INTRODUCTION
The element iodine (Greek world) was discovered by Courtois in 1811, though the discovery was announced in 1813. The trace element iodine with an atomic weight of 127, occupies the sixty-first place in the order of abundance of elements in the earth's crust.

Iodine is an essential micronutrient for all forms of life. It is an essential element for thyroid function, necessary for normal growth, development and functioning of the brain and body (WHO/UNICEF/ICCIDD, 1994). It is required in microquantities for the synthesis of thyroid hormone by the thyroid gland. Thyroid hormones have physiological effects causing alterations in essentially all metabolic pathways and organs; they modulate oxygen consumption and the metabolism of protein, carbohydrate, lipid and vitamins.

Normal daily requirement of iodine is 100-150 microgram for adolescents and adults (National Academy of Science-NAS, 1989). Similar recommendation for iodine intake have been made in the United States and other Countries (FAO/WHO, 1988). The recommendations made by the Indian Council of Medical Research (ICMR) for Indians is 150 microgram per day. The Recommended Dietary Allowances (RDA) of iodine given in Table-1. Ninety percent of daily iodine requirement is met from the food, while the rest is (ten percent) met from drinking water (Maeyer et al, 1979). Iodine cannot be stored for long a time in the body, tiny amounts must be consumed regularly, but food grown in iodine poor soil will not provide sufficient dietary iodine. The main causes of iodine deficiency is low iodine contents in foods and water.

Sources of iodine

The ocean is the primary source of iodine in the world. The inorganic environment presents the cycle of iodine. Iodine from the sea is carried with the rain and precipitated on the soil where it is washed out and carried back to the sea. The iodine cycle is illustrated in Figure-1. Iodine is added to the atmosphere by photo oxidation of iodide in seawater and falls back to the earth with rains and sea mist, where it is retained by the soil and plants and returned to the ocean via rivers. Contribution to iodine also originates from human (sewage and fossil fuel combustion) and animal sources (Vought, 1972). Hence, there is gradual
IODINE CYCLE IN NATURE

Source: The story of iodine deficiency (Hetzel, 1988)
Table-1: Recommended dietary allowances of iodine (RDA).

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Group</th>
<th>RDA (µg /day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Infants [0-12 months]</td>
<td>90</td>
</tr>
<tr>
<td>2.</td>
<td>Children [2-6 years]</td>
<td>90</td>
</tr>
<tr>
<td>3.</td>
<td>School children [7-12 years]</td>
<td>120</td>
</tr>
<tr>
<td>4.</td>
<td>Adults [beyond 12 years]</td>
<td>150</td>
</tr>
<tr>
<td>5.</td>
<td>Pregnant and lactating women</td>
<td>200</td>
</tr>
</tbody>
</table>

incremental increase in the iodine content of soil but glaciations by removal of topsoil deplete vast areas and are then poor in iodine. Leaching by rain and periodic flooding also depletes plain areas from iodine.

Ocean waters contain about 60 μg per liter of iodine mainly as iodate whereas surface water contains an average 1.0 μg per liter of iodine mainly as iodide (Fleischer, 1974). Because of great variation in the iodine content of terrestrial waters, there is a lack of uniformity of estimates by the various authors. Sea salt also contains very little iodine.

**Iodine content of terrestrial plants**

The iodine content of terrestrial plants varies considerably. In general it is proportional to the iodine content of the soil and the water in the area. Iodine uptake by plants is proportionate to the iodine present in the environment and that explains why the same food item may have a widely different iodine content depending on the locality where it has been produced. Most terrestrial plants have rather low iodine content averaging 1.0 mg per kg dry weight compared to 30-1500 mg per kg for plankton and some algae which actively concentrate iodine. Most plant iodine is in the inorganic form, however in corals and sponges most iodine is in the form of iodotyrosine (Matovinovic et al, 1974). Coal and oil contain larger amounts of iodine and hence on combustion they contribute substantially high amounts to atmospheric iodine.

Many additives markedly increase the iodine content of food. Feeding seaweed to the dairy cattle in Norway greatly increased the iodine content of milk (Renna and Stave land, 1974). In the United States the iodine content of bread was increased by the use of iodate (London, 1965). Adding iodine to the forage in several ways increases the iodine content of milk and dairy products. Iodine content of milk is increased by the use of iodophors for cleaning of udders.

**Iodine content of foodstuff**

Iodine content of some common Indian foods is given in Table-2. The data suggests that the iodine content of foods in the goitrous region was much less
when compared to that of the non-goitrous region. Foodstuff such as cereals, millets, pulses and oilseeds were considerably low in iodine in the goitrous areas when compared to non-goitrous areas. Recent estimated data was not available for the iodine content of vegetables and fruits of goitrous areas. Iodine content of foodstuff is indirectly proportional to the amount of iodine present in the soil and water. Due to low iodine content of soil, water and foods the region is suggested as goitrous, having cases of goitre.

Iodine contents of regional diets

Iodine content of regional diets is given in Table-3. The diets consumed by the low socio economic group and high socio economic group of different states of iodine are well above the daily requirement, though the diets of low socio economic group are low in iodine content when compared to the high socio economic group. Hence the daily requirement is met in both the groups, which is above 150 µg /day. The states mentioned in Table-3 such as Gujarat, Maharasthra, U.P.West Bengal, Kerala are now recently also known as iodine deficient areas though the diets contain sufficient amount of iodine. Iodine should be provided by the diet consumed, as it is an essential constituent of the thyroid hormones.

Iodine in human and animal tissue

The healthy human body contains a total of 15 - 20 mg iodine of which 70 - 80 % is present in the thyroid gland. It is found that the ovaries, pituatory gland, bile and salivary glands are appreciably higher in iodine than most other thyroidal tissue (Underwood, 1977).

The iodine content in animals depends on the concentration of this element in the plants on which they feed.

The iodine content of meat is on the whole higher than that of vegetables. In the marine and terrestrial vertebrates most of the iodine is in the thyroid gland (Matovinivic et al., 1974).
<table>
<thead>
<tr>
<th>Foods</th>
<th>Region</th>
<th>Goitrous</th>
<th>Non-goitrous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cereals and millets</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rice</td>
<td>10</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Wheat</td>
<td>15</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Maize</td>
<td>11</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Bajara</td>
<td>26</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Sorghum</td>
<td>21</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td><strong>Pulses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soyabean</td>
<td>4</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Bengal gram</td>
<td>13</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Black gram</td>
<td>17</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Red gram</td>
<td>19</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Cow pea</td>
<td>22</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Horse gram</td>
<td>17</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Lentil</td>
<td>4</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td><strong>Oil seeds</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mustard</td>
<td>-</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Groundnut</td>
<td>14</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Sesame</td>
<td>29</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td><strong>Vegetables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amaranth leaves</td>
<td>8</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Cucumber</td>
<td>5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Spinach</td>
<td>-</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Curry leaves</td>
<td>-</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Tomato</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mint leaves</td>
<td>-</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Ladies finger</td>
<td>-</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cabbage</td>
<td>-</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Carrot</td>
<td>-</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Brinjal</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cauliflower</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Snake gourd</td>
<td>-</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Fruits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apple</td>
<td>-</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Orange</td>
<td>-</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Banana</td>
<td>-</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Grapes</td>
<td>-</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Papaya</td>
<td>-</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Iodine contents of regional diets (μg iodine supplied /day)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>State</th>
<th>Low socio economic group</th>
<th>High socio economic group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Andhra Pradesh</td>
<td>265.36</td>
<td>270.00</td>
</tr>
<tr>
<td>2.</td>
<td>Gujarat</td>
<td>198.45</td>
<td>206.11</td>
</tr>
<tr>
<td>3.</td>
<td>Karnataka</td>
<td>261.11</td>
<td>302.06</td>
</tr>
<tr>
<td>4.</td>
<td>Kerala</td>
<td>173.90</td>
<td>273.06</td>
</tr>
<tr>
<td>5.</td>
<td>Madhya Pradesh</td>
<td>194.73</td>
<td>255.49</td>
</tr>
<tr>
<td>6.</td>
<td>Maharastra</td>
<td>194.73</td>
<td>255.49</td>
</tr>
<tr>
<td>7.</td>
<td>Orissa</td>
<td>264.36</td>
<td>280.94</td>
</tr>
<tr>
<td>8.</td>
<td>Tamilnadu</td>
<td>226.54</td>
<td>289.87</td>
</tr>
<tr>
<td>9.</td>
<td>Uttar Pradesh</td>
<td>198.38</td>
<td>224.37</td>
</tr>
<tr>
<td>10.</td>
<td>West Bengal</td>
<td>212.94</td>
<td>237 11</td>
</tr>
</tbody>
</table>

Source: Pandya (1996)
The iodine present in the tissue is in the inorganic and organic forms. Most of the organic iodine in the extra thyroidal tissue consists of thyroxin bound to protein and triiodothyronine. The total concentration of iodine in the thyroid gland varies with the iodine intake, the age of the animal and with the activity of the gland. The normal healthy thyroid gland contains a total of 8-12 mg of iodine, which can be reduced to 1 mg or less in endemic goitre. Iodine exists in blood in both the forms. Organic iodide comprises of the minute concentration of free thyroid hormone and protein bound iodine (PBI). PBI includes small amounts of mono and di iodotyrosine as well as thyroid hormone. In the saliva, it is present in the inorganic form.

Absorption of iodine

Iodine occurs in food primarily as the reduced iodine but also in lower amounts as inorganic iodine or as an organically bound complex. The latter is freed from its organic component and the free iodine is reduced to iodide before its rapid absorption. Inorganic iodides are absorbed in all parts of the gastrointestinal tract but primarily in the small intestine. Some organically bound iodine is not absorbed and may be excreted in the feces but it represents a maximum of 2% of the ingested iodine. Even small amounts are excreted by sweat glands. Iodine may also be absorbed through epithelial cells of the skin and inhaled as a contaminant from the combustion of fossil fuels.

Once absorbed the iodine appears immediately in the blood stream, where it constitutes the major part of the "iodide pool" - all extracellular iodide. The thyroid gland has to trap about 60 µg iodine per day to maintain an adequate supply of thyroxin. This is possible because of the very active iodide trapping mechanism, which maintains a gradient of 100:1 between the thyroid cell and the extracellular fluid. Thyroid gland absorbs about 30% of the iodide in the blood plasma and the rest is taken up by the kidney to be excreted in the urine.

The excretion of iodine not used by the thyroid gland provides protection against the accumulation of toxic levels in other tissues. Certain anions compete with iodide for transport, among these are bromide, perchlorate, thiocyanate and
other anions of approximately the same charge and molecular size but these are concentrated selectively very little, if at all.

Iodine absorption is usually complete but may be delayed in protein energy malnutrition (PEM). Loss of iodine content up to an extent of 50% has been shown in animal foods and other organic iodine compounds due to incomplete absorption (Koutras, 1996).

The thyroid gland

The human thyroid gland consists of two lobes located immediately below the larynx on either side of and anterior to the trachea Figure-2. Normally the right lobe is slightly larger than the left one. Thyroids are present in all vertebrates but they vary in size and shape and anatomic position. The function of the thyroid is to elaborate, store and discharge secretions that are concerned principally with the regulation of metabolic rate. The hormonal variants that derive from the thyroid gland are referred to by the term thyroid hormones.

Two layers of connective tissue encapsulate the thyroid; the outer layer is continuous with the cervical fasica and is loosely connected to the inner capsule that adheres intimately to the surface of the gland. The normal adult thyroid gland weighs about 25-40 g, but it is one of the most labile organs of the body and its size fluctuates with age, reproductive stages, habitation and diet. Blood supply is from two superior thyroid arteries (arising from the external carotids) and two inferior thyroid arteries (arising from the subclavians). Normal blood flow is about 100 ml per minute.

Microscopically the thyroid consists of an aggregation of spherical or ovate cyst-like follicles of variable size. A single layer of cuboidal or low columnar cells line each follicle. The cavity of the follicle is filled with a vivid homogenous material known as the colloid of the gland (Figure-3). The major constituent of the colloid is the large lipoprotein known as the thyroglobulin, which contains the thyroid hormones within it's molecule. The colloid is a storage product of the secretory epithelium. It's density varies in different glands and in different follicles of the same gland. The amount of colloid fluctuates in pathologic glands and may
Figure-2: Thyroid Gland

Source: http://www/thyroid.org
Figure-3: Morphology and Histology of thyroid gland.

Source: http://www/thyroid.org
be reduced or increased by controlled experimental conditions. The thyroid of the normal rat contains nearly 100,000 follicles and these vary widely in size. The larger follicles are generally located near the periphery and the smaller ones in the center.

When the thyroid gland is in the inactive form there is a tendency for colloid to accumulate and for the epithelium to become low cuboidal or squamous. When it is over active the colloid is depleted and the epithelium becomes columnar and plicated (Figure-4). There is an extreme endoplasmic reticulum (ER) with dilated cisternae and laid with microsomes. This active ER is very much involved with the synthesis of thyroglobulin. Golgi apparatus is seen near the apical portion of the cell. Mitochondria and lysosomes are scattered throughout the cytoplasm. Microvilli are prominent along the apical surfaces of the cells and their number is increased following the administration of TSH. The thyroid cells probably secrete several enzymes into the follicular cavities.

The most outstanding feature of the gland is its ability to concentrate large amount of iodine, the amount of iodine within the gland may be 50 to 100 times that of the blood plasma. Thyroid gland absorbs iodine from the circulating blood and this is used for the production of thyroxine (T₄) and triiodothyronine (T₃). The thyroid gland secretes two significant hormones T₄ and T₃ that have a prolonged effect on the metabolic rate of the body. Iodine is required for the formation of these two hormones.

Metabolism

Once iodide enters in circulation, it gets distributed throughout the extracellular fluid. There is no significant binding of iodide ion in plasma. Only the thyroid gland is capable of utilizing iodine in the synthesis of the thyroid hormones.
Figure-4: Inactive and Overactive Thyroid

Source: Guyton (1981)
THYROID HORMONE SYNTHESIS

It may divided into three stages.

1. The accumulation or trapping of iodine from circulation
2. The iodination of tyrosine and
3. The proteolysis of thyroglobulin (Tonglet et al. 1962)

The accumulation or trapping of iodine from circulation

The first stage in the formation of thyroid hormone (as shown in Figure-5), is the transport of iodine from the extra cellular fluid into thyroid glandular cells and follicles. The basal membrane of the thyroid cell has a specific ability to transport the iodine activity to the interior of the cell. This is called "iodide trapping". In a normal gland the iodide pump concentrates iodide to about 30 times it's concentration in the blood. However, when the thyroid gland becomes maximally active the concentration ratio can rise to several times this value.

Inside the follicular cells the trapped iodide is rapidly oxidized to iodine (I₂) (for this process, the enzyme peroxidase and hydrogen peroxide are necessary), which is then capable of combining directly with the amino acid molecule, tyrosine.
Figure-5: Biosynthesis of thyroid hormones

Thyroperoxidase

DIT + DIT → Thyroxine (T₄)
  + Alanine.
  PA + NH₃

MIT + DIT → T₃ + Alanine
  PA + NH₃

DIT + MIT → “Reverse” T₃ + Alanine
  PA + NH₃

Oxidation of iodide

H₂O₂

Iodide (I⁻)

Iodinium (I⁺)
or HIO⁻ (Hypoiodate) or both

Tyrosine residue (In thyroglobulin)

Thyroperoxidase

MIT (in thyroglobulin) → DIT (in thyroglobulin)

I⁺ or HIO⁻

Thyroperoxidase

Alanine

PA + NH₃

* “Reverse” Tri-iodothyronine, T₃ (in thyroglobulin)

Tri-iodothyronine, T₃ (in thyroglobulin)

* Thyroxine, T₄ (in thyroglobulin)

Source: Chatterjiea (1998)
The iodination of tyrosine

The second stage in the formation of thyroid hormone is iodination of the tyrosine molecule, "organification" of thyroglobulin takes place, the iodine binds with the thyroglobulin molecule. Iodine binds with about one sixth of the tyrosine residues within the thyroglobulin molecule in association with the iodinase enzyme that causes the process to occur within seconds or minutes. Tyrosine is first iodized to MIT and then to DIT. One molecule of MIT couples with one molecule of DIT to give $T_3$, and two molecule of DIT couple to give $T_4$. After synthesis the thyroid hormones are stored in the thyroglobulin (Figure-6A).

The proteolysis of thyroglobulin

The greatest part of the iodine in the normal thyroid exists in the form of thyroglobulin, a large protein molecule, with a molecular weight of 660,000. Almost all the thyroglobulin in the normal gland is present as a soluble protein stored in the follicular lumen. The thyroid cells are typical protein secreting granular cells. The endoplasmic reticulum and Golgi apparatus synthesize and secrete this large glycoprotein, thyroglobulin into the follicles. This contains 140 tyrosine amino acid molecules and these are the major substances which combine with iodine to form thyroid hormone.

The enzymatic elaboration and breakdown of the thyroglobulin occurs continuously and this ensures a regular turnover of thyroglobulin. Thyroglobulin stored in the colloid is apparently retrieved into the follicle cell by a kind of pinocytosis. The proteinase enzyme present in the thyroid follicle cell digests the thyroglobulin molecules and releases the $T_3$ and $T_4$, which then diffuse through the base of the thyroid cell into the surrounding capillaries. Thus the thyroid hormones are released into the blood.
Figure-6A: Structure of Thyroid Hormones and Thyroglobulin.

Structure of the major iodoaminoacids in thyroglobulin:

TYROSINE

3-MONIOODOTYROSINE

3,5-DIODOTYROSINE

3,3',5'-TRIODOTHYRONINE ("Reverse" T₃)

3,5,3'-TRIODOTHYRONINE (T₃)

3,5,3',5'-TETRAIODOTHYRONINE (THYROXINE)

Source: Chatterjeea (1998)
Secretion

Over 90% of the thyroid hormones secreted from the thyroid gland is T₄ and about 10% is T₃. Approximately 90 µg of T₄ and 35 µg of T₃ per day are received by the tissues. Once the two hormones enter the peripheral tissue cells, T₃ is about four times potent in stimulating the cellular metabolism and causing the other cellular effects as T₄. On the other hand, the duration of action of T₄ is 4 or more times as long as the duration of action of T₃.

Transport

The bulk of the thyroid hormone in blood is bound to specific serum proteins, thyroxine binding globulin (TBG) and thyroxine binding pre-albumin (TBPA). TBG is the principal carrier of thyroid hormones in the human serum. About 0.02% of T₄ is free and about 99.9% bound. About 60% of T₄ is bound to TBG, 30% to TBPA and 10% to albumin. T₃ is bound to TBG and albumin but not to TBPA. About 0.2% of T₃ is free and about 99.8% is bound. 10% of plasma T₃ and T₄ is excreted by the liver in bile then reabsorbed from the intestinal track (Davidsohn and Bernard, 1977).

Catabolism

The liver and kidney are the chief organs concerned in the catabolism of the thyroid hormones. Since the liver is an important organ in the destruction of the excessive hormone and in the regulation of the biliary excretion mechanism, it plays an important role in regulating the thyroid hormone content of the body. T₄ and T₃ are conjugated as glucuronides in the liver and are passed through the bile into the intestine. Oxidative deamination also occurs in the liver, where hormones form pyruvic acid derivatives. Small amounts of T₃ and T₄ and their deaminated metabolites are excreted through bile in an unconjugated form. Both conjugate and free forms of T₄ are excreted in small amounts through kidneys. Certain metabolites of thyroid hormones may be reabsorbed from the intestine and these circulate repeatedly through the liver. The iodide produced is reutilized by the gland or excreted by the kidney. Only minute amount of organically bound iodine are lost through the kidneys. The body shows great economy in handling
it's iodine stores and retains most of the iodine freed though the metabolism of thyroid hormones.

REGULATION OF THYROTROPIN (TSH)

It is an anterior pituitary hormone, a glycoprotein with a molecular weight of 28,000. It increases the secretion of T₄ and T₃ by the thyroid gland. It's specific effects on the gland are:

1. Increased proteolysis of the thyroglobulin, resultant release of the thyroid hormones into the circulating blood.
2. Increased activity of the iodide pump, which increases the rate of iodide trapping.
3. Increased iodination of tyrosine and increased coupling to form the thyroid hormones.
4. Increased number of thyroid cells changing from cuboidal to columnar cells and much infolding of the thyroid epithelium.

In short TSH increases all the activities of the thyroid glandular cells. Normal TSH level in the serum is 0-10 micro units per ml (Nelson et al, 1972). High T₄ level in the blood inhibits the secretion of TSH; whereas low level in the blood stimulates the secretion. Depending on circulating T₄ levels in blood, TSH secretion is regulated which is called "Feed back" mechanism (Figure-6B). The thyroid feed back system consists of three main components – hypothalamus (secretes TRF), anterior pituitary (secrets TSH) and the thyroid gland (secrets T₃ and T₄).

The thyrotropin releasing factor (TRF) a tripeptide secreted by the nerve ending in the hypothalamus, on secretion enters the anterior pituitary. In the pituitary TRF has two actions, it stimulates the release of preformed TSH and it causes the synthesis of the TSH (Davidson and Bernard,1971). TSH is controlled by thyrotropin releasing hormone (TRH) which is secreted by the hypothalamus in the brain (Ganong,1995)
Figure-6B: Feedback of Thyroid Hormones.

Feedback of the HP-thyroid system

Adequate iodine

- hypothalamus
  - TRH
    - anterior pituitary
      - TSH
        - normal thyroid
          - T4/T3

Feedback of the HP-thyroid system

Inadequate iodine

- hypothalamus
  - TRH
    - anterior pituitary
      - TSH
        - EXCESS
          - large thyroid goitre
            - T4/T3

Source: Chatterjea (1998)
FUNCTIONS OF THYROID HORMONES

Protein metabolism

The growth promoting effect of thyroid hormones is based on its ability to promote protein synthesis. Thyroxine is necessary for maintaining the normal rate of protein synthesis. Excess of thyroid hormone can cause rapid catabolism rather than synthesis of protein so that protein stores are mobilized and amino acids are released into the extracellular fluids. Thyroid hormones cause an increase in Ribonucleic Acid (RNA) and protein synthesis.

Moussari et al (1983) reported that rats could be made hypothyroidic by giving propylthiouracil through drinking water. Hypothyroidism is detected by low levels of thyroid hormones in the blood and produces sluggishness, sleepiness, dry skin, cold intolerance and constipation. Ingenbleek et al (1986) also stated that endemic goitre is associated with an overall stepwise down regulation in the protein metabolism. Concentration of amino acids significantly decreased as the degree of goitre increased. Most non-essential amino acids and intermediary metabolites also decreased with the severity of goitre (Barclay et al, 1986). Thyroid hormone action either promotes endothelial protein synthesis or impairs its clearance (Graninger et al, 1986)

Carbohydrate metabolism

Thyroid hormone stimulates almost all aspects of carbohydrate metabolism including the rapid uptake of glucose by the cells, enhanced glycolysis, mobilizes glycogen from the liver and heart, promotes gluconeogenesis, increases the rate of absorption from the gastrointestinal tract and even increases insulin secretion with its resultant secondary effects on the carbohydrate metabolism. These effects are due to the increase in enzymes caused by the thyroid hormone. Liver glycogen stores are diminished as a consequence of hepatic glycogenolysis and the blood sugar levels tend to rise. A lack of thyroid hormone depresses the rate of removal of exogenous glucose from the blood (Elrick et al, 1961). Rall et al (1964) suggested that in hyperthyroidism blood sugar rises higher than normal but in hypothyroidism the
curve appears to be flat. When glucose was administered intravenously, disappearance was normal in hyperthyroidism but slower in hypothyroidism. Thus in hypothyroidism the absorption of glucose and galactose as well as oxidation of glucose were observed to be retarded.

Levy et al (1970) reported that hypothyroidic patients injected with glucose showed a very slow rise in plasma glucose levels. Muller et al (1980) reported that hypothyroidism decreased the blood glucose concentration (81%), glucose pool (52%), and glucose disappearance (39%). Glycogen levels decreased whereas insulin levels showed no changes. Escrina et al. (1984) proved that when L-thyroxine was administered to neonatal rats, it produced hypoglycemia, hypoinsulinemia and led to an increase in blood lactate, pyruvate and ketone bodies.

Holeness and Sugden (1987) concluded that continued hepatic glucose output contributes to abnormal glucose tolerance in hyperthyroidism. In hypothyroidism the state of the thyroid gland is similar to that caused by excessive TSH. The gland is hyperplastic, increases in size, the number of cells also increase, increasing the rate of secretion several fold. McDaniel et al (1977) suggested that hypothyroidism is associated with impaired glycogen breakdown.

**Fat metabolism**

The concentration of most of the lipids of the serum especially cholesterol varies inversely with the level of thyroid hormones. Thyroid hormone increases the catabolism of cholesterol, free fatty acids and other lipids.

Decreased thyroid secretion greatly increases the concentration of cholesterol, phospholipids and triglycerides and hence causes excessive deposition of fat in the liver. Levy et al (1970) reported that when a glycogen dose was given the glycogenolytic response decreased and the free fatty acid levels increased. Ingbar and Woeber (1974) stated that in primary hypothyroidism the serum cholesterol level is usually increased. A classic effect of thyroid hormone is to lower the concentration of cholesterol in the plasma.
Michael et al (1984) showed hypercholesterolemia in thyroidectomized European badgers. In another study carried out by Stivaltelli et al (1986) a low protein diet was fed to thyroidectomized rats, the results showed that the lipid content increased and the protein content decreased in the aorta. When the animals were treated with T₃ the change induced by the low protein diet disappeared.

Extensive lipolysis occurred due to raised levels of TSH (Wollman et al, 1982). It has been reported that cholesterol synthesis is high in the hyperthyroid state associated with low plasma cholesterol levels (Dubey et al, 1980). Kutty et al (1978) stated that as T₄ levels decreased serum cholesterol levels increased. Das and Isichei (1988) showed that in patients suffering from hypothyroidism there was a marked increase in all the lipid fractions except free fatty acids in the serum and in thyroid tissue a marked raise in cholesterol and phospholipid but a reduction in triglycerides and free fatty acids.

Extensive studies by Abrams and Grundy, (1981) and Staels et al (1990) reported that thyroid hormone regulates serum levels of LDL through the catabolic rate than it's biosynthesis. In patients with hyperthyroidism a low level of LDL resulted from rapid catabolism of LDL, despite an enhanced biosynthesis of cholesterol. In hypothyroidism a decrease in LDL receptor activity (Gross et al, 1987) retards the clearance of LDL from the circulation (Yamamoto et al, 1995).

**Vitamin metabolism**

As thyroid hormone increases the quantity of many of the different enzymes and as vitamins are an essential part of some of the enzymes of co-enzymes, the thyroid hormone causes increased need for vitamins. Therefore a relative vitamin deficiency can occur when excess thyroid hormone is secreted unless at the same time increased quantities of vitamins are available.

Thyroxine regulates the formation of the enzyme flavokinase, the enzyme that converts riboflavin to flavin mononucleotide (FMN) and in the absence of this hormone the conversion of riboflavin to FMN and FAD is markedly reduced (Rivlin et al, 1970).
Higueret et al (1989) found that when rats were fed a vitamin A deficient diet, the formation of $T_3$ complexes with nuclear protein was reduced and scattered and a decrease in the growth was observed. Higueret et al (1989) also stated that there was considerable change in serum thyroxine transport in rats fed a vitamin A deficient diet.

**Basal Metabolic Rate (BMR)**

Thyroid hormone increased the metabolism in most cells of the body (with the exception of the brain, retina, spleen, testis and lungs), excessive quantity of the hormone can occasionally increase the BMR to as much as 50 to 100% above the normal. The rate of energy exchange and the quantity of heat liberated by an organism at relative rest is elevated in hyperthyroidism and reduced below the normal in hypothyroidism. Where thyroid output is limited by lack of dietary iodine the BMR is lowered. BMR can be restored to the normal by iodine supplementation or on thyroid hormone therapy. The BMR is reduced in hypothyroidism, in several cases, values of −50% were obtained but the common range is from −15 to −35 %. Administration of thyroid hormone leads to an increase in size, number and metabolic activity of mitochondria in the mammalian skeletal muscle (Underwood, 1977).

**Enzymes**

Muscle metabolism is clearly affected by the thyroid gland (Khaleeli and Edward, 1984). Hyperthyroidism causes an increase in the muscle metabolism with a reduction in creatinine production and a reduction in serum creatinine (Katz et al, 1975). The effect of hypothyroidism are less clear but data exist suggesting that hypothyroid myopathy leads to increased creatinine release by muscle (along with creatinine kinase, aldolase and LDH) therefore increasing serum creatinine levels (Lafayette et al, 1994).

Plasma enzyme activities that have been reported to be increased in primary hypothyroidism include creatinine kinase, aminotransferases, aldolase and LDH (Graig and Ross, 1963). Similar results were obtained by White and Walmsley (1984) when patients were detected with primary hypothyroidism.
Burnett (1994) detected increased levels of creatinine kinase, aminotransferases and lactic dehydrogenase (LDH) in patients with hypothyroidism.

**Growth and development**

Thyroid hormone has both a general and a specific effect on growth. It has an important role in promoting growth and development of the brain during fetal life and for the few years of postnatal life. Experiments in animals have shown extreme sensitivity of the fetal brain to iodine deficiency. A lack of thyroxine during brain ontogeny impairs cell division, growth, and the formation of synopsis between the nerves and suppresses mylenation (Hetzel et al, 1983). Severe iodine deficiency in the mother produces neurological damage during fetal development (Pharoah et al, 1971).

Potter et al (1979) reported that on iodine supplementation the rate of stillbirths and infant deaths due to congenital anomalies, declined substantially. Thyroid hormones also affect the mortality and secretions of the gastro-intestinal tract, which in turn hampers the absorption of various nutrients and ultimately affects the metabolism. Findings of Connolly et al (1979) indicated that iodine efficiency might lead to a spectrum of subclinical deficits, which place the children at a developmental disadvantage. Kochupillai et al (1984) suggested that a significant proportion of newborns from areas with environmental iodine deficiency might be suffering from brain damage due to thyroxine deficiency at birth.

Carrasco et al (1986) examined 200 school children and calculated the I.Q. of the goitrous children; significant reduction in the I.Q. was present when compared to that of nongoitrous children. This proves that thyroxine is very much necessary for proper brain functioning. The potential risk of goitrogenic stimulation in both mother and newborn in the presence of mild iodine deficiency. Further these results indicated the beneficial effects of supplementation of iodine to pregnant women with iodine deficiency and to women with excessive thyroid stimulation with a combination of iodine deficiency.
Little is known about the exact manner in which thyroid hormone influences the reproductive process. Some of the impairment may be consequent upon disturbances in protein metabolism; others may be attributable to pituitary malfunctions. Thyroid hormone exerts some control over the release of somatotropins, corticotropin and gonadotropins from the hypophysis.

Hetzel et al (1983) have shown through experiments on animals the extreme sensitivity of the fetal brain to iodine deficiency. Pharoah et al (1971) reported that severe iodine deficiency in the mother produced neurological damage during fetal development. Potter et al (1979) reported that on iodine supplementation the rate of stillbirth and infant deaths decline substantially.

**Thyroid hormone and dietary iodine**

Iodine is required by the thyroid gland for the production of thyroid hormones. If the supply of iodine to the gland is interrupted then the intrathyroidal iodine stores are used up for the secretion. Hence the thyroid becomes depleted of iodine. Iodine deficiency can be easily demonstrated on the rat as an experimental model. Continued lack of iodine in the diet leads to impaired function of the thyroid gland, which enlarges to form a goitre (Studer and Greer 1965 and 1968). Ohtake et al (1973) stated that excess iodide blocks the release of thyroid hormone in rats.

**Free radical**

Free radical production, a natural event in which cell, becomes highly dangerous if over production occurs. An antioxidant is that once absorbed by the body helps to prevent and repair damaged cells. However, a number of antioxidant defence systems are present within the cell, which helps to protect it from the deleterious effects of oxidative stress. The most important chain breaking antioxidant inhibitor of lipid peroxidation is \( \alpha \)-tocopherol, a physiological antioxidant and membrane stabilizer (Burton et al, 1989). As a major water soluble antioxidant, vitamin C is capable of maintaining sulphhydryl compounds in a reduced state, particularly in several redox reactions (Frei et al, 1989). Deshpande et al (2002) in this study investigated the protective effect of antioxidants [vitamin C, E, and Turmeric extract(TE)] on methimazole induced
hypothyroidism in rats. Male Wistar rats were fed MMI, MMI plus vitamin C, MMI plus vitamin E and MMI plus TE, supplemented diet. At the end of the experimental period, it was observed that MMI treated rats showed an increase in thyroid weights, very low levels of circulating T₄, T₃ and increased levels of total cholesterol as compared to control (p < 0.001). However, rats which received vitamin C, E or TE along with MMI showed reduced weights [38 – 55% less] in thyroid glands (p < 0.001), less suppression of T₄ and T₃ levels (2 to 6% and 7 to 35 %) respectively and less increase in total cholesterol (19 to 52%) which was statistically significant. The data suggests positive effect of antioxidants on the thyroid gland which could be due to direct involvement of antioxidants on the thyroid gland.

IODINE DEFICIENCY DISORDER (IDD)

Major etiological factors of IDD

The two major causes of IDD are:

- Environmental iodine deficiency and
- Presence of goitrogens in foods.

Of the two, environmental iodine deficiency accounts for the endemnicity in most of the areas.

ENVIRONMENTAL IODINE DEFICIENCY

Most of the daily requirement of iodine is met from food and part of it through drinking water. The food crops that are grown on iodine-deficient soils will naturally be deficient in iodine. The iodine content of a particular food item may vary not only according to the place or plant of production but also according to season.

Iodine content of drinking water is considered to be an indicator of environmental iodine status. Usually in iodine deficient areas, the levels will be less than 2 µg/L of water. It is found that iodine content of drinking water during winter months were higher than that of summer months (Broadhead et al, 1965).
Environmental iodine deficiency is known to affect the livestock as well, which includes cattle, sheep, pigs and poultry. They are subjected to abortion, stillbirth, low birth weight, alopecia, inadequate growth and functional disabilities (Pandav et al, 1997).

The most severe environmental iodine deficient areas of the world are the Himalayas, the Andes, the European Alps and the vast mountainous areas of China. The prevalence of iodine deficiency is also high in flooded river valleys of Asia such as the valley of India, Bangladesh and Myanmar (Pandav, 1994). The food crops grown on this type of soils will naturally be deficient and people subsisting on these crops and vegetables are susceptible to the risk of developing iodine deficiency disorder (Hetzel, 1989).

However, with the advent of fortification of common salt with iodine, the prevention and control of IDD has become feasible, in terms of both the cost and efficacy.

Goitrogens

Goitrogens are certain chemical substances which interfere with iodine metabolism in the body. Some of the known goitrogens found in the environment are thiocyanate, thio-oxazolidone, flavonoids, disulphide, phenols, phthalates, biphenyls and lithium (used in the treatment of some of the neurological disorders). Even excess of iodine is known to act as a goitrogen. These goitrogens are known to interface with iodine metabolism at various levels.

Several studies have been carried out on experimental models and humans to understand the effect of these goitrogenic substances on the thyroid hormones.

Among the several Goitrogens, thiocyanate is of significance not only because it occurs naturally in a wide variety of foods consumed in endemic goitre areas, but also because it is formed during the metabolism of different goitrogens (Gaitan, 1990).

Thiocyanate occurs as glycosides in radish, cabbage, cauliflower and other vegetables of the brassica family. The thiocynate ion has a molecular
volume and charge similar to that of iodide ion and competes with iodide for uptake into the thyroid gland (Thilly et al, 1993)

Chesney et al (1928) established the existence of goitrogenic substances, they showed the development of goitre in cabbage fed rabbits. Since then the vegetables of the genus 'Brassica ' (Cruciferae family) have been identified to have goitrogenic properties. Astwood et al. (1949) isolated a potent antithyroid compound "goitrin"a thioglycoside from yellow turnips and from brassica seeds. Cyanogenic glycosides present in some of the foods from the third world, after ingestion is readily converted to thiocyanate by myrosinase enzyme. The goitrogen interferes in the iodine metabolism at various stages of oxidation, organic binding or coupling whereas lithium acts at the stage of proteolysis, release and dehalogenation process (Gaitan,1985).

Delange (1988) stated that the ingestion of vegetables of the cruciferae family, cassava, flavonoids containing millet and sorghum are clearly implicated in the etiology of goitre. Brizer et al (1987) observed that when a methanol extract of pearl millet was added to sorghum grains and fed to rats, it caused goitre and an imbalance in the thyroid hormone ratio. Osman et al (1993) found that on eating cassava leaves for 12 consecutive days, thyroid hormone, T₃ and T₄ were significantly lowered. Lineback et al (1980) stated that iodine deficiency was prevented by ensuring an adequate intake of iodine or by the removal of goitrogenic substances from the diet.

Figure-7 shows the naturally occurring goitrogens and their site of action in the thyroid gland.

Goitrogens can be divided into three categories (Class I,II, and III) according to the level at which they interfere with iodine metabolism.

Class I: The thiocyanates and isothiocyanates inhibit the concentration mechanism of iodide uptake by thyroid gland. Since they a have molecular weight similar to that of iodine, these goitrogens compete with iodide.
Figure-7: Naturally occurring goitrogens and their site of action in the thyroid gland.

<table>
<thead>
<tr>
<th>Thiocyanate (cyanogenic glycoside)</th>
<th>Thioglycosides: “Goitrin” Isothiocyanates, Disulfides “Waterborn goitrogen”</th>
<th>Iodide (sea weeds) “coast goitre”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodide transport</td>
<td>Oxidation organic binding and coupling</td>
<td>Proteolysis release and dehalogenation</td>
</tr>
</tbody>
</table>

Source: Guyton (1985)
Class II: The thiourea and thionamides interfere with the process of organification of iodine and coupling.

Class III: The third group of goitrogens viz, lithium and iodine itself interfere with the processes of proteolysis and release of thyroid hormones (Hetzel, 1989).

Other substances like high mineral content, especially magnesium and calcium salt and bacterial contamination in water also have goitrogenic effects. Studies also revealed that protein energy malnutrition (PEM) interferes with iodine absorption, iodide trapping and thyroglobulin formation (Gaitan, 1985).

**Disorders of iodine excess**

Adverse effect of excess iodine from foods and dietary supplements are also observed where the intake of iodine is extraordinarily high. In addition it has been well documented that excessive intake of iodine may induce goitre in certain subjects or in some species of animals (Suzuki, 1980). Table-4 shows some of the adverse effects due to excess iodine.

The IDD iceberg showing the very large invisible "hidden" component of IDD associated with the small visible compound cf cretinism.
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Source</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964</td>
<td>Higuchi</td>
<td>Seaweed (foods)</td>
<td>Goitre in residents of coastal areas of Hokaido, Japan</td>
</tr>
<tr>
<td>1986</td>
<td>Tajiri et al</td>
<td>Seaweed (foods)</td>
<td>Of 20 adult Japanese patients with hypothyroidism from seaweed in the usual diet (1-5 mg I/day for one year) became euthyroidic with iodine restriction.</td>
</tr>
<tr>
<td>1981</td>
<td>Lewis</td>
<td>Milk (iodophor)</td>
<td>Increase in thyrotoxicosis in Tasmania, Australia.</td>
</tr>
<tr>
<td>1977</td>
<td>Sobrinho</td>
<td>Iodized salt</td>
<td>Increase incidence of goitre and hypothyroidism in Lisbon, Portugal</td>
</tr>
<tr>
<td>1986</td>
<td>Shilo and Hirsch</td>
<td>Sea kelp tablets</td>
<td>Hyperthyroidism in Jerusalem, Israel who used these tablets.</td>
</tr>
<tr>
<td>1992</td>
<td>Mokarzel et al</td>
<td>Parental nutrition</td>
<td>Possibility of thyroid dysfunction in children</td>
</tr>
</tbody>
</table>

Source: Pandya (1996)
THE SPECTRUM OF IDD

IDD causes a wide spectrum of clinical and sub-clinical manifestations depending on the stage of life at which one is exposed to it and the severity of iodine deficiency. These are listed below:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foetus:</td>
<td>Abortions</td>
</tr>
<tr>
<td></td>
<td>Stillbirths</td>
</tr>
<tr>
<td></td>
<td>Increased infant mortality</td>
</tr>
<tr>
<td></td>
<td>Neurological cretinism</td>
</tr>
<tr>
<td></td>
<td>Myxoedematous cretinism</td>
</tr>
<tr>
<td></td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td></td>
<td>Increased cretinism</td>
</tr>
<tr>
<td></td>
<td>Psychomotor defects</td>
</tr>
<tr>
<td>Neonate:</td>
<td>Ne°natal goitre</td>
</tr>
<tr>
<td></td>
<td>Neonatal chemical hypothyroidism</td>
</tr>
<tr>
<td>Children &amp;</td>
<td>Goitre</td>
</tr>
<tr>
<td>Adolescents:</td>
<td>Juvenile hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Impaired mental functions</td>
</tr>
<tr>
<td></td>
<td>Retarded physical development</td>
</tr>
<tr>
<td>Adult:</td>
<td>Goitre with it’s complications</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Impaired mental function</td>
</tr>
<tr>
<td>All Ages:</td>
<td>Physical sluggishness</td>
</tr>
<tr>
<td></td>
<td>Increased susceptibility to nuclear radiation</td>
</tr>
</tbody>
</table>

Source: Hetzel (1989)
Foetal iodine deficiency

Severe iodine deficiency during pregnancy will have adverse effects on the foetus, which leads to increased incidence of stillbirths, abortion and congenital anomalies. Studies in Zaire (Hetzel, 1989) have shown that iodized oil injections given during later half of the pregnancy can significantly increase birth weights and reduce perinatal mortality and infant mortality rates.

Goitre

Goitre is defined as a non-neoplastic, non-inflammatory and non-toxic enlargement of the thyroid gland. The normal thyroid gland is not palpable or is barely palpable. A thyroid gland whose lobes have a volume greater than the terminal phalanx of the thumb of the subject examined will be considered goitrous. The prevalence of goitre is generally seen more among adolescents, young adults, and school age children and among females as compared to males (Perez et al, 1980).

Cretinism

Endemic cretinism is associated with severe iodine deficiency during intrauterine life. It's prevalence is seen in areas with very high prevalence of goitre. It is associated with a wide range of defects such as mental deficiency, deaf-mutism and spastic paralysis of legs in varying degrees (Hetzel and Potter,1983).

Hypothyroidism

Hypothyroidism is characterized by coarse and dry skin, husky voice, delayed tendon reflexes, epiphysial dysgenesis as evidenced by X-rays and Electro CardioGram (ECG) showing small voltage QRS and flattened T-waves. Serum T4 levels will be low with normal T3 and elevated TSH levels. This condition is encountered generally among adults (Hetzel, 1989).
Psychomotor defects

Studies have shown that the child population from iodine deficient areas show poor scores on IQ tests and impaired school performance. They also exhibit poor motor coordination (Hetzel, 1989).

Impaired mental function

Population residing in iodine deficient areas usually show reduced mental function, low intelligence levels and high degree of apathy, reflected in lack of initiative and decision making capacity of the people (Hetzel, 1989).

INDICATORS OF IDD

If in an area, the Total Goitre Rate (TGR = Numbers with goitre of grade 1 and 2/total number examined) x 100 among the children aged six to twelve years is equal to or more than 5%, that area is said to be endemic for goitre (WHO/UNICEF/ICCIDD 2001).

GRADING OF IDD ENDEMIAS

Depending upon the median urinary iodine excretion levels and prevalence of Total Goitre Rate (TGR) in the community, the severity of endemicity of IDD is graded as follows:

1. Mild IDD

An area with urinary iodine excretion level 50.0-99.9 µg/L and TGR 5.0-19.9% is considered as mildly endemic. At this level, thyroid hormone levels are usually adequate with normal mental and physical development.

2. Moderate IDD

In this category of endemias, the median urinary iodine excretion level is 20.0-49.9 µg/L and TGR is 20.0-29.9% in these communities, there may be impaired thyroid hormone levels, with the risk of hypothyroidism. However, there will not be overt cases of cretinism.
3. Severe IDD

Endemic with median urinary iodine level of 20.0 μg/L or less and TGR of \( \geq 30\% \) are considered to be severe. The population will be at risk of marked hypothyroidism, mental retardation and overt cretinism.

GLOBAL SCENARIO

The daily requirement of iodine is very small, 150 μg/day per person, which amounts to a mere teaspoon full for a lifetime. The problem of IDD assumes an important position, next to protein energy malnutrition (PEM), vitamin A deficiency (VAD) and iron deficiency anemia (IDA). IDD is a major public health problem in about 198 countries all over the world and over 12% of the world’s population is living in iodine deficient areas. It is estimated that 1571 million people worldwide live in iodine deficient environments and are at risk of IDD. In the new millennium also IDD persists as a public health problem with 2.2 billion people at risk worldwide (ICCIDD/UNICEF/WHO, 2001).

PREVALENCE OF IDD IN THE WORLD

An epidemiological study in Egypt among 6,750 school children aged 8-10 years revealed a goitre prevalence of 34.06%. Median urinary iodine level was 50.4 μg/L for children with goitre, while it was 148 μg/L in non-goitrous children. The prevalence of goitre was positively correlated with female gender and exposure to drinking water with low iodine content or in areas with low soil iodine (el-Sayed et al, 1998). In the same year another study in Nigeria (1998) among 4,230 school children showed that 67% of the subjects were iodine deficient. Drinking water was reported to be low in iodine whereas urinary thiocyanate levels were high (Das et al, 1998). Table-5 shows the data on the prevalence of IDD in the WHO region.

A study carried out in Nigeria on borderline malnourished and well-nourished breastfed children (9-8 months) revealed that the mean urinary iodine was 99 μg/L whereas mothers showed mean urinary iodine level 145 μg/L (Akanji et al, 1996). A study carried out in 1997 in Africa, identified Reunion Island as
endemic for IDD. The goitre prevalence ranged from 0 in young children through 12% in school age children, 23% in teenagers and 38% in women. The corresponding urinary iodine excretion levels among these groups respectively were 120, 78.56 and 42 \( \mu \)g/L (Jaffiol et al., 1997). A study in the Langkloof area of South Africa (Jooste et al., 1997) revealed that the prevalence of goitre ranged from 14-30% among 565 primary school children. A study in Cuba on 3,027 primary school children showed that the median urinary iodine excretion level was 95 \( \mu \)g/L. Moderate to severe deficiency was found in the foothills and mountainous regions as the median urinary iodine excretion level was <20 \( \mu \)g/L (Rodriguez et al., 1998).

Zein et al. (2000) in Yemen undertook a study to estimate the prevalence of goitre and severity of Iodine Deficiency Disorder (IDD) and the proportion of household consuming iodized salt. The country was divided into two ecological zones and 30 clusters. Total 2,984 pupils age 6-12 yrs (2003 boys and 981 girls) were covered. Results showed that the total goitre rate in the whole country, coastal area and mountainous regions were 16.8%, 31.1% and 7.4%, respectively. IDD was severe in 4.7% of mountainous areas and 2.6% in coastal areas. Mild and moderate IDD were found to be 18.5% and 8.7% respectively amongst the children of Yemen. ICCIDD (2002) stated that Europe is iodine deficient. Out of the 28 countries studied 13 countries were found to be iodine deficient.

**PREVALENCE OF IDD IN SOUTH - EAST ASIA**

South-East Asia is in the global focus for iodine Deficiency Disorders, because of high prevalence both in terms of magnitude and severity. Environmental iodine deficiency not only exists along the length of the sub Himalayan belt but is also encountered in plains affected by frequent floods.

In 1985, WHO identified eight countries in the South East Asian region as having IDD as a significant public health problem. They included Bangladesh, Bhutan, Myanmar, India, Indonesia, Nepal, Sri Lanka and Thailand. A significant proportion of their population was at risk from IDD as they were living in iodine deficient areas.
Table-5: Prevalence of goitre in WHO region (2001)

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Population 'at risk' (in million)</th>
<th>Population with goitre (in million)</th>
<th>Percent with goitre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>612</td>
<td>124</td>
<td>20</td>
</tr>
<tr>
<td>America</td>
<td>788</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>S.East Asia</td>
<td>1,477</td>
<td>172</td>
<td>12</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>473</td>
<td>152</td>
<td>32</td>
</tr>
<tr>
<td>Europe</td>
<td>869</td>
<td>130</td>
<td>15</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1,639</td>
<td>124</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>5,858</td>
<td>741</td>
<td>13</td>
</tr>
</tbody>
</table>

Ramalingaswami et al (1973) estimated about one third of the population to be hypothyroid in some of the South-East Asian countries. A study carried out by Karmarkar et al (1974) reported goitre endemicity in the countries of India, Nepal and Ceylon. The study also revealed a significant correlation between endemic goitre and severe environmental iodine deficiency in these areas. The severity was reportedly higher in Ceylon than in India and Nepal.

A study conducted by Pardede et al (1998) in Indonesia among school children (8-10 years) revealed that the total goitre rate was 35.7% by the palpation method and 54.4% by ultrasonography. Low urinary iodine excretion levels were reported in 64% of the subjects.

**PREVALENCE OF IDD IN INDIA**

The most intensive belt of endemic goitre in the world is in the Sub-Himalayan region extending from Jammu and Kashmir in the north through western parts of Punjab, Haryana, Uttar Pradesh, Bihar, West Bengal and North Eastern states. However, the study carried out later in other parts of the country revealed several endemic pockets in peninsular India, which are known as 'extra-Himalayan' foci of IDD. These include the hilly state of Central India particularly among the Chotta Nagpur plateau; Sidhi, Sadol, Sarguja and Raiga'h districts in the Sub-Vindhya belt of Madhya Pradesh, the Aravalli ranges in Rajasthan along the Narmada Valley of Gujarat, the city of Bombay, Aurangabad and Pune district of Maharashtra, the tribal area of Vishakhapatnam and East Godavari district in Andhra Pradesh, the tea estates of Tamilnadu, Kerala, Karnataka and also the Union Territory of Delhi (WHO, 1995).

A study carried out by Swarajyalaxmi (1985) in Visakhapatnam district revealed that endemic goitre was a major public health problem in the tribal population of the district and the overall prevalence of goitre was 43%. A study carried out by National Institute of Nutrition (NIN, 1992) in the tribal group of Maharashtra (Maria Gond) revealed goitre prevalence ranging from 19 % among adolescents to 11.3 % in school age children and 8% in adults. The prevalence was significantly more among females compared to males. A study by Zargar et al (1996) on 712 school children aged 5 to 15 years (538 boys and 174 girls) in
Kupwara district of Kashmir Valley showed an overall prevalence of goitre of 44%.

An ICMR task force study carried out in 1989, showed a very high prevalence of goitre (65.8%) in Dibrugarh District of Assam and cretinism (6.1%) in west Manipur District of Manipur. Another survey conducted during 1992-1993 with support from UNICEF also showed a consistently high prevalence of goitre (42.2%) in Dibrugarh district. A study carried out by Mittal et al (2000) among 770 children in the age group of 10–12 years in the northern parts of U.P. revealed an overall goitre prevalence of 38.2%. The study also revealed that a total of 41.1% of children suffered from IDD in the Tarai region. A pilot study conducted by Kapil et al (2002) in Kottayam district of Kerala among 1872 children in the age group of 6-12 years revealed a total goitre prevalence of 71%. According to Kapil et al (2002) goitre prevalence in Bharatpur district of Rajasthan was 7.2% in children between 6-12 years of age.

**PREVALENCE OF IDD IN THE STATE OF GUJARAT**

Mc Carrison (1913) first reported that people living in the Valley of Narmada region in Gujarat were suffering from the problem of goitre. Edibam et al (1972) reported the prevalence of goitre to be 36.7% in the age group of 6-11 year old children from the same area.

The Central Goitre Survey Team in 1977 also found that the prevalence of goitre was 33.6% and 31.4% in urban and rural areas of Gujarat, respectively. Higher prevalence rates were observed in Dadiopara (65%), Sagbara (55%) and Nandod (42%) talukas. In 1977 the Central Survey Team declared that various areas of Bharuch district were endemic for IDD.

Desai et al (1984) stated that the overall prevalence rate of goitre in Narmada Valley was 34.8%. It was significantly higher in females 43.7% than in males 24.7%.
A district wise survey done by the Director General Health Services (DGHS, 2000) showed the prevalence rate of goitre in Gujarat to range from 5.9 to 44%.

A study carried out by Brahmbhatt et al (2001) showed that among school children in Gujarat IDD was a severe public health problem. It identified Vadodara district as a new pocket of IDD. It was concluded that high amounts of dietary flavanoids in Vadodara and Dang district and lack of iodine in water was responsible for IDD.

Sadhukhan (2003) showed that the overall prevalence rate of goitre in Urban Vadodara was 10.6%. It was found to be high in low-income groups of the community (17.8%). Sayantani Maitra (2004) showed that the overall prevalence of goitre in Baroda city was observed to be 16.3%, out of a total number of boys covered for the study (n=318), the prevalence of goitre was 14.4% in case of girls the prevalence rate was higher i.e. 18.9% and total girls covered were 232.

The Central Goitre Cell, DGHS, Government of India, studied the prevalence of goitre in different districts of Gujarat. Table-6 gives this data. Highest prevalence was observed in Surat and Valsad while the lowest prevalence was observed in Gandhinagar.

PREVALENCE OF IDD IN ANAND

A survey carried out by Desai et al in 1991 has shown a goitre prevalence of about 6.5% among school children in Kheda district. A total of 22,036 school children and 24,066 village population from ten talukas of Kheda district were examined. Out of the total school children and village population examined, 1432 (6.5%) and 1183 (4.9%) respectively had goitre. Talukawise goitre prevalence rate was highest (10.01%) in Matar taluka and lowest (1.61%) in Borsad taluka in the village survey. In the school survey goitre prevalence rate was highest (10.5%) in Borsad taluka and lowest (2.64%) in Mehmndabad taluka. In Anand taluka it was found to be 5.0% and 6.0% in the village survey and the school survey, respectively.
PREVENTION AND CONTROL OF IDD

IDD is easily preventable and its control is recognized as one of the major achievable public health goals. Supplementation of iodine in one-way or the other is the only way to prevent and control the problem of IDD in the community. This can be achieved by either fortification of foods items with iodine or by direct iodine supplementation and if necessary by discouraging people from consuming foods known to contain low levels of goitrogens.

Salt can be fortified with potassium iodide or potassium iodate. Salt fortified with potassium iodate is relatively more stable than that with potassium iodide. Hence potassium iodate is commonly used for fortification of salt. Daily consumption of 10g of iodated salt (25 ppm of potassium iodate) provides about 150 μg of iodine. Using iodinated salt can effectively control goitre endemias of mild to moderate degree.

Oil fortified with iodine is available for oral or intramuscular injections. France is the only country in the world which is producing on a commercial scale, iodized oil from poppy seed oil for injection [Lipiodol] as well as for oral administration [Oriodol] (Dann and Harr 1990). Supplementation of iodized oil is the best method for the immediate prevention of new cases of cretinism and mental retardation in communities living in severe iodine deficiency areas.

NATIONAL PROGRAMME FOR PREVENTION AND CONTROL OF IDD IN INDIA

Encouraged by the results of the iodized salt supplementation experiment in Kangra valley of Himachal pradesh, Government of India (GOI), in the year 1962, launched the National Goitre Control Programme (NGCP) with the following objectives:

➢ To identify goitre endemic areas,
➢ To produce and supply iodized salt to goitre endemic areas, and
➢ To conduct a resurvey after 5 years of continuous supply of iodized salt.
Table-6: Prevalence of goitre in Gujarat

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>District</th>
<th>Year of survey</th>
<th>Prevalence of goitre</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Surat</td>
<td>1989</td>
<td>44.00</td>
</tr>
<tr>
<td>2</td>
<td>Valsad</td>
<td>1983</td>
<td>36.60</td>
</tr>
<tr>
<td>3</td>
<td>Bharuch</td>
<td>1977</td>
<td>31.70</td>
</tr>
<tr>
<td>4</td>
<td>Sabarkantha</td>
<td>1989</td>
<td>25.80</td>
</tr>
<tr>
<td>5</td>
<td>Junagadh</td>
<td>1997</td>
<td>23.30</td>
</tr>
<tr>
<td>6</td>
<td>Panchmahal</td>
<td>1999</td>
<td>22.40</td>
</tr>
<tr>
<td>7</td>
<td>Dang</td>
<td>1987</td>
<td>22.70</td>
</tr>
<tr>
<td>8</td>
<td>Vadodara</td>
<td>1986</td>
<td>16.80</td>
</tr>
<tr>
<td>9</td>
<td>Amreli</td>
<td>1989</td>
<td>14.00</td>
</tr>
<tr>
<td>10</td>
<td>Mehsana</td>
<td>1991</td>
<td>7.50</td>
</tr>
<tr>
<td>11</td>
<td>Kheda</td>
<td>1991</td>
<td>6.50</td>
</tr>
<tr>
<td>12</td>
<td>Surendranagar</td>
<td>1991</td>
<td>5.90</td>
</tr>
<tr>
<td>13</td>
<td>Ahmedabad</td>
<td>1999</td>
<td>5.40</td>
</tr>
<tr>
<td>14</td>
<td>Gandhinagar</td>
<td>1999</td>
<td>2.20</td>
</tr>
</tbody>
</table>

Source: Central Goitre Cells, (2002)
In light of these observations and in view of various world wide reports of wide spread problems of IDD, GOI in 1984, launched the Programme of Universal Iodization of Salt: with objectives to iodize the entire edible salt in the country in a phased manner. In the year 1992, the NGCP was renamed as National Iodine Deficiency Disorder Control Programme (NIDDCP). Under National Nutrition policy, it has been envisaged to virtually eliminate IDD in the country by 2000 AD.

In India, the total annual production of salt is about 135 lakh metric tones, of this 38% is used for industrial purpose, 30 % is exported, while a fourth of it is in surplus. The current level of production of iodized salt is about 4.4 million metric tones (1999) as against an estimated requirement of 6 million metric tones (Salt Department, GOI,2002). A majority of the iodized salt is manufactured by the private sector. Most of the salt in the country is manufactured in the State of Gujarat, followed by Rajasthan and Tamil Nadu, in this order and this is transported to the rest of the country either by road (60 %) or by rail (40 %), which adds to the cost of salt.

Ministry of health and Family welfare, Government of India, in it's Gazette notification dated 13th September, 2000, has lifted the Ban on sale of Un-iodized salt in the country. However, the State Governments, so far have not made any changes in the rules prevailing in their respective States, in this regard.

RATIONAL OF THE PRESENT STUDY

Since the survey conducted so far were at different periods, often dating back to 10-15 years, there is an urgent need to update this information periodically, by conducting fresh surveys in the State/district. Such surveys would help not only help in monitoring the impact of the programme, but also in identifying newer areas, which are endemic for IDD.

The survey conducted by Desai Vikas (1991) has shown a goitre prevalence rate about 6.5 % among school children. No survey has been conducted recently in the semiurban community of Vallabhb Vidyaganagar town.
Studies indicate that very little information is available on iodine deficiency disorder from the local areas of Anand and Vallabh Vidyanagar. Therefore the present investigation was planned in three parts.

The objective of the first part of the study was to determine the iodine content of different water sources, food stuff commonly consumed and salt samples available in the local area of Anand and Vallabh Vidyanagar as an indicator of soil iodine. Storage and cooking losses of salt were also to be investigated to assess the extent of loss of iodine.

In the second part of the study, three animal experiments were planned to study the effect of feeding low, normal and high levels of iodine on growth, tissue hormonal levels as well as on the reproductive performance of rats. Further the effect of the goitrogen, thiocyanate will also be studied on these animals. In continuation, the first generation animals will be continued on the same respective diets as the parental generation and then studied for their reproductive performance and tissue iodine status. In the final experiment the protective effect of antioxidants such as vitamin C, E, A and β-carotene will be examined against methimazole (MMI) induced hypothyroidism.

In the third part of the study, human experiments were planned. In the first part of the human study, school children of the age group 6 to 12 years will be screened for iodine deficiency. In the second part of the human study adult subjects both normal and subjects suffering from hypothyroidism will be compared for their awareness on IDD and the use of iodized salt. Further serum thyroid hormone levels and urinary iodine excretion levels will also be compared from these subjects.

Specific objectives

(i) Water and food based

➢ To assess the iodine content of drinking water and foodstuff from the most common sources of the areas as a proxy indicator of the iodine content of soil.
➢ To determine the iodine content as well as iodine loss during storage and cooking of commonly used brands of salt consumed by subjects in the area of study.

(ii) Animal experimentation

➢ To study the effect of different levels of dietary iodine with or without goitrogen on the growth, tissue protein, enzymes and hormonal levels as well as lipid profile of weanling and adult animals. The reproductive performance of these animals will also be assessed.
➢ The first generation animals of the parental generation from above will also be studied to assess the effect of different levels of dietary iodine with and without goitrogen on the growth, serum hormonal levels and reproductive performance.
➢ To assess the protective effect of nutritional intervention in the form of dietary antioxidants such as vitamins C, E, A and β-carotene on MMI-induced hypothyroidic albino rats.

(iii) Human studies

➢ To assess the prevalence of iodine deficiency among 6-12 year old school children of Vallabh Vidyanagar on the basis of clinical examination.
➢ To assess the growth pattern and correlate it with the urinary iodine excretion levels and type of salt consumed on a sub-sample of children.
➢ To study the socio-economic background, awareness of mothers regarding iodized salt, type and quantity of salt purchased, frequency of consumption of goitrogenic foods etc and compare it with urinary iodine excretion levels of children, identified with IDD on the basis of clinical examination.
➢ To assess the knowledge levels of shopkeepers selling salt in the local area of Vallabh Vidyanagar on the selling, storage and packing of salt.
➢ To compare the awareness of IDD, consumption of iodized salt and frequency of consumption of goitrogenic foods in normal adult subjects and subjects suffering from hypothyroidism.

➢ To compare the serum T₃, T₄ and TSH levels as well as urinary iodine excretion of normal subjects with subjects suffering from hypothyroidism.