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THE EFFECT OF IODIZED OIL ON GOITRE SIZE, THYROID FUNCTION AND THE DEVELOPMENT OF THE JOD BASEDOW PHENOMENON*

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SUMMARY

In the Lubok Antu district of Sarawak, Malaysia, 240 subjects with 75% prevalence of goitre were studied before and at intervals of 1 and 2 years following iodized oil injection. After 1 year the prevalence of goitre was reduced to 33%, but 2 years after injection, goitres had regrown in fourteen subjects (6%). The mean urinary iodine concentration was low initially at $0{\cdot}17 \pm 0{\cdot}08$ (SD) μmol/l, consistent with iodine deficiency, and rose to a level of $2{\cdot}6 \pm 2{\cdot}5$ μmol/l at 1 year, before falling to $0{\cdot}46 \pm 0{\cdot}38$ μmol/l, again consistent with deficiency. Such a rapid depletion of iodine may be related to the high consumption of cassava. Before injection serum TSH concentrations showed a wide scatter from normal up to 62 mU/l and at 1 year, serum TSH concentrations were undetectable. At 2 years serum TSH was again detectable in 50% of subjects with levels up to 8·6 mu/l. During the 2 years, there was a progressive rise in the mean serum T4 concentration from 92 ± 22 (SD) nmol/l to 110 ± 22 nmol/l ($P < 0{\cdot}05$). Serum T3 concentrations rose serially in all subjects from a pre-injection mean of $1{\cdot}9 \pm 0{\cdot}3$ nmol/l to $2{\cdot}5 \pm 0{\cdot}9$ nmol/l ($P < 0{\cdot}001$) and then fell significantly below the baseline level to a mean of $1{\cdot}7 \pm 0{\cdot}6$ nmol/l 2 years after injection ($P < 0{\cdot}01$). The mean serum rT3 levels followed the same trend. At 1 or 2 years following injection, eight subjects were clinically hyperthyroid. Four of these consented to venesection and hyperthyroidism was confirmed biochemically. These data reveal that:

1 goitres decreased rapidly in size in response to iodized oil injection;

2 significant though incomplete depletion of the iodine stores occurred within 2 years of injection;

3 the consistent increase in serum T3 was associated with a fall in serum TSH to undetectable levels;

4 the prevalence of the Jod Basedow phenomenon was 1·7%.

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These data suggest the need for closer biochemical monitoring of subjects receiving massive doses of iodine and a reappraisal of the use of iodized oil in the treatment of endemic goitre.

In Sarawak, Malaysia, endemic goitre is highly prevalent (Polunin, 1951; Ogihara *et al.*, 1972a,b) and in the region studied by us (Maberly & Eastman, 1976) 99% of the population from the age of 11 years was affected. Polunin (1951) and Ogihara *et al.* (1972a,b) have attributed this to iodine deficiency, however, we have found that a goitrogen in cassava is probably a contributory aetiological factor (Maberly *et al.*, 1978). Circulating thyroid hormone levels are comparable with those reported from severely affected goitrous populations (Maberly *et al.*, 1979).

Attempts at distribution of iodized salt in Sarawak have failed (Polunin, 1970). A single intramuscular injection of iodized poppy seed oil in goitrous people is reported to maintain an adequate supply of iodine for from 5 to 7 years, to rapidly reduce goitre size and to prevent endemic cretinism (Pretell *et al.*, 1969; Ibbertson *et al.*, 1971; Pharoah *et al.*, 1971; Thilly *et al.*, 1973, 1980). The Jod Basedow effect, i.e. an increased incidence of thyrotoxicosis (Kocher, 1910) following iodized oil injections, is said not to occur (Hennessy *et al.*, 1964; Pretell *et al.*, 1969; Ibbertson *et al.*, 1971; Thilly *et al.*, 1973, 1980; Lagasse *et al.*, 1980). Therefore, a programme was designed to inject the villagers of Lubok Antu with iodized oil in an attempt to alleviate their endemic goitre.

SUBJECTS AND ASSAY PROCEDURES

In the village communities of the Lubok Antu district of Sarawak, 240 people over 4 years of age were studied before and for 2 years following injection with iodized poppy seed oil (Lipidol Viscous, May and Baker). The injections were administered according to the scheme of Stanbury *et al.* (1974).

Clinical thyroid function was assessed and goitres graded in all subjects according to size on a scale of 0–4 (Polunin, 1970). Because of local superstition of blood collection, not all volunteers could be followed serially over the study period. Sera were collected from 100 volunteers prior to injection, from forty-five subjects after 1 year and from fifty subjects 2 years after injection. All volunteers were older than 14 years and their mean dose of iodized oil was $1{\cdot}4 \pm 0{\cdot}75$ (SD) ml.

Urine samples were collected from fifty volunteers prior to injection and from fifty and ten subjects respectively, at 1 and 2 years after iodized oil injections. Urinary iodine levels were measured using the arsenious autoanalyser technique. Serum T4, T3, 3,3′5′ triiodothyronine (rT3) and TSH were measured by methods reported previously (Corcoran *et al.*, 1973, 1976; Eastman *et al.*, 1975).

Statistical analysis

Statistical analysis was performed using Student's *t* test for paired and non paired data. Results are reported as means $\pm$ SD.

RESULTS

Goitre size (Table 1)

In the first 12 months following injection, the prevalence of goitre was reduced from

Table 1. Prevalence of goitres before and at 1 and 2 years after iodized oil injections

Grade	Before (%)	Year 1 (%)	Year 2 (%)
0	25	66·3	62·5
1	11·3	10·4	14·3
2A	36·7	10·4	12·6
2B	10·4	6·3	5·5
2C	5·8	2·5	1·3
3	10·4	4·1	3·8
4	0·4	0	0

75% to 33%. Excluding those of grade 0 prior to injection, 80% showed a reduction in goitre size from a higher to a lower grade. At 2 years following injection, five of the larger goitres continued to regress, but in fourteen subjects, in whom goitres had previously regressed, the goitre grade had increased. Within this group 70% were female and 80% were under the age of 25 years. No male over 25 years showed a detectable increase in goitre grade.

Clinical thyroid function (Table 2)

Before injection, all subjects were judged euthyroid. Seven subjects at 1 year and one subject at 2 years after injection gave a history which included weight loss, heat intolerance, palpitations and nervousness. All were warm, with rapid pulses and displayed a fine tremor, lid lag and lid retraction consistent with thyrotoxicosis. The ages of these six female and two male subjects ranged from 24 to 60 years. Before injection, goitres were graded from 2A to 3; after injection all showed a reduction in size. Toxic levels of thyroid hormones were unequivocally confirmed in four of these subjects.

Table 2. Thyroid hormone results in patients judged clinically thyrotoxic after iodized oil injections

Subject number	Sex	Age (years)	Goitre grade Before	2 years after	Thyroid hormone levels (nmol/l) Pre-injection	1 year post injection	2 years post-injection
1	F	47	2A	0	T4 103 T3 2·6	T4 189 T3 5·41	—
2	M	32	2B	SA	—*	T4 157 T3 4·59	—
3	F	54	2C	2B	—	T4 315 T3 6·8	T4 149 T3 4·6
4	F	50	3	2C	—	—	T4 167 T3 4·8

* Missing data where patients refused venepuncture.
Serum T4 euthyroid Australian range 70–150 nmol/l; Serum T3 euthyroid Australian range 1·2–2·8 nmol/l.

Table 3. Mean (±SD) thyroid hormone levels before and at 1 and 2 years after iodized oil injection

Time	T4 (nmol/l)	T3 (nmol/l)	rT3 (nmol/l)
Before	92±22*	1·9±0·3*†	0·35±0·04*
1 year	103±40	2·5±0·9†	0·45±0·1*
2 years	110±22*	1·7±0·6*	0·2±0·1*

* ($P<0·01$); ($P<0·001$).

Urinary iodine concentrations

Prior to injection, the mean urinary iodine concentration was low (0·17±0·08 μmol/l). Twelve months following injection the mean urinary iodine concentration had risen significantly to 2·6±2·5 μmol/l ($P<0·001$). Two years after the oil injections, the mean urinary iodine concentration of 0·46±0·38 had fallen to near the pre-injection mean but was still significantly increased ($P<0·05$).

Serum hormone levels (Table 3)

There was a serial rise in mean serum T4 at 1 and 2 years after injection. Individuals followed serially did not all show the same trends as the mean values. At 12 months following iodized oil the mean serum T3 rose, but at 2 years has fallen significantly below the pre-injection mean. These changes were reflected in all but one result in subjects studied serially. This subject was thyrotoxic with serum T3 being highest at 2 years. The mean serum rT3 levels followed the same pattern as mean serum T3 levels.

Prior to injection with iodized oil, the serum TSH was elevated in 24% of subjects with levels as high as 62 mU/l (upper limit of normal = 5 mU/l). Twelve months after injection, serum TSH in all subjects had been suppressed to below assay sensitivity (< 1·6 mU/l).

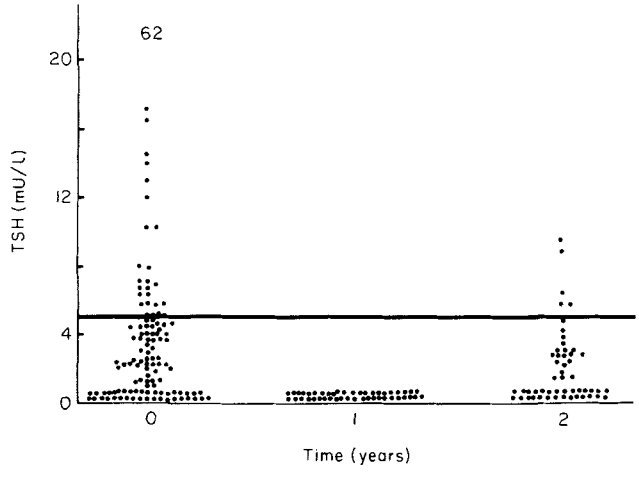

Fig. 1. Serum TSH concentrations before and after iodized oil injections.

Two years after injection, serum TSH levels were still below assay sensitivity in 50% of subjects. Serum TSH levels had risen marginally above the upper limit of normal in 10% of the group with the highest level being 8·6 mU/l (Fig. 1).

No correlation was found between goitre regrowth, age or sex and these single basal serum TSH concentrations (linear regression, $P > 0{\cdot}05$).

DISCUSSION

In this community prior to injection with iodized oil, the low urinary iodine excretion, the scatter of elevated serum TSH levels and the profile of thyroid function were consistent with chronic iodine deficiency, producing a 75% prevalence of goitre. The changes observed 1 year after iodized oil injections were consistent with the effect of an acute, large iodine load. The marked reduction in goitre size, in 80% of the treated population, was similar to the findings in other studies using iodized oil (Hennessy, 1964; Pretell *et al.*, 1969; Thilly *et al.*, 1973; Lagasse *et al.*, 1980). After iodized oil, urinary iodine concentrations rose 15-fold to $2{\cdot}6 \pm 2{\cdot}5$ μmol/l, which is six times higher than that required to prevent goitre (Koutras *et al.*, 1980). Serum TSH was suppressed in all subjects in agreement with the report by Croxson *et al.* (1976) of suppression of TSH and a rapid rise in both serum T3 and T4 within several days of injection. However, in our treated population there was only a small but non-significant rise in serum T4 in the first year. There are few long term studies measuring both serum T4 and T3 after iodized oil injections. Most show a small increase in mean serum T4 and a decrease in mean serum T3 concentrations consistent with return to the iodine replete state (Lagasse *et al.*, 1980; Hetzel *et al.*, 1980). In contrast to these studies, we noted at 12 months a substantial elevation in serum T3 levels in all subjects studied; the mean level being in the upper part of the euthyroid range for non-endemic areas. This sustained elevation of serum T3 with suppression of the pituitary–thyroidal axis has not been reported previously.

Further significant results emerged from the studies conducted 2 years after injection. Some of the clinical and laboratory findings were suprising compared with other reports in which the depot iodine supply was more sustained (Hetzel *et al.*, 1980). Five of the larger goitres showed further reduction, yet fourteen subjects in whom goitres had originally regressed, showed an increase in goitre grade. In this, our observations agree with Thilly *et al.* (1980), that early goitre regrowth occurs in the young and more often in females. Moreover, the mean urinary iodine (0·46 μmol/l) had fallen and was again indicative of iodine deficiency. This rapid fall in urinary iodine was faster than observed by both Pretell *et al.* (1969) and Thilly *et al.* (1973). In agreement with this, serum TSH was no longer suppressed in half of the subjects and was in fact above the normal range in 10% of the treated population. Both serum T3 and rT3 fell significantly to below the pre-injection mean, whereas serum T4 rose slightly to 110 nmol/l, and became significantly higher than the pre-injection mean. These changes indicate a new thyroidal equilibrium where iodine deficiency was not as severe as before injection. These results may also be explained by the fact that cassava forms a substantial part of the diet in Lubok Antu. This plant contains variable but significant concentrations of hydrocyanic acid which increases renal secretion of iodine (Bourdoux *et al.*, 1980). Whatever the reason, iodized oil injection failed to provide the long term protection (5–7½ years) reported by many studies (Hetzel *et al.*, 1980).

Thiocyanate, the goitrogenic metabolite from cassava has also been shown to decrease

the thyroidal diiodotyrosine (DIT) to monoiodotyrosine (MIT) ratio (Ermans *et al.*, 1972) which would therefore result in a lower T4:T3 ratio. In a previous study in this region (Maberly *et al.*, 1979), the serum T4 response to TRH stimulation was shown to be reduced when compared with T3.

In this study, the immediate effect of correction of the iodine deficiency resulted in a disproportionate increase in serum T3 levels. A partial intrathyroidal block in DIT production by continued ingestion of cassava may explain the sustained high serum concentration of T3 and rT3 after 1 year.

Of 240 subjects studied, eight were suspected clinically of being thyrotoxic 1 or 2 years after iodized oil and the diagnosis was confirmed in four subjects by biochemical assessment. The other four would not agree to venepuncture because of superstitious beliefs. In one of the subjects studied at both 1 and 2 years after iodized oil injection, the thyroid hormone levels were highest in the first year, suggesting that the degree of thyrotoxicosis is related to the availability of iodine. Two of the thyrotoxic subjects were 50 years of age or older which is the predicted age at risk of iodine induced thyrotoxicosis (Hetzel *et al.*, 1980). One subject was 32 years of age with a grade 2B goitre which was not particularly large in this population. Thus, individuals susceptible to the Jod Basedow effect cannot be pre-selected by age and goitre size alone from the rest of the population. It was of interest to note that, even in these subjects, goitres regressed in size. Isolated cases of the Jod Basedow phenomenon following iodized oil injection were reviewed by Matovinovic (1980) who reported all forms of thyrotoxicosis including elevation of both T3 and T4 or either T4 or T3 alone. Explanations which have been advanced for the rarity of observed iodine-induced hyperthyroidism after iodized oil injection include infrequent or lack of examination and subtlety of clinical signs.

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