Chapter 1

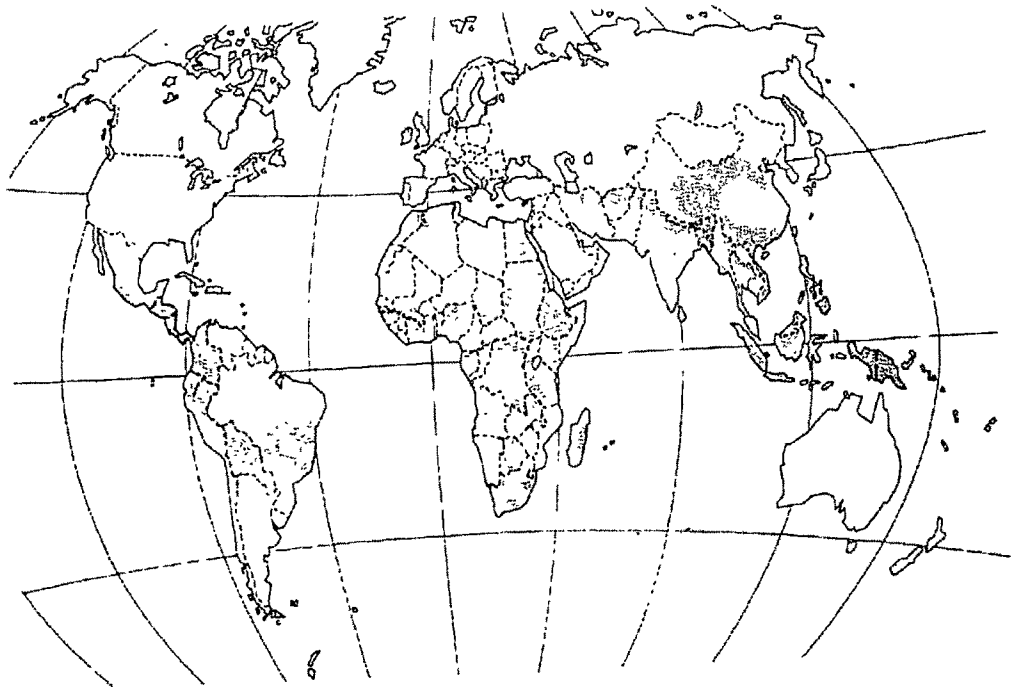
STATEMENT OF THE PROBLEM

Iodine-deficiency disorders (IDD) is the inclusive term used to refer to the various effects of iodine deficiency, which is among the body's essential trace elements. Iodine deficiency occurs when daily intake of iodine falls below the jointly recommended levels for each target group (World Health Organization (WHO), United Nations Children's Fund (UNICEF), and International Council for the Control of IDD (ICCIDD). These levels are: 90 μg for preschool children (0 to 59 months); 120 μg for schoolchildren (6 to 12 years); 150 μg for adults (above 12 years); and 200 μg for pregnant and lactating women.

Iodine is the raw material for thyroid hormone synthesis that occurs in thyroid gland factory and when iodine intake falls below the recommended levels mentioned above, the thyroid gland might not be able to synthesize sufficient amounts of thyroid hormone any longer. The resulting low level of thyroid hormones in the blood (hypothyroidism) is the principal factor responsible for the damage done to the growth, developing brain, and the other harmful effects known collectively as the IDD (Hetzel BS, 1985). In recent years it has been shown that even mild iodine deficiency is a risk to physical growth and mental development of children. The adoption of this term emphasized that the problem extended far beyond simply goitre and cretinism.

IDD continue to threaten the health and well being; and the social and economic productivity and advancement, of a billion people throughout the developing world and pockets of Europe (Figure 1.1.).

FIGURE 1.1.IDD IN DEVELOPING COUNTRIES



The sad reality of people who live in iodine deficient environment is that they suffer from reduced mental ability. An iodine deficient environment occurs due to a natural ecological phenomenon in many parts of the world. The erosion of soils in riverine areas due to loss of vegetation from clearing for agricultural production, overgrazing by livestock and tree cutting for firewood, results in a continued and increasing loss of iodine from the soil. Groundwater and foods grown locally in these areas lack iodine. Humans consuming exclusively this iodine lacking locally grown foods can suffer from reduced

mental ability and other IDD. The human implication of these conditions is at large the economic burden caused to the family in a developing country and to the community in Europe.

The most critical period for IDD is from the second trimester of pregnancy to the third year after birth. Normal levels of thyroid hormones are required for optimal development of the brain. In areas of iodine deficiency, where thyroid hormone levels are low, brain development is impaired. In its most extreme form, this results in cretinism, but of much greater public health importance are the more subtle degrees of brain damage and reduced cognitive capacity that affect the entire population. As a result, the mental ability of ostensibly normal children and adults living in areas of iodine deficiency is reduced compared to what it would otherwise be. Endemic goitre is the most common IDD and its prevalence rises commensurate with the degree of iodine lack, reaching 100% in communities with severe iodine deficiency.

In 1985, it was reported that a huge number of people-over 400 million in Asia alone was at risk of IDD (Dunn JT, 1985).

In 1990, it was reported that at least one billion people were at risk of IDD because they were dependent on food from iodine-deficient soil. This massive population included 200 million people with goitre and 20 million with preventable brain damage (Hetzel BS, 1990). The World summit for children pledged the virtual elimination of IDD by the year 2000 that was endorsed by World Health Assembly as well as International Conference of Nutrition.

In 1993, Iodine deficiency was recognized as a major international significant public health problem in 118 countries (ICCIDD/UNICEF/WHO).
In 1994, an estimate showed that 1,572 million people worldwide lived in an iodine-deficient environment where IDD was prevalent and detected areas were goitre endemic because total goitre rates (TGR) were above 5%. At least 655 million of these were affected by goitre and 43 million of these were

believed to be significantly mentally handicapped (ICCIDD/UNICEF/WHO, 1994).

In 1999, key estimates reported were: that of the world's 191 countries, IDD was a public health problem in 130, and data were insufficient in another 41 countries. Only 20 countries were classified as no longer having IDD and these are the developed countries. A total of approximately 740 million people were affected by goitre that is about 13% of the world's population. Given that goitre represents the tip of the IDD iceberg it is likely that a much greater proportion of the population suffers from IDD and, in particular, from some degree of mental retardation. About 5 billion people live in 130 countries affected by IDD, and about 38%, or 2 billion, are at risk for IDD. This was based on estimates of TGR by palpation of the thyroid gland (the report recognized that TGR was not the best indicator, but was still the most widely available for estimates such as these). About 68% of the population in these affected countries did consume some iodized salt (de Benoist, Todd, Delange, and Dunn, ICCIDD, 1999).

While the struggle to conquer IDD started in the early years of the twentieth century, the last decade had seen the greatest progress. That progress had been particularly rapid in Asia and Africa. In spite of this progress, however, the estimated number of the total affected population at the global level had not changed substantially compared with the figure previously published in 1994. The reason lies in the fact that in 1994 the magnitude of the problem had been underestimated because some of the information was not yet available.

Thus the problem has increased in 5 years from 1994 to 1999, in Europe, Africa and Eastern Mediterranean (Table 1.1 and Figure 1.2). At the same time there is an increase in the number of countries at risk of IDD and also the absolute number of people affected overall by goitre. All this happened despite the interest taken by the International agencies like WHO, UNICEF,

ICCIDD to control the IDD and the measures taken by them. Americas and Western Pacific regions have drastic decline in the percentage of population affected by goitre. There is no much change in the South East Asia in the population affected by goitre or their percentage in the region (Figure 1.2.).

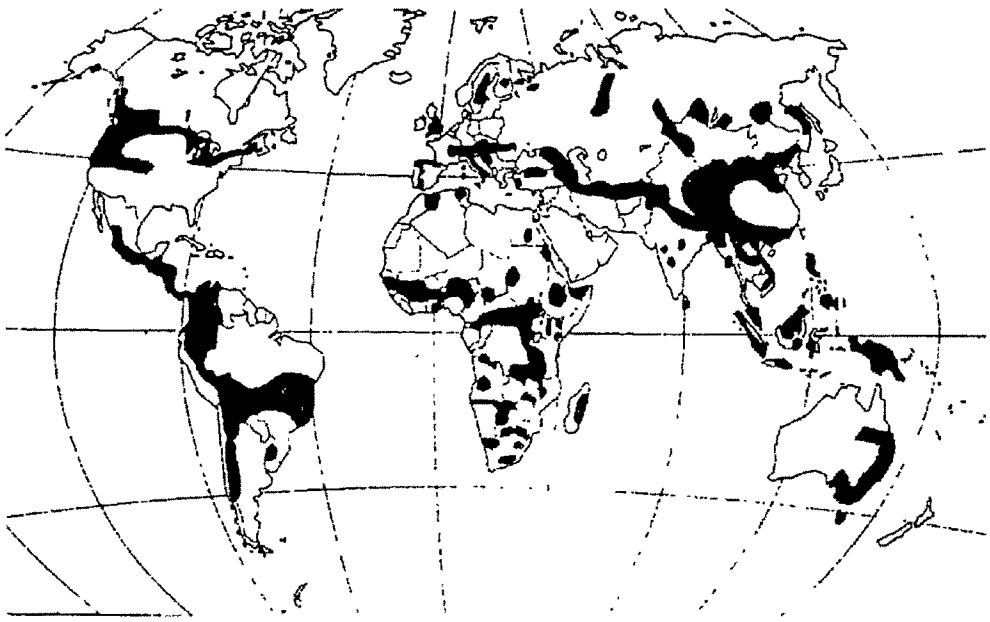
TABLE 1.1. CURRENT MAGNITUDE OF IDD BY GOITRE IN MILLIONS BY WHO REGION

*WHO Region**	*Population*		*Goitre affected*		*% of the Region*	
	1994	*1999*	1994	*1999*	1994	*1999*
Africa	550	*612*	86	*124*	15.6	*20.0*
The Americas	727	*788*	63	*39*	8.7	*5.0*
South-East Asia	1355	*1477*	176	*172*	13	*12.0*
Europe	847	*869*	97	*130*	11.4	*15.0*
Eastern Mediterranean	406	*473*	93	*152*	22.9	*32*
Western Pacific	1553	*1639*	141	*124*	9	*8.0*
Total	**5438**	***5858***	**655**	***741***	**12**	***13***

Source: WHO Global IDD Database

*Based on UN Population Division estimates, 1997.

FIGURE 1.2. ELIMINATION OF IDD FROM AMERICAS



India is a second most populous country in the world with a population of more than one billion. A WHO report on IDD in South East Asia reported that there was a breakdown of IDD in India with at least 200 million people at risk for IDD (Hetzel BS, 1986). A high prevalence of goitre and cretinism existed in the broad Himalayan and sub-Himalayan belt. Problem of IDD was first observed as goitre in the Sub-Himalayan belt and since then it is still found throughout India. Several district level goitre prevalence surveys were done over past 20-30 years in 29 of the 32 States and Union Territories of India. Of the 236 districts surveyed in 29 states/ Union Territories (of the total of 32), 194 districts were found endemic. Since iodination started over 30 years ago, goitre has been reduced, though remains relatively high.

In 1989 a conservative Indian estimate suggested that 150 million were at risk of IDD, 54 million had goitre, 2.2 millions suffered from cretinism and 6.6 million were affected from milder neurological defects attributable to environmental iodine deficiency (Figure 1.3.).

FIGURE 1.3. ENDEMIC GOITRE AREAS OF INDIA

The TGR obtained by palpation was based on 1960 World Health Organization (WHO) classification of goitre grades for the thyroid gland. The cause of goitre was not discussed for this prevalence but the entire country was declared as endemic goitre prone.

Entire India was shown as mildly iodine deficient in the world map of 1980 (Figure 1.3.) with an exception of Himalayan belt that was declared as severely affected. If iodine deficiency was the main cause of endemic goitre then following four arguments should have supported it:

1. The close association between a low iodine content in food and water and the appearance of the disease in the population;
2. The sharp reduction in incidence when iodine is added to the diet; and
3. The demonstration that the metabolism of iodine by patients with endemic goitre fits the pattern that would be expected from iodine deficiency and is reversed by iodine repletion.
4. Finally, iodine deficiency causes changes in the thyroid glands of animals that are similar to those seen in humans.

The term endemic goitre is a descriptive diagnosis and reserved for a disorder characterized by enlargement of the thyroid gland in a significantly large fraction of a population group, and is generally considered to be due to insufficient iodine in the daily diet. Endemic goitre may be said to exist in a population when more than 5% of the preadolescent (at 6-12) school-age children have enlarged thyroid glands (WHO/ICCIDD/UNICEF, 1994), as assessed by the clinical criteria of the thyroid lobes being each larger than the distal phalanx of the subject's thumb. In the past endemic goitre was said to be a problem if more than 10% of the population had thyroid enlargement.

There was Salt Legislation in most of the 32-states/union territories. 28 States of India had full bans and 2 States had partial bans against non-iodized salt but there was no Legislation for Animals salt consumption. Level Salt

Iodization required was 30 parts per million at production and 15 parts per million at consumption with potassium iodate.

Ministries of Health and Family Welfare in collaboration with the salt commissioner in the Ministry of Industry ensured the production, distribution and quality control of iodinated salt. There was a Central IDD Cell at the Directorate General of Health Services (DHGS), and each State had its own IDD Control Cell. State Health Departments were responsible for quality control of salt within State, creating consumer demand, monitoring iodized salt consumption, training and IEC. Iodized salt was available to 65% and India is self sufficient in its salt production.

The importance of eliminating IDD and improving public health had resulted in rapid progress towards Universal Salt Iodization (USI). The production of large crystal salt that posed a problem for the iodization program had been largely discontinued. This was done deliberately because during storage and transport, dust and dirt accumulated on the crystals, so consumers washed the iodized salt thereby washing away the iodine on the surface of the crystal and so very little iodine would actually reach the consumer (UNICEF). It was recommended that states should ban the sale of loose salt.

The Indian food industry was using iodized salt in products such as pickled vegetables, fruit juice concentrates, chocolate, carbonated drinks (Pepsi and Seven Up), and western style bread. No negative reports had been received so far about the effects of iodized salt on these products.

Cost of Iodized Salt is Rupees 10/-kg pack whereas the cost of uniodized Salt Rupees 1 to 2/ kg packs.

India has made considerable progress in its IDD control program, particularly in light of its huge size and reliance solely on iodized salt. Several publications summarize the large amount of data. A review reported the plan

to achieve a goal to reduce IDD prevalence below 10% in endemic districts (The indicators used to monitor the IDD control program in India are thyroid size estimation by palpation) by the year 2000 (Ministry of Health and Family Welfare, India, 1997). Major activities included in the plan were IDD surveys, supply of iodized salt, re-surveys every five years, laboratory monitoring, and education.

Food is the major source of iodine as 90% of iodine is obtained from it. At the same time it is the source for iodine supplementation programs including iodinated salt and ingestion of goitrogenic substances. Vegetables and fruits grown and obtained from sea shore and also sea fishes are rich in iodine. Vegetables and fruits in hilly regions lack iodine. Thus dietary iodine is needed in minute amounts to maintain healthy functioning of the body where it is used to make thyroid hormone. When iodine intake consistently falls below normal requirements, individuals are at risk of developing iodine deficiency disorders (IDD). Of all the groups in the population, iodine deficiency most affects the newborn.

Iodine content of plant-food is low compared to animal-food (seafood). Most terrestrial plants have low iodine content averaging 1mg/kg dry weight. Iodine is vulnerable to moisture and heat. Loss of iodine is observed during cooking. Loss is maximum in boiling and minimum in roasting. Higher loss during boiling can be attributed to the fact that iodine is volatile and gets evaporated during boiling.

Although goitre was long ago reported from Gujarat State (West India) in 1902, only one study of goitre survey by palpation was reported thereafter from Bharuch district in 1987 (Map India). The first question needing answer was the magnitude and distribution of IDD prevalence in other districts of Gujarat?

A combination of mainly clinical and biochemical parameters is used to assess the iodine status of a population. The biochemical indicators comprise urinary excretion of iodine, serum thyroglobulin levels and serum thyrotropin levels (TSH), whereas the clinical indicators include prevalence measures of thyroid size (goitre) and neurological disability such as cretinism. For nearly half a century the benchmark method for determining the state of iodine nutrition has been the measurement of iodine excretion in the urine. Urinary iodine is the main impact indicator of current iodine intake. The method of determination for UI is entirely objective and non-invasive, but has several potential sources of error. Blood spot TSH measurement is an excellent indicator for the case detection of hypothyroidism in neonate but may be used as a surrogate measure of iodine nutrition in the entire community by looking at the skewness of the distribution of the entire set of blood TSH values. However, by its very nature it requires that universal neonatal screening be in place, a situation that is not generally found in a developing country like India. No major survey that used biochemical prevalence indicators of IDD had been carried out in Gujarat State.

There was a need to study at least two districts; one from plain land and another from mountainous hilly area because IDD is said to have geographical diversity. Which populations (Rural, tribal or urban) were at high-risk? Was socio-economic background affecting the prevalence? In 1982 a survey of schoolchildren in Chile showed that children from lower socioeconomic status and rural areas had greater goitre prevalence. If this was in the condition in Chile what could be the condition in India? In Italy, endemic goitre was widespread in mountainous area while big cities with populated areas were free of it. Coastal population of Portugal was not affected by goitre but the interior regions were severely affected by it. There was also a need to identify severely affected communities for intervention and more efficient use of resources was needed. To test the value and suitability of biochemical testing of children in remote and isolated communities was the important task indeed. There was a need to establish severity of IDD for a

biochemical baseline in a sub-sample of the larger population of Gujarat so that the effectiveness of iodine replacement programs could be monitored. In this study 1,363 children (0-15 years) were studied and data were collected on dietary habits and anthropometric and biochemical parameters such as height, weight and urinary iodine (UI) and blood TSH respectively. BSA and BMI were calculated. Drinking water and salt consumed in different places were analyzed for iodine content. It was seen that the Median UI was 65 µg/l and the interquartile range was 38 – 108 µg/l suggesting mild to moderate iodine deficiency. The mean TSH was 2.1 mU/L and the standard deviation was ± 2.1 mU/L, which is quiet high. Six percent of the studied population had whole blood TSH values > 5 mU/L. Females from both districts were more affected by iodine deficiency as evidenced by lower true urinary iodine and higher mean TSH levels. Most of the subjects were vegetarian and consumed goitrogens. The interfering substances in the urine samples, postulated to be the goitrogens, were significantly higher in Baroda boys and Dang girls as compared to their counterparts ($p < 0.001$). Boys were more malnourished than girls as evidenced from lower BMI were. Dang district was more severely affected by IDD as compared to Baroda. Drinking water in Dang district was lacking in iodine content. Iodine in salt varied around 7 to 2000 parts per million. The data therefore suggested that IDD is a public health problem in both districts of Gujarat. Baroda district (rural) was a new pocket of IDD. High amounts of dietary flavonoids in Baroda and Dang, and lack of iodine in Dang water, accounted for IDD.

The next study of assessing the severity of IDD was conducted by screening adult women and men through household survey by biochemical prevalence indicators. The regional IDD control cell was established in 1962 and most of the subjects were born after that. What was the result of such a control program evolution when in addition to iodine deficiency multiple confounding factors like malnutrition and goitrogens may be responsible for goitre. 959 adults (16-85 years) were studied from Baroda and Dang districts. The

normative accepted WHO values for UI and TSH for the severity of IDD as a significant health problem are not available for target population of adults till today. UI normative limits and cut-off were established by ICCIDD/WHO only for school aged children. Blood spot TSH upper limit and cut-off values are available for neonate populations. The IDD had not been eliminated so far as more than 20% of both adult male and female subjects had UI < 50 μg/l. Pearl millet from Baroda contained flavonoids like apigenin, vitexin and glycosyl-vitexin.

Both studies in children and adults of biochemical parameters for the extent of severity of IDD suggested that there was a mild IDD in Gujarat and involvement of goitrogens. Both rural and tribal populations were affected but the tribal one was affected more than rural when compared. It was beyond doubt that socioeconomic status played a big role in IDD.

IDD is a global problem with goitre as a compensatory adaptation to iodine deficiency. Goitre and cretinism are the only visible effects of IDD and account for only as much as 10% of the ramifications whereas 90% of IDD consequences remain hidden, hence it became necessary to evaluate thyroid enlargement first. This led to determining the thyroid size by palpation and ultrasonography. Thyroid size was determined first by traditional method of palpation and then measured by ultrasonography to get an estimate of thyroid volume in milliliters. The specific gravity of thyroid being one would give the exact weight of the gland in grams from milliliters. How should palpation be scored was the next decision to be made? In 1994, WHO/ICCIDD recommended a simplified 2-grade system thereby replacing the old 1960 classification having 4-grade system. We preferred the recent simplified 2-grade system. At the same time WHO also recommended that goitre prevalence should be measured by ultrasonography as it was a safe and noninvasive technique and provided a more precise and objective method of determining thyroid size. Ultrasonography gives a quantitative measure of

thyroid volume that is largely free of observer bias. Although in areas of severe or moderate iodine deficiency, thyroid palpation provides a reliable method for goitre prevalence rate (TGR) assessment, serious problems are encountered in areas with mild iodine deficiency, where most goitrous subjects have small goitres. It was known that rest of India besides the Himalayan and sub- Himalayan belt was mildly iodine deficient (map of India from SOS for a billion) hence ultrasonographically determined thyroid size was a necessity for finding the IDD prevalence in the population of Gujarat. At the same time thyroid palpation is less reliable in children than in adults. The more refined method for determining the magnitude of iodine deficiency in a population is by estimating the proportion of children with enlarged thyroid volumes based on ultrasonography. Correct interpretation of ultrasonography results depends upon the availability of valid reference values. World Health Organization (WHO) has adopted a new thyroid volume international reference for assessing IDD (WHO 1997). Palpation, an initial signal of IDD, pointed to the grave endemic goitre problem in Gujarat hence more refined assessment was needed. As WHO has strongly recommended the use of ultrasonography technique to define the goitre endemia in areas of mild iodine deficiency epidemiological surveys, this reliable method for the evaluation of thyroid volume proved a useful and practical method. The availability of portable ultrasound equipment facilitated its application to our epidemiological field studies. The procedure was used to measure thyroid volumes in several hundred subjects in a day.

Applying the WHO ultrasonography reference to Gujarat children resulted in an enlarged TV-for-body surface area in almost 100% of subjects (529/530). Why was total goitre rate 100%? Was there an interaction of iodine deficiency with other nutritional factors in the development of goitre? Several agents, both naturally occurring and man-made, pose the danger of thyroid disease by interfering with thyroid function. These compounds can alter thyroid structure and function by acting directly on the gland or by affecting its regulatory mechanisms. The gland may increase in size to become a goitre.

Thyroid hormone secretion may remain adequate or become insufficient depending on dietary iodine intake or the presence of underlying thyroid disease. This study in schoolchildren showed that measuring the thyroid size by ultrasound was the best prevalence indicator of IDD and iodine deficiency was the principal but not the only cause of endemic goitre in Gujarat. The additional role of naturally occurring goitrogens was postulated along with primary protein energy malnutrition.

Importance of thyroid volume in adult population over the age of thirty years as a prevalence indicator for the aetiology and severity of IDD remains unclear (WHO). We selected 472 adults through household surveys in Gujarat and collected data on anthropometric, biochemical and clinical parameters as used for children. As criteria in adult populations are not available for IDD status as recommended by World Health Organization (WHO), the data applicable to school-aged-children/neonates were used to provide IDD status of adults. Total goitre rate (TGR) of 10% by palpation and 82% by ultrasonography indicated mild and severe IDD respectively. 90% women in childbearing age group below 50 years had enlarged thyroid. Goitre prevalence of 82% by ultrasound is very high compared to the degree of iodine-deficiency that was mild. This pointed to a probable multifactorial involvement of iodine deficiency, dietary flavonoids and malnutrition for the development of goitre. Thyroid palpation was of limited value as grade 0 and 1 goitre predominated whereas thyroid volume measurement by ultrasound proved to be a more sensitive and an important prevalence indicator for the past history of IDD in adults over the age of 30 years.

Agents and pollutants that cause goitre – are also known as environmental goitrogens. The study of environmental goitrogens is difficult, important and controversial. With the exception of iodine deficiency, the public health and socioeconomic impact of environmental goitrogens are practically unknown. The goitrogens acted on which stage of hormone formation?

The main goitrogens consumed were thiocyanates and goitrin (cruciferae, capparidaceae and resedaceae family vegetables), isothiocyanates (mustard seeds), aliphatic disulfides (onion)[c] and a variety of different flavonoids consumed in bulk because they constitute an integral part of vegetables, fruits, pulses and grains.

The main flavonoids consumed were arachidoside (peanuts and its oil; peanut oil was used by almost all families for cooking, and in milk), catechin and kaemferol (tea and all vegetables), quercetin (onion), flavenol glycosides (red kidney beans and tomato), anthocyanidin and biflavan (vegetables, cereals, tubers, bulbs, and natural pigments), genistin, daidzin, glycitein, formononetin, biochanin-A and isoflavanone (soy, green and black beans and in Leguminosae family vegetables), vitexin and apigenin (pearl millet).

Agents acting directly on the thyroid:

The first Step of thyroid hormone syntheses involves the active uptake or concentration of inorganic iodide by the thyroid. Environmental goitrogens such as thiocyanates interfere with this process. This effect of thiocyanates is overcome by iodine administration.

The second step entails the incorporation of oxidized iodine into the amino acid tyrosine –within the peptide sequence of thyroglobulin- to form mono-iodo-tyrosine (MIT) and di-iodo-tyrosine (DIT). This is organification and the process is mediated by the action of thyroidal per oxidase (TPO) enzyme. Resorcinol, and its Other Phenolic and pheno-carboxilic (DHBA) parent compounds, flavonoids, aliphatic disulfides and "Goitrin" inhibit organification. The effect of goitrin and flavonoids cannot be overcome by iodine administration. Flavonoids inhibit TPO hence iodination of tyrosine to form MIT and DIT is decreased. This IDD caused by goitrin and flavonoids can not be corrected by iodine supplementation. Is the goitre due to the combined

effect of different goitrogens like flavonoids and goitrin and do they act together or separately?

Because of their antithyroid effects, administration of any of these agents eventually resulted in goitre formation and in some instances in hypothyroidism. For this reason they are called goitrogenic compounds. It became apparent that an absolute lack of dietary iodine or a decrease in iodine utilization due to environmental pollutants, or both, can result in "sporadic" or "endemic" goitre.

Environmental pollutants operating in genetically predisposed individuals may as well trigger the pathologic mechanisms that lead to goitre formation and autoimmune thyroiditis. Although this process has been induced experimentally in certain strains of rats, its occurrence in man has not been demonstrated (Weetman AP, 1984).

TABLE 1.2. AGENTS ACTING ON STEPS OF THYROID HORMONE SYNTHESIS:

Thiocyanates **Isothiocyanates**	Resorcinol, Other Phenolics DHBAs, **Flavonoids, Disulfides, "Goitrin"**	Iodide Lithium
Iodide Transport	Oxidation Organic Binding and Coupling With thyroid peroxidase	Proteolysis, Release and Dehalogenation
$I^- \rightarrow$	$I^- \rightarrow I_2$ **Thyroglobulin MIT DIT→** Thyroid gland	→ T4 and T3

Agents acting indirectly on the thyroid:

A decrease in thyrotropin secretion results in decreased synthesis and release of T4 and T3 and involution of the thyroid gland. The antithyroid effect of 2,4-dinitrophenol (DNP) is due in part to an inhibition of the pituitary TSH mechanism. Polymers of the Flavonoid, phloretin, also interact with TSH preventing its action at the thyroid cell. (Gaitan E, 1986)

All circulating T4 and 20% of T3 are derived from the thyroid gland. The rest of T3 is produced by outer ring monodeiodination of T4 in the peripheral tissues. Flavonoids not only inhibit the thyroid peroxidase (TPO), but also the peripheral metabolism of thyroid hormones by acting on iodothyronine deiodinase enzymes (Gaitan).

A tremendous gap from a public health point of view persists between the well documented biochemical knowledge of these goitrogenic compounds and their action in human beings.

The first step in the formation of thyroid hormones (active uptake of inorganic iodide) may be compromised in these children due to competitive inhibition by thiocyanates (SCN) or aliphatic disulfides (major components of onion and garlic). This step is overcome by iodine administration. However it is also possible that iodine trapping mechanism efficiency was only 10-20% due to inverse relationship to serum I_2 concentration.

Isothiocyanates in Mustard seeds can react spontaneously with amino acids forming di-substituted thiourea derivative, which produces a thiourea like antithyroid effect hence these may be one of the possible mechanism responsible for goitre in these otherwise euthyroid subjects.

The second step for thyroid hormone synthesis entails the incorporation of oxidised iodine into the amino acid tyrosine –within the peptide sequence of

thyroglobulin- to form mono-iodo-tyrosine (MIT) and di-iodo-tyrosine (DIT). This is organification and the process is mediated by the action of thyroidal per-oxidase enzyme (TPO). Flavonoids, aliphatic Disulfides and "Goitrin" inhibit organification.

Progoitrin in Brassicae vegetables may be converted by hydrolysis to goitrin by normal GIT (large intestine and caecum) bacteria such as Escherichia coli and Proteus vulgaris. Goitrin inhibits TPO. Its action can not usually be antagonized by iodine. Goitrin (L-5 vinyl -2 thiooxazolidone) is acting like thionamide type of goitrogen such as thiourea.

Food preparation does not damage flavonoids because they are very stable and resistant to heat, oxygen, dryness and acid but destroyed by illumination. Flavonoids present in foods were considered once non-absorbable but later it was known to be absorbable in the large intestine after action of intestinal bacteria. It was also recently reported that the human small intestine possesses an ability to liberate the aglycone from quercetin glycosides. Nevertheless, quercetin glycosides are found to be present in human plasma without metabolic conversion.

Acute and chronic administrations of naturally occurring and synthetic flavonoids in animal experiments have demonstrated marked effects on thyroid hormone homeostasis, metabolism and action. Flavonoids (synthetic F 21388) mimic the three-dimensional structure of thyroxine hence there is a competition for binding to transthyretin (TTR); a carrier protein in serum. Thyroxine is displaced from its binding thereby increasing free T4 levels and their transfer to cells that is followed by elimination. Whether TTR interaction with naturally occurring flavonoids or their metabolites is of relevance in thyroid hormone physiology remains to be elucidated.

Flavonoids are potent antithyroid drugs. Well documented effects include inhibition of TSH secretion, direct inhibition of TSH, inhibition of TPO,

competition for thyroid hormone binding to TTR, and potent inhibition of I 5' – deiodinase activity. These multifaceted actions might represent the amazing power of active principles of these plant constituents, but also raises problems of identifying the mechanisms of action and characterizing clear pharmacological profiles.

Antithyroid effects of purified flavonoid, quercetin and rutin were investigated (Jeney et al) by oral ingestion of very small amount in water for 5 months. Thyroid weights increased whereas the iodide content of the thyroids was reduced. Histological examination demonstrated typical thyroid hyperplasia. The investigators suggested the role of flavonoids in the etiology of endemic goitre. If such small amounts of flavonoids can cause goitre then could large quantities of almost all different types of flavonoids consumed daily for many years result in the goitre in iodine sufficient and well nourished children?

The vegetables produced and consumed in Gujarat (Western India) are exclusive to those consumed in all other parts of India (north, south and East India). We carried out a study in the sub-Himalayan belt where these vegetables were not available. As Indian children weigh substantially lower and are shorter than same-age European children, it is possible that normal thyroid size would be small.

Were dietary goitrogens present equally in the diets of various communities of Gujarat?

All communities eat different cereals, vegetables, oils used for cooking, pulses, nuts and fruits. The main cereals used are wheat, rice, pearl millet, jowar, maize, and nagli. The vegetables consumed belong to roots and tubers, leaves, stems, seeds and fruits. Pulses used are Tuver, udad, moong, various split grams, whole beans etc. The main oils used are groundnut oil, palmolein oil and cottonseed oil.

Food articles named above needed quantitative and qualitative analysis for flavonoids like arachidoside, vitexin, glycosyl-vitexin and apigenin contained in all of them.

Was there any relationship of malnutrition to thyroid size?

The world has a strong image of malnutrition. It is the image of a child with eyes too large for a face that is old before its time, a child whose grey and dehydrated skin is drawn taut over a fragile ribcage, a child almost too weak to lift the empty bowl to be filled with food donated from overseas. Such malnutrition is real in Somalia, real in Rwanda, real in Liberia. But it is unusual and extreme, affecting less than 1% of the developing world's children and almost always as a result of some quite exceptional circumstance - war, or famine, or both.

But there is another malnutrition that is not visible, either to parents or health workers or to a worldwide public. It is the malnutrition of the 1-year-old child who weighs only 6 kilograms, of the child who looks to be 7 years old but turns out to be 10 or 11, of the child who is sitting in the shade, dull-eyes, without even the energy to ward off the flies, of the child who rarely joins in the games and adventures of others, of the child whose eyes are glazed over behind a school desk and who does not understand or remember what he or she is being taught. For poor nutrition in the early years of life does not only mean low walls of resistance to disease, or poor physical development. It also means disruption of proper brain development that would make lifelong learning possible.

This is the protein-energy malnutrition that, in some degree, affects over one third of all the children under five in the developing world. It is not caused by the lack of any one particular nutrient, but by the complex interaction of poor diet and frequent illness. And it strikes at the foundations of development in both people and nations.

Recent research has also made significant new contributions to our understanding of the relationship between malnutrition and child mortality. Briefly, about 55% of the 13 million under- five deaths in the world each year are the deaths of children who were malnourished. And of those 7 million nutrition-related deaths, some 80% are the deaths of children who were only mildly or moderately malnourished.

Malnutrition remains amongst the most devastating problems worldwide encompassing a spectrum of nutrient-related disorders, deficiencies and conditions including intrauterine growth retardation, protein-energy malnutrition (PEM), iodine deficiency disorders (IDD), vitamin A deficiency, iron-deficiency anaemias and other diet-related non-communicable diseases. The term "malnutrition" encompasses the severe form of wasting characterized by the clinical conditions of marasmus and kwashiorkor as well as milder forms of under-nutrition, characterized by a significant deficit in one or more of the anthropometric indices. Malnutrition is synonymous with protein-energy malnutrition, which signifies an imbalance between the supply of protein and energy and the body's demand for them to ensure optimal growth and function. This imbalance includes both inadequate and excessive energy intake; the former leading to malnutrition in the form of wasting, stunting and underweight, and the latter resulting in overweight and obesity. In children, malnutrition is synonymous with growth failure - malnourished children are shorter and lighter than they should be for their age. PEM is by far the most lethal form of malnutrition and is "the silent emergency". These young lives are prematurely - and needlessly - lost. The minerals are needed in tiny quantities, on the order of a few thousandths of a gram or less each day. They are consequently called micronutrients and are needed for the production of enzymes, hormones and other substances that are required to regulate biological processes leading to growth, activity, development and the functioning of the immune and reproductive systems. While micronutrients are needed at all ages, the effects of inadequate intake are particularly serious during periods of rapid growth, pregnancy, early childhood and

lactation. We are learning more every day about the importance of micronutrients for the physical and the cognitive development of children.

Malnutrition is frequently part of a vicious cycle that includes poverty and disease. These three factors are inter-linked in such a way that each contributes to the presence and permanence of the others. Socioeconomic and political changes that improve health and nutrition can break the cycle; as can specific nutrition and health interventions. The WHO Global Database on Child Growth and Malnutrition seeks to contribute to the transformation of this cycle of poverty, malnutrition and disease into a virtuous one of wealth, growth and health.

In the developing world in 1995, of the estimated 10.4 million deaths among children under 5 years of age, protein-energy malnutrition was associated and causative factor in 5.1 million of these deaths (ie 49%).

Growth assessment not only serves as a means for evaluating the health and nutritional status of children but also provides an indirect measurement of the quality of life of an entire population. Anthropometry is the single most portable, universally applicable, inexpensive, and non-invasive technique for assessing the size, proportions, and composition of the human body. It reflects both health and nutritional status of an individual. It is a valuable tool for guiding public health policy and clinical decisions. Anthropometric indices are internationally accepted as key indicators of nutritional status of the population. Among the anthropometric measurements that are commonly employed in nutrition surveys are body weight, height, sitting height, BMI, skinfold thickness (TSF), mid-upper-arm and thigh circumferences. In a given population, a high prevalence of anthropometric deficit will be indicative of significant health and nutritional problems, however, it is not only those individuals below the cut-off point who are at risk; the entire population is at risk.

Since the Global WHO Database is a dynamic surveillance system and new information is continually being collected, screened and entered, data collection can never be considered complete. Despite the considerable effort made to compile all available information, gaps in knowledge are inevitable. PEM occurs primarily in developing nations in endemic forms. The prevalence may approach 25%. Of the World's undernourished people more than half live in India.

Experimental and clinical studies have shown that acute and chronic starvation and calorie restriction significantly alter the endocrine system in general and affect the thyroid gland in a number of ways.

Although IDD is a specific nutritional disorder due to a deficiency of the micronutrient iodine the effects of generalized malnutrition on the expression and severity of IDD remains to be elucidated. The probability that factors other than iodine deficiency contribute to the production of endemic goitre was perceived as early as 1924. Ingenbleek has suggested a close relation between nutrition and goitre based on the findings of his study. Because of the high cost of animal protein and constraints imposed by caste and religious norms, most Indians are vegetarians and depend on pulses for their protein requirements. Expected malnutrition in Gujarati tribal population due to poverty and non-consumption of balanced diet for their vegetarian habits led to measuring nutritional status of confirmed iodine deficient population of Gujarat (tribal and rural schoolchildren and adults). Thus we tried to elucidate the relative contribution of PEM on thyroid size (as determined by ultrasound) as this confounding factor would further compromise thyroid hormone homeostasis. The principle aim was to study the impact of malnutrition in the mild to moderate iodine deficient population of Gujarat. PEM was assessed by direct anthropometric measurements like height, weight, mid upper arm circumference (MUAC), thigh circumference (TC) and triceps skinfold (TSF) thickness and derived indices like body surface area (BSA), body mass index (BMI), arm muscle area (AMA) and arm fat area (AFA). AMA measures lean

body mass whereas AFA reflects the subcutaneous adipose tissue. PEM prevalence was assessed in children as by the WHO percentage prevalence of three indicators of stunting, wasting and underweight and by Waterlow classification. Goitre by ultrasonography was seen in almost 100 % of children. Regression analysis was conducted to determine the relation of PEM with thyroid volume. The results indicated a strong relation of nutritional factors with thyroid size independent of the effects of iodine. In children there was a positive correlation between TV and the indices that are directly or indirectly related to growth in children and a negative correlation between TV and the variables triceps skin fold thickness and wasting (which is the preferred index for thinness in children). In adults there was a negative correlation between TV and arm circumference that measures persistent malnutrition.

The thyroid sizes of these malnourished iodine deficient children were compared with European reference developed from otherwise normal children (adopted by WHO as normative reference). The Indian normative thyroid size reference is lacking till today. So it was necessary to develop normative (standard reference) values for clinical (anthropometric), biochemical and sonographic indicators of IDD and general nutrition in the various segments of populations in Gujarat for comparisons. The first step was to measure the urinary iodine of schoolchildren consuming iodized salt and good nutrition so that the iodine deficiency and malnutrition could not act as confounding factors for goitre. Thyroid size by ultrasound was then determined for iodine sufficient and well nourished schoolchildren. To our surprise 85% of children had enlarged thyroid. This finding pointed to a very strong role played by goitrogens alone and challenged the recent definition that IDD refers to all of the ill-effects of iodine deficiency in a population, that can be prevented by ensuring that the population has an adequate intake of iodine. It was also stated that goitre in greater than 5% of schoolchildren can be only due to primary iodine deficiency (Dunn JT, 1999). It is quite clear from our results that secondary iodine deficiency due to goitrogens can cause

compensatory adaptation in the form of goitre in a much greater percentage than 5%.

The vegetables produced and consumed in Gujarat (Western India) are exclusive to those consumed in all other parts of India (north, south and East India). There was a need to study the subjects who could not access these exclusive vegetables and grains. We carried out a study in the sub-Himalayan belt (Himachal Pradesh Capital: Shimla) from the schoolchildren in a private school boarding where these vegetables are not available. The cooking oil used was definitely, not the ground nut oil. The median urinary iodine and anthropometry pointed to iodine sufficiency and a good nutrition respectively. The thyroid sizes of these children were much smaller than the WHO normative referencing of 1997 or even the corrected 2001 reference. WHO report (1994) anticipated that normal thyroid size in Indian children would be small because they weigh substantially lower and are shorter than same-age European children. These iodine replete children however were neither short in height nor light weighted in comparison to European children. Despite being on par to European children nutritional status wise, 100% children had smaller thyroid size in this severely endemic goitre area of the past. Was this due to mandatory salt iodization policy of the State Government or due to non-consumption of flavonoids? Well it remains yet to be elucidated.

Urban iodine replete and well-nourished affluent schoolchildren in Shimla had restricted flavonoids intake being on mountains. . As there is regional dietary variation in all the States of India, a state other than Himachal Pradesh in North India was selected from South India. The capital City of Tamil Nadu, Chennai is on plain land. Study was conducted to assess iodine deficiency disorders in schoolchildren of lower socioeconomic status so that comparison was possible with rural and tribal children of same status in Gujarat. Iron deficiency anaemia study was also conducted alongwith IDD study. The thyroid size was measured by ultrasonography.

The vegetables and cooking-oils consumed in this area are different to those used in Himachal Pradesh. The nutritional status was established. Due to literacy population of this State consumed iodised salt and was iodine replete. The schoolchildren were malnourished based on stunting and undernutrition indices. 65% of schoolchildren were pale. None of the children had vitamin A deficiency. Goitre prevalence by palpation was 9 - 14% and by ultrasonography was 10% in schoolchildren.

The battle against IDD still continues into the new millennium though the solution for its control is relatively simple. A teaspoon of iodine is all a person requires in a lifetime, but because iodine cannot be stored for long periods by the body, tiny amounts are needed regularly. In areas of endemic iodine deficiency, where soil and therefore crops and grazing animals do not provide sufficient dietary iodine to the populace, food fortification and supplementation have proven highly successful and sustainable interventions. Iodized salt programs and iodized oil supplements are the most common tools in the fight against IDD.

1. Iodized Salt, first choice for intervention:
2. Iodized Oil, practical supplementation:

IDD can be prevented, but cannot be cured. Long-term consumption of iodine through iodized salt is not toxic. Iodized salt should be consumed within six months of purchase and it improves the health and productivity of livestock. Dairy cattle who are fed iodized salt produce iodine rich milk.

Many countries have already successfully eliminated iodine deficiency disorders, largely as a result of salt iodization with potassium iodate. Switzerland, where salt iodization began in 1992, is a remarkable example, since the cretinism has been eliminated and goitre has disappeared as a public health concern, while there has been negligible evidence of any adverse effect from the iodine intake.

Universal salt iodization for eliminating iodine deficiency disorders has been endorsed in numerous international forums, including the International Conference on Nutrition (Rome, 1992). In response to concerns expressed, and to facilitate decision-making in countries, WHO decided to issue a statement that summarizes the cumulative scientific and epidemiological evidence in this regard.

The statement specifies that a safe daily intake of iodine should be between a minimum of 50 micrograms and a maximum of 1000 micrograms. A generally accepted desirable adult intake is 100-300 micrograms a day. Although potassium iodide was first used in salt iodization, the use of iodate is now recommended since it is more stable than iodide under varying climatic conditions. Average daily salt intakes vary from country to country from 5 to 15 grams per day. Instead of increasing salt consumption, the quantities of iodate added to salt should be adjusted to provide approximately 150 micrograms of iodine per day, taking into account factors like heat and humidity, which can affect retention of this element during storage of iodized salt.

Why should IDD control remain such a problem when the technology is available? The most important reason is probably lack of political will. The following facts are worth noting:

1. IDD affects millions.
2. It encompasses a spectrum of effects dating from conception, through fetal life, the neonatal period, and childhood, to adulthood.
3. The new concept of IDD, rather than goitre, is not appreciated by many health professionals or by planners and decision-makers.

IDD can be prevented by the correction of iodine deficiency; this has been shown in controlled trials in various geographic situations. Early examples were with iodinated salt (Akron, Ohio; Guatemala; Kangra Valley, India), and iodinated oil (Papua New Guinea). The expense of iodine technology is

modest compared with the benefits gained. Iodinated salt costs 3-5 cents/person/year; the cost of iodinated oil injections is similar—10-15 cents/person/year if the primary health care system is available. The cost of oral oil approximates that of salt.

There is a high return in improved quality of life, greater productivity, and improved school performance by children from IDD control programs.

These studies were carried out for five years (1998-2003). Fieldwork was organized and undertaken in rural, tribal and urban areas of Gujarat and Capital cities of Himachal Pradesh and Tamil Nadu. All the laboratory work was carried out at endocrinology and urinary iodine laboratory in Institute Clinical Pathology and Medical Research of Western Sydney Area Health Services.