

Pathophysiology of Himalayan endemic goiter¹

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The mountain slopes of the Himalayas, Alps, Pyrenees, and Andes have been the world's most notorious foci of endemic goiter (1). The northern frontiers of India extending from Kashmir in the west to Assam in the east form an extensive Himalayan goiter belt (2). Forty million persons are believed to be exposed to the risk of goiter in this belt and approximately nine million are afflicted with it. The pioneering work of the late Sir Robert McCarrison in the early part of this century focused attention not only on the extent of the Himalayan endemic goiter but also on its cause and on the reaction of the thyroid to various noxious influences, i.e., nutritional, toxic, and infective (3).

Despite all that has been written about the etiology and pathogenesis of endemic goiter, many problems still remain unresolved. The study by Stanbury and his co-workers (4), the first of its kind, of the metabolism of iodine in people with endemic goiter in western Argentina, employing radioactive iodine and modern chemical methods of assay of stable iodine, indicated that lack of iodine in the diet was the most probable cause in that area. Similar observations confirming the primary role of iodine deficiency have been made in other parts of the world such as Venezuela, Holland, Finland, Greece, Eastern and Western New Guinea, and the Congo. Studies in Tasmania, Scandinavia, Central Europe, and Colombia suggest the operation of other goitrogenic factors of dietary origin in the development of the disease (5). It has been suggested that the iodide deficiency hypothesis cannot explain endemic goiter in every area and that other factors may be significant. A naturally occurring goitrogenic substance was isolated from human foods (6). Clements (7) felt that endemic goiter among the children in Tasmania was probably due to ingestion of a goitrogenic substance capable of interfering with the iodide trapping mechanism. There are other scattered observations that incriminate factors other than iodide deficiency (8–10), but to this date no naturally occurring goitrogen has been shown

conclusively to be responsible for endemic goiter in any community, although it may be playing an adjunct role in some areas (11). Even in Tasmania where there seemed to be a definite possibility of a goitrogen playing a role, recent studies indicate that iodine administration can effectively reduce goiter prevalence there (11, 12).

The etiological factors of Himalayan and sub-Himalayan endemic goiter have been under investigation for the past 16 years in our laboratory and the results of some of these studies have been reported (13–16). The studies carried out so far in various areas in the Himalayan goiter belt included field surveys of prevalence, clinical evaluation, and biochemical investigations. In recent years, our studies have been extended to include Nepal (which is in the Himalayan goiter belt), Ceylon, and further studies were made in the Indian goiter belt itself. This paper presents the results of these more recent studies. The areas where studies of endemic goiter have been made by our group in India, Nepal, and Ceylon are indicated in Fig. 1. The studies made in Ceylon have been published (17), and are not discussed in detail here again; only the results obtained are given in relation to those obtained in the Himalayan goiter belt in India and Nepal.

The results of studies made in goats living in the endemic area and in rats under an experimental iodine-deficient regimen in our laboratories are also presented in brief as they throw considerable light on the findings obtained in human studies.

Materials and methods

As indicated in Fig. 1, the study was carried out in several places located in the goiter belt but widely separated from each other in each of the three countries, India, Nepal, and Ceylon.

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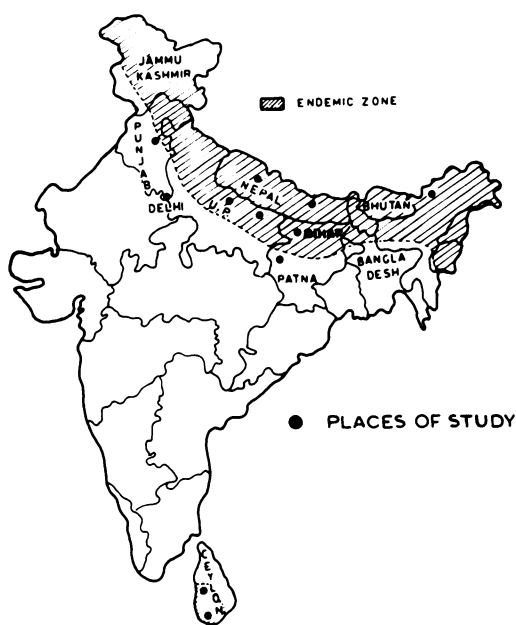


FIG. 1. Map showing the goiter belt and areas studied.

India

Bihar. The study was made in the township of Betia in the State of Bihar. A survey of several hundred schoolchildren in Betia showed a goiter prevalence of nearly 100%. The schoolchildren who had visible goiter of varying grades were studied for ^{131}I uptakes and biochemical parameters. Some adult men and women who were permanent residents of this area were also investigated.

Uttar Pradesh. The study was carried out in Padrauna, located in Deoria district of eastern Uttar Pradesh (U.P.) A rapid clinical survey was conducted in two schools, one college and neighboring villages. In all, a total of 1,300 subjects were examined. The prevalence of goiter in the school children and inhabitants of surrounding villages was approximately 55%. Radioiodine and biochemical studies were performed among schoolchildren and a representative group of the adult population in this area.

Nepal

We surveyed two areas, one in Trishuli, situated roughly in the central part of Nepal and the other in Jumla, a valley situated in the high mountains of the northwestern section. Schoolchildren in both areas showed a goiter prevalence ranging between 74% and 100%. The villagers adjoining Trishuli had a frequency ratio of approximately 65%, whereas the residents of villages near Jumla showed a frequency of 87%. For detailed clinical studies and measurement of thyroid function, schoolchildren and adults of both sexes and who were permanent residents of the area were selected.

Studies in humans

Clinical assessments. To determine prevalence, the classification proposal by the late Prof. Ryle (18) was followed and clinical evaluation of thyroid status was made by looking for the well-known signs of hypo- and hyperthyroidism.

Radioiodine uptakes. Twenty-five to fifty microcuries of ^{131}I was administered orally as a rule, and neck uptakes were determined at the end of 24 hr. Uptakes at earlier and later intervals were also determined whenever feasible. The thyroid uptake of ^{131}I was measured with a Tracerlab Scintillation Probe (P-20D) (Tracerlab, Richmond, California) attached to a Tracerlab Rate Meter. The detector was kept at a distance of 254 mm from the neck. In Nepal, uptake measurements were performed using a scintillation probe especially designed for field studies by the Bhabha Atomic Research Centre, Trombay, Bombay, India.

Venous blood samples. These were collected in iodine-free glass containers; serum or plasma was separated and transported under ice to the laboratories of the Institute in Delhi within a few days of collection. Protein-bound iodine (PB^{127}I) in serum or plasma was estimated by the modified method of Barker and co-workers (19) and the results were expressed as micrograms/100 ml.

For protein-bound radioactive iodine (PB^{131}I) determinations, 48 hr after a tracer dose of radioiodine blood samples were collected and serum separated. Proteins were precipitated in 1 or 2 ml of serum with zinc sulfate and sodium hydroxide. The precipitate was separated by centrifugation and ^{131}I activity in the precipitate measured in a well-type scintillation counter (Tracerlab). The results were expressed as percentage of dose administered per liter of serum.

Plasma inorganic iodide (PII) was estimated by the isotopic dilution technique, using a tracer dose of ^{131}I (20) according to the formula:

$$\text{PII} = \frac{\text{chemical I in urine (micrograms/100 ml)} \times ^{131}\text{I in plasma (percent of dose per milliliter)}}{^{131}\text{I in urine (percent of dose per milliliter)}}$$

Urinary iodide. This was estimated on casual urine samples, using the same method as for plasma PB^{127}I . Creatinine was estimated on the same samples by the alkaline picrate method and the results were expressed as micrograms of iodide per gram of creatinine.

To estimate the amount of iodide in drinking water, we again employed the Barker et al. procedure (19). The results were expressed as micrograms per liter.

T_3 suppression test. Triiodothyronine suppressibility was studied using the method of Werner and Spooner (21). Basal 24-hr ^{131}I uptakes were determined initially. After 8 days of triiodothyronine therapy at 120 $\mu\text{g/day}$ per person, 24-hr ^{131}I uptakes were repeated on the 8th day of therapy.

TSH stimulation test. A tracer dose of ^{131}I was administered orally on the 1st day and ^{131}I uptake was measured 3 hr after the dose. Ten international units of thyrotropin (Thyropar, Armour Pharmaceutical Co., Kankakee, Illinois) were then administered

intramuscularly. Twenty-four hours after the first tracer dose, residual thyroidal radioactivity was measured, and then a second tracer dose of ^{131}I was given orally to the fasting patient. A 3-hr uptake was again measured after correcting for residual activity from the first tracer.

Perchlorate or thiocyanate discharge test. A tracer dose of ^{131}I was administered orally and 2-hr neck uptakes were measured. At 2 hr, the subjects received orally either 500 mg potassium perchlorate or 1 g thiocyanate. One-hour and six-hour neck uptakes of the radioactive iodine were recorded after administration of the drug.

Iodoamino acid distribution in plasma. Plasma iodoamino acids were separated by ascending paper chromatography. The plasma samples, with the carrier, were chromatographed on Whatman No. 3 paper using butanol: ethanol: 2 N ammonia (5:1:2 v/v) solvent system. The chromatograms were sprayed with palladium chloride to identify the inorganic iodide spot and with ninhydrin in acetone to identify the iodoamino acids. The spots corresponding to origin, DIT, MIT, I, T_4 , and T_3 were cut out and ^{131}I activity was measured in a well-type scintillation counter (Tracerlab). The results were expressed as percentage of total radioactivity.

Studies in animals

Goat studies. Goats in the endemic area were given 75 to 100 μCi of ^{131}I 48 hr prior to being killed after which the thyroids were collected in ice and brought to the laboratory in Delhi. Thyroid glands from Delhi goats were collected in a similar manner. The ^{131}I incorporation in iodoproteins of these glands was studied using polyacrylamide gel electrophoresis and the incorporation in iodoamino acids was estimated by paper electrophoresis. Details of the methodology used is described elsewhere (16).

Rat studies. Forty albino rats, weighing between 130 and 160 g, were divided into four groups of 10 rats each. 1) *Group A* received a stock diet with an adequate amount of iodine. 2) *Group B* was given a low iodine diet obtained from Nutritional Biochemicals Corporation, Cleveland, Ohio. 3) *Group C* was fed a stock diet with an adequate amount of iodine and, in addition, each rat received orally 150 mg potassium perchlorate/day. 4) *Group D* received a stock diet with

an adequate amount of iodine plus an oral dose of 5 mg propylthiouracil/day.

The animals were kept on the above diet schedule for 45 days. After 45 days, each rat was injected with 5 μCi of ^{131}I intraperitoneally 24 hr before being killed. Then the thyroid glands were removed and ^{131}I incorporation in iodoproteins of these glands was studied in the same manner as described for the goat studies.

Results

The results obtained in the endemic areas of the three countries are presented in Tables 1–3. At the bottom of each table, corresponding values obtained in a nonendemic area (Delhi) and with identical methods of analysis being used are presented for comparison. Results in males and females are not shown, as they are not significantly different from one another. The data presented in the three tables deal mainly with schoolchildren.

Table 1 shows the values of 24-hr neck uptakes of ^{131}I and urinary stable iodide excretion. It is evident that in all the endemic areas studied, 24-hr uptakes are markedly elevated, whereas urinary iodide excretion is low as compared with the values obtained in the nonendemic area of Delhi. The mean uptake at 24 hr in Jumla (Nepal) is higher than that in other endemic areas studied, indicating a high degree of endemicity. This is also borne out by other indices. In Bihar, 2- and 6-hr ^{131}I neck uptakes were studied in 43 subjects. The mean uptakes at both intervals were markedly elevated; at 2 hr, the mean uptake was 55% and at 6 hr it was 67%. The ^{131}I uptakes in Padrauna (eastern U.P.) were followed up to 96 hr in 10 cases. The uptakes remained markedly high even at 96 hr in these subjects. The values for iodide excretion per gram of creatinine were

TABLE 1
Twenty-four-hour ^{131}I neck uptake and urinary iodide excretion in endemic goiter of India, Nepal, and Ceylon

Country	Place	Percent 24-hr neck uptake of ^{131}I	Urinary excretion of iodide, $\mu\text{g/g}$ creatinine
India	Uttar Pradesh	68.7 \pm 8.3 (70)	30.2 \pm 2.87 (46)
	Bihar	67.1 \pm 12.3 (43)	
Nepal	Trishuli	71.1 \pm 1.65 (41)	21.6 \pm 1.59 (40)
	Jumla	84.7 \pm 1.88 (17)	20.2 \pm 3.04 (11)
Ceylon	Horana	77.6 (33)	20.15 \pm 3.00 (6)
Controls values ^a	Delhi	42.4 \pm 3.00 (15)	76.4 \pm 10.2 (10)

Numbers in parentheses indicate number of samples analyzed.

^a From (29).

TABLE 2
Serum protein-bound iodine, protein-bound radioiodine, and plasma inorganic iodide values in endemic goiter areas

Country	Place	PB ¹²⁷ I, $\mu\text{g}/100\text{ ml}$	PB ¹³¹ I, % dose/liter	PII, $\mu\text{g}/100\text{ ml}$
India	Uttar Pradesh	3.87 \pm 0.31 (24)	0.53 \pm 0.130 (11)	0.096 \pm 0.021 (12)
	Bihar	3.00 \pm 1.43 (13)		
Nepal	Trishuli	4.10 \pm 0.26 (15)	1.87 \pm 0.625 (12)	0.088 \pm 0.017 (8)
	Jumla	4.43 \pm 0.44 (12)	1.53 \pm 0.504 (12)	
Ceylon	Horana	5.60 \pm 0.31 (18)	1.09 \pm 0.14 (13)	0.089 \pm 0.013 (14)
Control values	Delhi ^a	6.00 \pm 0.70 (15)	0.115 \pm 0.02 (15)	0.137 \pm 0.018 (10)

Numbers in parentheses indicate number of samples analyzed.

^aFrom (29).

TABLE 3
Mean iodine content of water samples in endemic goiter.

Country	Place	Iodine content of water, $\mu\text{g}/\text{liter}$
India	Uttar Pradesh	0.298 (11)
	Bihar	0.205 (8)
Nepal	Trishuli	0.125 (5)
	Jumla	0.107 (4)
Ceylon	Horana	1.25 (4)
Control values	Delhi	9.00 (3)

Numbers in parentheses indicate the number of samples analyzed.

comparable in all the areas of endemic goiter studied and were less than 40 μg , the lower limit of normal as suggested by Follis and co-workers (22).

Table 2 gives the data on protein-bound iodine, protein-bound radioactive iodine, and plasma inorganic iodide. The values for PB¹²⁷I from endemic goiter areas in India and Nepal were either below normal or near the lower limit of normal. The PB¹²⁷I values obtained from Ceylon were, however, comparable to the values obtained from the nonendemic area of (Delhi). Endemic goiter in Ceylon is not as severe as in India and Nepal as is borne out by the prevalence rates of goiter. The PB¹³¹I values in plasma 48 hr after administration of a tracer dose of ¹³¹I in all the areas studied were extremely high. This indicates the rapidity with which the thyroid hormones are synthesized and released into the circulation. Obviously, the iodide pool in the thyroid is markedly diminished. A significant reduction in plasma inor-

ganic iodide concentration is evident in all the endemic areas as compared with the values obtained from the nonendemic area.

Table 3 shows the iodine content of water from endemic areas in the three countries. Iodine content of water in Jumla (Nepal) was the lowest of all the endemic areas studied. Indeed, the endemicity of Jumla represents one of the most severe we have encountered. It was at Jumla that a striking number of deaf mutes, cretins, and persons with various other disturbances of mental and physical development were encountered.

Triiodothyronine suppression was carried out in 12 subjects, 6 in Pandrauna (eastern U.P.) and 6 in Nepal. Of the six subjects studied in U.P., five showed suppression of 45 to 50% of the basal value, whereas one showed 38% suppression. In Nepal, of six subjects, two showed suppression of uptakes up to 46 to 48% of the basal value; in three others, the suppression was approximately 29 to 38%, and one showed no response.

A TSH stimulation test was done in four subjects in U.P. and two in Nepal. None of the persons studied showed any stimulation after administration of TSH, indicating that their thyroids were already being stimulated maximally.

The perchlorate or thiocyanate discharge test was carried out in eight subjects from eastern U.P. and six in Bihar. None showed any discharge after receiving the drug.

Table 4 shows iodoamino acid distribution in plasma 48 hr after a tracer dose of radioiodine was administered in eight subjects. These samples were collected during the studies carried out in Nepal. It is evident that in all

except one, the proportion of radioactivity found in triiodothyronine is equal to or greater than that of thyroxine. In normal persons, the proportion of radioactivity in triiodothyronine is approximately 5% of the total radioactivity in iodothyronine (23). There would seem to be

a preferential secretion of triiodothyronine in endemic goiter.

Animal studies

Goats. Table 5 shows the distribution of iodoamino acids in the thyroid glands of goats living in endemic and control areas. Thyroids of goats from the endemic area have higher MIT/DIT and T_3/T_4 ratios than those from the control area.

Table 6 shows the ^{131}I incorporation in iodoproteins of thyroid glands of goats from endemic and control areas. The results show that there is more incorporation in 27S iodoproteins in the glands from the endemic area than in those from Delhi. Consequently, incorporation of ^{131}I in 19S iodoprotein in glands of goats living in endemic areas is less than those living in Delhi.

TABLE 4
Iodoamino acid distribution in plasma^a

Subject no.	Original	DIT	MIT	I	T ₄	T ₃
14	19.0	3.6	11.1	1.6	25.0	40.1
21	3.4	10.1	5.0	16.9	28.8	35.5
65	0.0	4.5	7.2	11.8	35.5	40.9
66	0.0	2.1	18.2	13.9	30.1	35.5
74	12.0	0.0		28.0	48.0	12.0
84	5.0	8.9		18.8	31.1	35.5
85	18.8	15.3		8.2	28.2	29.3
86	6.9	21.4		18.8	25.5	28.3

^a Expressed as percent of total radioactivity.

TABLE 5
Distribution of iodoamino acids in the goat thyroid glands from endemic and control areas^a

Area	Original	DIT	MIT	I	T ₄	T ₃
Endemic (10)	0.7 ± 0.16	35.9 ± 1.71	39.1 ± 2.42	16.3 ± 2.42	2.4 ± 0.43	6.2 ± 0.75
Control (10)	3.3 ± 0.35	53.8 ± 1.26	30.8 ± 0.89	6.4 ± 0.98	4.3 ± 0.47	0.9 ± 0.10

Numbers in parentheses indicate the number of goat glands analyzed.

^a Expressed as percent of total radioactivity.

TABLE 6
Gel electrophoretic pattern of goat thyroid proteins from endemic and control areas^a

Area	33S	27S	19S	12S	8S	3S
Endemic (7)	6.4 ± 1.87	24.7 ± 4.34	65.8 ± 3.41	1.1 ± 0.39	1.2 ± 0.24	0.9 ± 0.29
Control (9)	5.5 ± 0.33	10.9 ± 0.33	80.3 ± 0.75	1.5 ± 0.27	1.0 ± 0.23	1.0 ± 0.17

Numbers in parentheses indicate the number of goat glands analyzed.

^a Expressed as percent of total radioactivity.

TABLE 7
Gel electrophoretic pattern of rat thyroid proteins in different experimental groups^a

Group	No. of animals	33S	27S	19S	12S	8S	3S	Total I contents of gland, µg	Total weight of gland, mg
Stock diet	10	2.10 ± 0.24	10.04 ± 0.65	83.00 ± 0.86	2.70 ± 0.42	1.22 ± 0.18	0.72 ± 0.13	93.00 ± 3.78	28.0 ± 1.96
Low iodine diet	10	4.58 ± 0.46	26.35 ± 0.50	66.06 ± 0.87	1.45 ± 0.36	0.60 ± 0.11	0.51 ± 0.09	24.0 ± 1.60	54.5 ± 4.37
KClO ₄ treated	10	5.00 ± 0.34	30.00 ± 0.85	61.40 ± 0.74	2.15 ± 0.23	1.21 ± 0.25	0.61 ± 0.10	15.5 ± 0.88	67.5 ± 3.11
PTU treated	10	2.47 ± 0.28	19.35 ± 0.62	74.20 ± 1.03	2.11 ± 0.32	1.11 ± 0.19	0.68 ± 0.14	25.0 ± 2.71	66.00 ± 2.33

^a Expressed as percent of total radioactivity.

Rats. Table 7 shows ^{131}I incorporation in iodoproteins of rat thyroid glands in different experimental groups. The incorporation in 27S iodoprotein was highest in the group receiving potassium perchlorate followed by the low iodine group, then the PTU treated group and then lastly, the stock diet groups. There was consequential reduction in ^{131}I incorporation in 19S iodoprotein in these groups. The ^{131}I incorporation in 27S iodoprotein seems to be inversely related to the amount of iodine present in the gland.

Thyroid histology

Human thyroids obtained at autopsy from the Indian goiter belt and from nonendemic areas in India have been studied (15). Even at birth the gland is enlarged two to three times normal in the goiter zone and shows intense hyperplasia. The hyperplasia and hypertrophy of the thyroid continues to be persistent at all ages with little or no involution and colloid accumulation. Nodular transformation takes place at multiple sites throughout the gland at a relatively young age in the people of the Himalayas and progresses with age.

Discussion

Studies of iodine metabolism in the Himalayan goiter zones of India and Nepal showed: *a*) markedly increased avidity of the thyroid to radioiodine, *b*) reduced excretion of stable iodine in urine, *c*) extremely low levels of iodine in the drinking water, *d*) normal or reduced protein-bound iodine in plasma, and *e*) low inorganic iodide concentration in plasma. These findings are compatible with the hypothesis that environmental deficiency of iodine is the primary factor responsible for endemic goiter in these areas. In Ceylon, the protein-bound iodine in plasma was normal and the iodine content of drinking water was not as low as observed in other areas. This may be because the endemicity is not as severe in Ceylon as compared with the Himalayas. Goiter prevalence rates confirm this.

Perchlorate or thiocyanate discharge tests provided no evidence of a peroxidase defect. It appears unlikely that genetic isolation and consequent inherited defects in the synthesis of thyroid hormones play a major part in the etiology. The responses are not indicative of goitrogens. The data suggest that iodine defi-

ciency is more severe in Nepal and India than in Ceylon.

The thyroid makes an interesting adaptation to maintain internal homeostasis in the face of severe iodine deficiency. The increase in uptake and clearance of ^{131}I and the rapid turnover of labeled iodine within the gland are reflections of attempted functional compensation. The preferential synthesis and secretion of triiodothyronine is another compensatory mechanism, for in its manufacture, an atom of iodine is conserved for each molecule of hormone, and, in the process, a much more potent hormone is formed. Triiodothyronine suppresses the activity of the gland in most subjects studied, indicating that the gland is under TSH stimulation. Recently, in another area in eastern U.P., studies were carried out by us to measure the levels of circulating TSH and the reserves of TSH in endemic goiter by stimulating the pituitary with TRH (24). These studies indicate that TSH levels are high in endemic goiter as are also the reserves of TSH. It is possible that the levels of TRH are also increased in this condition. The fact that TSH administration could not further stimulate the already stimulated thyroid is an indication that the gland is already subjected to maximal stimulation. Despite all this elaborate adaptation to iodine deficiency, in severely endemic areas like Nepal, there is evidence that in some persons this mechanism has failed to maintain internal homeostasis, as reflected in low PB^{127}I in plasma and in the emergence of symptoms of hypothyroidism. If the hypothesis that endemic deaf mutism and cretinism commonly seen in the Himalayan endemic region are manifestations of earlier intrauterine damage as a result of iodine deficiency or hypothyroidism, or both, is accepted, then the adaptive failure assumes even greater proportions in this population.

We conducted a study of goats to investigate further the mechanism of adaptation of thyroid gland to iodine deficiency. Earlier work from this laboratory (15) revealed that goat thyroid glands from endemic areas show pathophysiological changes similar to those found in the glands of humans living in the same area. Goats raised in Delhi, an area that has abundant iodine and that is free from endemic goiter, served as controls. The results showed that the thyroids from the endemic area had higher MIT/DIT and T_3/T_4 ratios than those from the control area. Presumably, more T_3 was being

synthesized in endemic glands than T_4 . As mentioned earlier, we had observed more T_3 in the circulation of subjects with endemic goiter. A similar finding was reported by Ibbertson et al. (25) in the goitrous population from northeastern Nepal.

The mechanism of thyroid hormone synthesis was investigated in detail by Taurog and Howells (26). They showed that the tertiary structure of thyroglobulin is important in the coupling reaction of iodotyrosines to form thyroid hormones. The coupling reaction is intramolecular and perhaps is not enzyme mediated (27). Thus, the tertiary structure of thyroglobulin is such that the DIT residues are situated in a favorable position at the coupling site. As there are more MIT residues than DIT in iodine-deficient glands, it is probable that at the coupling site in the thyroglobulin molecule, instead of two DIT residues there may be one MIT and one DIT residue in these glands. This would result in the production of more T_3 than T_4 , which, in endemic goiter then may be viewed as a direct consequence of iodine deficiency rather than as an adaptive mechanism.

The incorporation of ^{131}I in iodoproteins showed that there is more incorporation in 27S iodoproteins in the glands of those living in an endemic area than in those from the Delhi area. Consequently, incorporation of ^{131}I in 19S in the former is relatively less than that in the latter. The 27S iodoprotein has the same subunits as that of 19S (thyroglobulin) and has a high iodine content compared with 19S (thyroglobulin). 27S iodoprotein accounts for a significant fraction of iodine stores in the thyroid gland (28). In the thyroid of goats residing in endemic areas, the synthesis of more 27S iodoprotein, which is more iodinated and can produce more hormone mole per mole than 19S, may be considered as an adaptive mechanism of the gland to iodine deficiency. It is logical to consider that just as 19S iodoprotein in iodine deficiency can produce more T_3 than T_4 , 27S iodoprotein may also do so under similar conditions, provided that the mechanism of coupling reaction in both iodoproteins is similar.

In order to explore which factors, such as iodine concentration in the gland or TSH influence, are responsible for differential aggre-

gation of subunits to form more 27S iodoprotein in iodine-deficient glands, experiments using rats were conducted. The results indicate that the iodine concentration in the gland per se has more influence on the differential aggregation of the subunits to form either 27S or 19S than TSH.

The thyroid makes an adaptation to maintain internal homeostasis in iodine deficiency. Severe iodine deficiency produces low PBI values with increased circulating TSH levels. There is a possibility of more TRH influence in such a situation. Thus, the control seems to be both at the hypothalamus-pituitary axis and the pituitary-thyroid axis. Within the gland, due to low iodine concentration, there is presumably preferential formation of 27S iodoprotein, which is more efficient in producing thyroid hormones than 19S (thyroglobulin). The inter-relationship between all these events is the present fascination in the study of endemic goiter.

Summary

Goiter prevalence and iodine metabolism were studied in areas of endemic goiter in the Himalayas in India and Nepal. Similar studies were also made in Ceylon. The results are compatible with the hypothesis that severe environmental deficiency of iodide is the primary factor responsible for endemic goiter in these areas. The endemicity was less severe in Ceylon than in India and Nepal. The thyroid glands of persons living in endemic areas show an interesting adaptive response to maintain internal homeostasis in the face of severe iodine deficiency.

The mechanism of this adaptation was studied in thyroids of goats raised in endemic and nonendemic areas. Thyroids of goats living in an area of severe iodine deficiency showed higher MIT/DIT and T_3/T_4 ratios than glands of those in an area of iodine abundance. There was a higher incorporation of ^{131}I in 27S iodoproteins in the iodide-deficient glands. A decrease in iodine concentration of the thyroid and an increase in circulating TSH levels are possibly involved in mediating this response but of the two, the former mechanism seems more likely than the latter. ❏



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