution resulted in a significant decrease in goiter prevalence and in a decrease in hypothyroidism. The implication of this finding with respect to mental and somatic development of these populations remains to be established.

It is well known that thyroglobulin levels increase in a variety of thyroid diseases. In nodular goiter, TG levels were elevated and unsuppressible in most cases (9) from an area with low grade iodine deficiency (7) and these findings were independent of radionuclide uptake in the nodules and independent of thyroid function including TSH levels. In this study, grossly elevated thyroglobulin release in children living in severe iodine deficiency is more closely correlated with the degree of hypothyroidism as reflected by the TSH levels than with the increase of thyroid volume or the morphological alterations in the gland as demonstrated by ultrasound. In contrast, in adults elevated thyroglobulin levels are more closely correlated with thyroid volume. Since most of these adults have nodular goiter, the thyroglobulin release may be due to intrathyroidal pathology, which would agree with our previous study (9) but differ from that of Fenzi and coworkers (12) who found reciprocal correlation of thyroglobulin and thyrotropin levels in adults living in an area with moderate iodine deficiency.

In iodine-deprived laboratory animals (13) an increase in nutritional iodine is believed to induce focal thyroid necrosis. Boukis et al. (14) reported rising antibody titers in an adult population from an iodine-deficient region of Crete after application of iodized oil intramuscularly. In our study, spontaneous prevalence of thyroglobulin antibodies was 2.3% and that of microsomal antibodies 1.1%. This prevalence did not increase in the study population 1-2 years after iodine injections, at least in children and young adult females. Thus, the appearance of focal thyroiditis after increasing the iodine supply may be a question of the quantity or the duration of iodine exposure or both, and perhaps of the age of the population. This study does not indicate that focal thyroiditis may be a major drawback to this kind of iodine supply.

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