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Iodine metabolism in children and women with endemic goitre in Ceylon

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1. Iodine metabolism was studied using labelled sodium iodide in subjects with endemic goitre which is prevalent in the south-west part of Ceylon, where the iodine content of the drinking water was shown to be low. The study was confined mostly to children of school age.

2. The patients showed raised thyroidal uptake of ^{131}I and 48 h serum protein-bound radioactive iodine, lowered plasma inorganic iodide and urinary iodide.

3. These findings suggest that the goitre which is endemic in Ceylon is due to environmental iodine deficiency rather than to a goitrogen.

Unlike in many parts of the world, knowledge of endemic goitre in Ceylon is of recent origin (Greenwald, 1955; Kelly & Snedden, 1958). The first systematic survey of the incidence of goitre in the island was conducted by Wilson (1950) who reported its prevalence in the south-west region of Ceylon. The exact pathogenesis of endemic goitre in Ceylon is not known. Although Wilson found that the iodine content of water in the affected areas was low, she felt that factors other than environmental iodine deficiency, such as goitrogens in food, were also involved (Wilson, 1950, 1954). Similar views have been expressed recently by Mahadeva & Shanmuganathan (1967). The pioneering work of Stanbury and his associates on iodine metabolism in endemic goitre in Argentina (Stanbury, Brownwell, Riggs, Perinetti, Itoiz & del Castillo, 1954) and subsequently of several other investigators in different countries, indicates that environmental iodine deficiency is the cause of most of the endemic goitre in the world (Roche, De Vananzi, Vera, Coll, Spinetti-Berti, Mendez-Martinez, Gerardi & Forero, 1957; De Visscher, Beckers, van den Schrieck, De Smet, Ermans, Galperin & Bastenie, 1961; Ramalingaswami, Subramanian & Deo, 1961; Follis, Vanprapa & Damrongsakdi, 1962; Choufoer, van Rhijn, Kassenaar & Querido, 1963). The present communication deals with a study of iodine metabolism in endemic goitre in Ceylon.

EXPERIMENTAL

Preliminary surveys

Four provinces in the south-west portion of the island are known to be affected (Western, Central, Southern and Sabaragamuwa) (Fig. 1). The rest of the island is free from endemic goitre. Using the classification of Murray, Ryle, Simpson & Wilson

(1948), a clinical survey of the incidence of goitre in schoolchildren of the age group 8–16 years was made in four areas in the endemic zones, namely Nuwara Eliya (1859 m above the mean sea-level), Kandy (610 m above the mean sea-level), Horana and Galle (both almost at sea-level). Incidence of goitre varied from 12 to 54% in these areas (Table 1). It was greatest in Horana (area 1); females were more affected than males. Clinical examination revealed no goitre in schoolchildren of Jaffna, a township situated in the northern part of the island (area 3). These children were therefore used as controls. Field laboratories were established to study iodine metabolism, using ^{131}I as the tracer, in schoolchildren of the two areas in the endemic zone, namely Horana and Galle (areas 1 and 2 respectively), and the control area (Jaffna, area 3). A group of adult females with visible goitre from Horana (area 1) was also investigated.

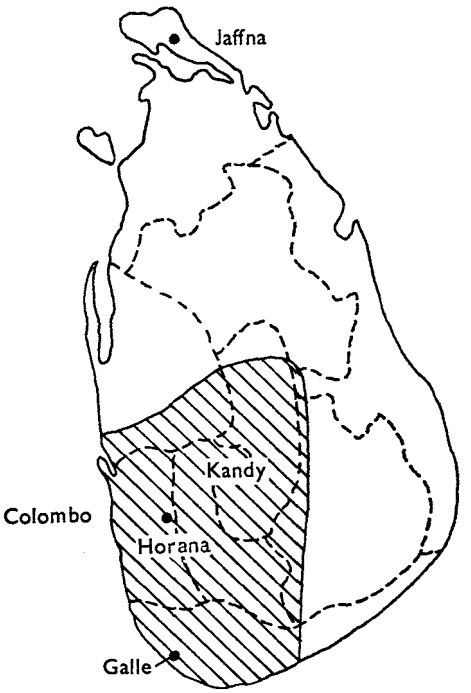

Fig. 1. Map of Ceylon showing the area where goitre is endemic (▨) and the area in which the investigation now reported was made (●).

Procedure

Uptake of ^{131}I. Studies on the uptake of ^{131}I were carried out in ninety-three patients with goitre from the two endemic areas mentioned above and in twenty schoolchildren from Jaffna (controls). Of the ninety-three cases from the endemic areas, sixty were between the ages of 8 and 16 years; the rest were adult females. After a clinical assessment of the thyroid gland and of general nutrition, each person was given orally 50 μCi of ^{131}I as carrier-free sodium iodide (obtained from Bhabha Atomic Research Centre, Trombay, India) in about 100 ml of distilled water. The thyroidal uptake of ^{131}I in 24 h was measured with a Tracerlab scintillation probe (P-20D) attached to a

Tracerlab ratemeter (Tracermatic Ratemeter SC-79). The detector was kept at a distance of 254 mm from the neck.

Thyroidal iodide clearance. One hour after the administration of the isotope, thyroidal clearance (neck:thigh ratio) was recorded in fourteen children of area 1 (endemic) and nineteen children from area 3 (control) using the method of Foote & Maclagan (1951).

Blood analysis. Serum protein-bound radioactive iodine (PB ^{131}I) was measured in fourteen children from area 2 (endemic) 48 h after the administration of the isotope by the method of Silver, Fieber & Yohalem (1952). Radioactivity was measured with a Tracerlab well-type scintillation probe attached to a Tracerlab spectrometer.

Serum protein-bound iodine (PB ^{127}I) was estimated in eighteen children from the endemic area by the method of Barker, Humphrey & Soley (1951).

Plasma inorganic iodide (PII) was measured in fourteen children of area 1 (endemic) by the isotopic technique described by Harden, Mason & Watson (1965). After administration of the isotope, urine was collected from 60 to 150 min while a venous blood sample was drawn at 105 min. PII was estimated by the formula:

$$\text{PII } (\mu g/100 \text{ ml}) = \text{chemical } ^{127}I \text{ in urine } (\mu g/100 \text{ ml}) \times \frac{^{131}I \text{ in plasma (\% of dose/ml)}}{^{131}I \text{ in urine (\% of dose/ml)}}.$$

Determination of iodine in drinking water and urine. It was not possible to collect 24 h samples of urine. However, casual urine samples were collected from six children of area 1. Two samples of drinking water from each area were also collected for iodine determination. Iodine contents of urine and water were measured by the modified method of Barker *et al.* (1951). Urinary creatinine was measured by the alkaline picrate method (King & Wootton, 1956).

RESULTS

General impression of the extent of the problem

From the clinical survey it was evident that the incidence of endemic goitre is high in south-western Ceylon (Fig. 1, Table 1). Affected schoolchildren show grade I to grade II symmetrical enlargement of the thyroid. In adults, the goitres are large, asymmetrical and nodular, and are more frequent in females than in males. One of the features of goitre in Ceylon is its occurrence in people living along the coastal strip. It is our impression that endemic goitre in Ceylon is not associated with cretinism or deaf-mutism to any significant extent.

Uptake of ^{131}I

The values for the 24 h uptake of ^{131}I in patients with endemic goitre and schoolchildren of the control area are shown in Table 2. The uptake of ^{131}I is markedly raised in patients with goitre. Only two children out of sixty (6·6%) had normal uptakes, whereas the majority showed an uptake above 80%. By comparison, the uptakes in male and female children of Jaffna (control) were within normal limits (less than 50%). In adult females with goitre from area 1 (endemic) the uptakes were also high (Table 2).

Table 1. *Prevalence of goitre in schoolchildren of Ceylon (names of villages are given in parentheses)*

Area	Sex	No. of persons examined	Incidence of goitre	
			No. of persons	%
Endemic:				
Nuwara Eliya	♀	43	16	37·2
(Blackpool)	♂	33	4	12·2
Kandy	♀	37	20	54·0
(Gampola)	♂	23	8	34·7
Horana	♀	41	22	53·6
(Pelenwatte)	♂	57	24	42·1
Galle	♀	30	7	23·3
(Uluvitake)	♂	30	5	16·6
Total endemic	♀	151	65	43·0
	♂	143	41	28·6
Non-endemic:				
Jaffna	♀	20	Nil	Nil
(Uduvil)	♂	20	1*	5

* This patient had been staying in Horana District before migrating to Jaffna. He was, therefore, not included in tracer studies.

Table 2. *The 24 h uptake of ^{131}I in patients with goitre from endemic areas and schoolchildren of the control area*

Uptake (% dose)	No. of persons						
	Controls (Jaffna), children, 8–16 years		Endemic area (Galle), children, 8–16 years		Endemic area (Horana)		
					Children, 8–16 years		Adult women
	♀	♂	♀	♂	♀	♂	
< 20	—	—	—	—	—	—	—
20–30	—	2	—	1	—	—	—
30–40	2	1	—	—	—	—	—
40–50	5	2	—	—	1	—	1
50–60	2	2	—	1	2	—	4
60–70	—	—	—	1	1	2	1
70–80	—	—	—	—	1	2	6
80–90	—	—	3	4	5	3	9
90–100	—	—	4	—	13	16	12
Total	9	7	7	7	23	23	33
Mean	47·3	40·8	90·1	70·1	83·5	83·4	77·5
Standard error	2·37	4·67	3·13	8·93	3·37	2·42	2·46

Thyroidal iodide clearance (neck:thigh ratio)

Table 3 gives the neck:thigh ratio 1 h after the administration of the isotope. The mean neck:thigh ratio was higher (3·0) in the children of the endemic areas than in those from the control area (1·82). The differences were statistically significant.

Table 3. *Thyroidal iodide clearance (neck:thigh ratio of ^{131}I) in children suffering from endemic goitre and in controls*

Neck:thigh ratio	No. of persons	
	Endemic area	Control area
< 1·0	—	—
1·0–1·9	3	13
2·0–2·9	4	6
3·0–3·9	3	—
4·0–4·9	2	—
5·0–5·9	2	—
Total	14	19
Mean	3·0	1·8
Standard error	0·39	0·09

Table 4. *Serum protein-bound iodine ($PB^{127}I^{-}$) concentrations in children of Horana (endemic goitre area) and in controls*

Serum $PB^{127}I$ (μg/100 ml)	No. of persons	
	Horana (endemic)	Control*
< 3·0	—	—
3·0–3·9	1	—
4·0–4·9	6	6
5·0–5·9	3	2
6·0–6·9	6	—
7·0–7·9	2	1
Mean $PB^{127}I$ (μg/100 ml)	5·6	5·1
Standard error	0·31	0·45

* From Ramalingaswami *et al.* (1961).

Table 5. *Serum protein-bound radioactive iodine ($PB^{131}I$) clearance and plasma inorganic iodide concentrations in residents of Horana, Ceylon (endemic goitre area) and in controls*

Measurement	Horana (endemic)		Controls	
	No. of patients	Mean clearance	No. of subjects	Mean value
$PB^{131}I$ clearance (% dose/l)	13	1·090 ± 0·14	15	0·11*
Plasma inorganic iodide concentration (μg/100 ml plasma)	14	0·089 ± 0·013	10	0·190 ± 0·045†

* Control from Ahuja & Kochupillai (1967); standard error not available.
† Control from Harden *et al.* (1965).

Serum protein-bound iodine ($PB^{127}I$)

$PB^{127}I$ concentration in children with goitre from area 1 (endemic) and of a non-endemic area (Delhi, India) are shown in Table 4. The $PB^{127}I$ concentrations in children of the endemic area were within normal limits.

Serum protein-bound radioactive iodine ($PB^{131}I$) at 48 h

The mean concentration of $PB^{131}I$ in goitrous children was 1·09% of the administered dose/l plasma, which was significantly greater than the value for the controls. It is noteworthy that there was no overlap and even the lowest value of 0·43 observed in the endemic area was higher than the highest value of 0·14 observed in the controls (Table 5).

Iodine content of drinking water and urine

The mean iodine contents of the samples of drinking water from the goitre areas of Horana and Galle were 1·34 and 1·16 μg/l respectively. By comparison, water from Jaffna, a non-endemic area, contained 9·2 μg iodine/l. The mean stable iodide concentration in urine of six children with endemic goitre was 20·15 μg/g creatinine (Table 6). Unfortunately, urine from the children of the control area could not be collected.

Table 6. *Urinary iodide excretion in male schoolchildren of Horana (endemic goitre area) in Ceylon*

Subject	Age (years)	Urinary iodide (μg/g creatinine)
B.A.G.	11	20·2
D.C.	11	21·1
G.T.U.	10	11·3
R.D.K.	10	24·3
D.D.P.	10	30·9
P.D.N.	10	13·1
Mean		20·15

DISCUSSION

The results of our study and of the earlier reports by Wilson (1950, 1954) and Mahadeva & Shanmuganathan (1967) indicate that endemic goitre is an important public health problem in Ceylon. Several factors have been incriminated in the pathogenesis of endemic goitre (McCarrison, 1917; Stott, Bhatia, Lal & Rai, 1931; Wilson, 1941; Greer & Astwood, 1948; Clements & Wishart, 1956). Although most of the world's endemic goitre is recognized to be due to environmental iodine deficiency (Follis, 1964; McGirr & Greig, 1968), there is good evidence that other factors are responsible in some areas such as Tasmania (Clements & Wishart, 1956), Finland (Petola, 1965), Chile (Beckers, Barzelatto, Stevenson, Gianetti, Pardo, Babadilla & De Visscher, 1965), Nigeria (Ekpechi, 1967) and Eastern Kentucky, USA (London, Koutras, Pressman & Vought, 1965). Recently, Vought, London & Stebbing (1967) presented evidence supporting the concept originally put forward by McCarrison 60 years ago for Himalayan endemic goitre, that pollution of water may be an important aetiological factor in the endemic goitre in Northern Virginia, USA. In 1954, Wilson (1954) and, recently, Mahadeva & Shanmuganathan (1967) felt that iodine deficiency might not be responsible for endemic goitre in Ceylon in spite of the fact that both groups of workers recorded a low iodine content of drinking water in the endemic area.

Endemic goitre in Ceylon is characterized by high 24 h thyroidal uptake of ^{131}I, raised thyroidal iodide clearance and 48 h PB^{131}I, lowered excretion of urinary iodide and low PII. Several workers have reported high thyroidal uptake of ^{131}I in endemic goitre in other countries (Stanbury *et al.* 1954; Roche *et al.* 1957; Ramalingaswami *et al.* 1961; Follis *et al.* 1962). A raised uptake of ^{131}I along with a high rate of thyroidal iodide clearance (neck:thigh ratio) in the permanent residents of the endemic area is strongly suggestive of environmental iodine deficiency. The high uptakes are evidence against the existence of a goitrogen of the type suggested by Clements in Tasmania (Clements & Wishart, 1956) or pollution of water as proposed by Vought *et al.* (1967) in Northern Virginia, USA, for such factors would have depressed the thyroidal uptake of iodide.

The findings of a low iodine content of water in the endemic area and low levels of urinary iodide and PII further confirm that endemic goitre in Ceylon is due to environmental iodine deficiency. There is thus no laboratory or epidemiological evidence to support the view expressed earlier by Wilson (1954), and Mahadeva & Shanmuganathan (1967), that the endemic goitre in Ceylon may be due to goitrogens.

The difficulties of obtaining a satisfactory 24 h urine sample under field conditions are well appreciated. Follis *et al.* (1962), while investigating endemic goitre in Thailand, used the concentration of iodine/g creatinine in a casual sample of urine as an index of the iodine intake in the population. Results obtained by this technique correlate very well with the 24 h urinary excretion of iodide (Vought, London, Lutwak & Dublin, 1963). On the basis of information obtained from 2000 urine samples collected in endemic and non-endemic areas, Follis (1964) reported that most individuals from areas where intake of iodine was presumed to be adequate excreted in the urine 50 μg iodide/g creatinine, whereas a large majority of residents from iodide-deficient areas excreted less than 25 μg iodide/g creatinine. In our study, schoolchildren of the endemic area excreted in the urine, on an average, 20·15 μg iodide/g creatinine. In Himalayan endemic goitre, 24 h urinary iodide excretion was less than 10 μg (Ramalingaswami *et al.* 1961). Roche, Perinetti & Barbeito (1961) reported urinary iodide excretion of 21·2 μg/d in a tribe of Venezuelan Indians who did not have goitre but who showed high uptakes of ^{131}I. In New Guinea (Choufoer *et al.* 1963), patients with endemic goitre excreted on the average 5·0 μg of iodine/d. Our results thus indicate that although urinary iodide excretion in patients with endemic goitre is lower than normal, it is generally higher than that observed in several other endemic areas, indicating that the environmental iodine deficiency is mild in the endemic area in Ceylon.

Plasma inorganic iodide concentration is probably one of the best indicators of iodine intake. In the study reported here PII concentration is significantly lowered in schoolchildren with goitre from the endemic area. Our findings are in agreement with those of Wayne, Koutras & Alexander (1964); these authors also reported low PII values in patients with simple goitre in Glasgow who also showed other evidence of iodine deficiency, such as raised ^{131}I uptake and lowered urinary iodide excretion.

Serum PB^{127}I concentrations are within normal limits in Ceylon. This is at variance with those reported in patients with endemic goitre from India (Raman & Beierwaltes,

1959; Ramalingaswami *et al.* 1961), Congo (De Visscher *et al.* 1961) and New Guinea (Choufoer *et al.* 1963). However, it is possible that because of adaptation of the gland, for example by increased uptake of iodine and faster release of the thyroid hormones into circulation, the serum PB^{127}I concentrations may not be altered in Ceylon where environmental iodine deficiency is mild. In fact, the serum PB^{127}I values are within normal limits in other mildly endemic countries such as Argentina, Holland, Finland and Italy (Stanbury, 1958).

Raised plasma PB^{131}I concentration 48 h after the administration of ^{131}I, a feature of our study, has also been observed by several other workers (De Visscher *et al.* 1961; Choufoer *et al.* 1963; Srinivasan, Subramanian, Sinha, Deo & Ramalingaswami, 1964). Choufoer *et al.* (1963) suggest that it is an early manifestation of iodine deficiency and that the goitre appears later. Raised plasma PB^{131}I values may reflect increased turn-over of thyroid hormones, consequent upon increased activity of thyroid-stimulating hormone (TSH). In rats given an iodine-deficient diet thyroidal turn-over is faster (Bois & Larsson, 1958). Although we have no information about the status of TSH in the patients with endemic goitre in Ceylon, recently Adam, Kennedy, Choufoer & Querido (1968) have demonstrated high plasma TSH concentrations in endemic goitre in New Guinea.

Alternatively, raised PB^{131}I values in endemic goitre may be explained on the basis of a decrease in the intrathyroidal iodide pool. We were not able to obtain thyroid glands in Ceylon for estimation of iodide content. However, in Himalayan endemic goitre, both in man and animals, the iodide contents of the thyroid gland are low (Roy, Deo & Ramalingaswami, 1964).

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