# Chapter 2

# HISTORICAL REVIEW AND REVIEW OF THE LITERATURE

## *2.1. THE HISTORY OF IODINE DEFICIENCY DISORDERS:*

"History is the spiritual form in which a culture accounts for its past" (Geschichte and Kultur, 1954). The story of iodine deficiency disorders (IDD) begins with a review of the history of goitre because the word "IDD" was first used in 1983 whereas the word "goitre" is old. Goitre is the most obvious physical abnormality presenting as a lump in the neck of the human body.

### *ANCIENT CIVILIZATION (2838-2698 BC TO MIDDYNASTY 1552-1578):*

The first records of goitre date back to the Chinese and Hindu cultures, and then to Greece and Rome. One of the oldest references (2838-2698 BC) to goitre is attributed to the legendary Chinese Shen-Nung Emperor who, in his book *Pen-Ts'ao Tsing (A treatise on herbs and roots)* mentioned the seaweed Sargasso as an effective remedy for goitre. In the ancient Hindu literature (Atharva-Veda) from around 2000 BC, incantations against goitre were found.

Between 770-100 BC, goitre was mentioned in the book, *Shan Khai Tsing (A treatise on waters and dry lands)* as a disease and was attributed to the poor quality of the drinking water. Other references during the Han dynasty (206 BC to AD 220 and the Wei dynasty (AD 200-264) attributed deep emotions as a cause of goitre. Even the "father of medicine", Hippocrates of the Greek island of Cos, regarded poor drinking water as a cause of goitre, as revealed in the famous volume, *Air, Water and places* (25 BC- AD 45). Several Roman authors commented on the prevalence of goitre in the Alps. The poet Juvenal (First century AD) asked, "Who wonders at a swelling in neck in the Alps?" The architect Vitruvius (first century BC) stated that the Aqui in Italy and the Medulli in the Alps got a swelling of the neck from their drinking water. The importance of drinking water in causing a swelling in the neck was agreed upon thereafter (Pliny the Elder AD 100).

The great physician Galen deduced that the glands in the neck, including thyroid, had the function of secreting a fluid into the larynx and the pharynx (132-200 AD). Soon thereafter goitre was attributed to certain conditions of life in the mountainous regions (200-264 AD) and by 300AD a picture of Buddha frieze from Gandhara (now in Pakistan) showed a goitrous subject with features of cretinism. There are animals and human beings on all sides of Buddha that try to disturb his meditation. Among these figure is a man with a large goitre and idiotic facial expression. He is carrying a drum, which the man behind him is beating with a crook. His facial expression suggests idiocy and in view of the close proximity of the drums to his ears one may even speculate that he is deaf. This "cretin" is representative of many goitrous individuals that are still to be seen in Northern Pakistan today (Blumberg and Baruch 1964).

Between AD 317-419 goitre treatment began with seaweed by a famous Chinese medical writer Ge-Khun and by AD 420-501 chinese physicians used animal thyroid preparations (deer and pig) for treating the goitre and this continued up to Ming dynasty 1552-1578. Meanwhile in AD 1220, Jacques

De Vitry highlighted deafness as one of the distinguishing features in the first non-medical description of cretins.

## *THE MIDDLE AGES (1215-1600):*

It is of great interest to note the attention given to goitre in paintings and sculptures in the Middle Ages. Goitrous cretins appeared in the pictorial art, often as angels or demons. This had been a subject of particular interest to the late Professor F. Merke of Basle (1984) who carried out investigations over many years. He unearthed the following examples from manuscripts and churches.

This starts with 1215 AD as illustrations of goitre and cretinism with stupid facial expression in the *Reuner Musterbuch (a book coming from the Cistercian Abbey in Reun near Graz in Styria, Austria),* in Austrian National Library in Vienna where goitre was endemic until recent times.

In the 13$^{th}$ century, two encyclopaedias recorded fables of human monsters from Greek and Indian mythology. Some descriptions of giant goitres were also included based on observations "*in extrerius Burgundiae circa Alpes*". One of the encyclopaedists, Jacques de Vitiga was much travelled and passed several times through Alpine, and so had the opportunity to see goitrous and cretin subjects.

In the middle of the 14$^{th}$ century, another figure appeared in the Psalter of St. Lambrecht (a village in Austria) that had a vacant pasty face with an infantile expression. These sufferers were often considered as angels or innocents with magical power. It was between 1493-1541 that the relation between goitre and cretinism was recognised by the Paracelsus. The Swiss Chronicles included illustrations of goitrous Bernese and Valaisian Warriors in the description of their raids on one another between 1575-1600.

## *THE RENAISSANCE (15TH TO 19TH CENTURY):*

The first detailed description of goitrous cretin subjects occurred during this period. The 15th century paintings of the Madonnas in Italy Galleries had a goitre and a hypothyroid child.

Eustachius Rudius, a physician from Utrecht reported in his travels through Austria in 16th century: *"Hence while travelling in a certain region in the County Tyrol, under the jurisdiction of the Bishop of Gurk, I was astonished at a very large number of madmen, fools and dolts; but when I considered the frigidity and humidity of the air, and also perceived the crudity of the waters from the very frequence occurrence of goitres, all astonishment ceased entirely".*

Felix Platter (1562) described goitre and cretinism as: *"Many infants suffer from innate folly. Besides the head is sometimes a misshapen: the tongue is huge and swollen; they are dumb; the throat is often goitrous. Thus, they present an ugly sight; and sitting in the streets and looking in to the sun, and putting little sticks in between their fingers, twisting their bodies in various ways, with their mouths agape they provoke passers by to laughter and astonishment".*

The cause of cretinism was explained to be the deformation of the skull with resultant constriction of the brain (Vesalius, 1564).

There were many views about goitre in this century, from a belief that it can be cured by the touch of a king to the recognition of well known features of cretinism, mainly idiocy.

The 17th century was full of descriptions for goitre and cretinism. The first medical description of cretinism that it showed several neurological features

including extrapyramidal dysfunction, was offered in the beginning of the century (Platter, 1602).

The description (Thomas Wharton, 1652) of the thyroid gland in the neck was made as: "It contributes much to the rotundity and beauty of the neck, filling up the vacant spaces round the larynx, and makes its protuberant parts almost to subside and become smooth, particularly in females, to whom for this reason a larger gland had been assigned, which renders their necks more even and beautiful".

However, the function of the thyroid was not understood- it was thought to produce secretory fluid to "humidify" the walls of the larynx, the pharynx, and the trachea. Prior to this, neck swellings were termed "swollen throat", "hernia gutturis", "bronchocoele" or "struma".

The 18$^{th}$ century established the relationship between cretinism and endemic goitre. The term cretin probably appeared in print for the first time in 1754 in an article by Diderot's co-editor, d'Alembert and was a novel one in the medical literature. The word cretin was derived from the French word for "christianus" (=Christian). The definition of a cretin given was "an imbecile who is deaf and dumb with a goitre hanging down to waist".

The endemic nature of goitre led to the use of the term "endemic cretinism". Many reports were published especially a book in French and German named *Traite du goitre et du crétisme* by a physician (B. E. Fodére, 1796) who registered the importance of parental goitre as a risk factor for the development of cretinism.

At the beginning of 19$^{th}$ century an escalation of interest and concern about the possibility of controlling the problem of cretinism and endemic goitre occurred. The concept that a deficiency disorder was the prime cause of endemic goitre was generally not accepted even by the middle of the century.

Napoleon ordered a systemic investigation of goitre because young men were rejected for military duties and declared as unfit.

Iodine was first isolated from the ashes of the seaweed (Courtois, 1813) and subsequently its presence in the animal body was demonstrated (Courtois, 1819).

Iodine preparation was recommended for the treatment of goitre (Coindet, 1820). The use of iodised salt for prevention of goitre was suggested (Boussingault, 1833) but when goitrous families received iodised salt, symptoms of excess thyroid secretion occurred and treatment fell into disrepute. Thus the toxic effects of iodine supplementation like heart disorder, wasting and disturbed menstruation were noted.

Very low doses of iodine were sufficient to cause regression of goitre that led to deduction that goitre may be caused due to iodine deficiency and might be prevented by giving iodine (Louis Prévost, 1790-1850). The theory that goitre was due to iodine deficiency was put forward for the first time (Prévost and Maffoni A. S, 1846). There was no uniform clinical manifestation of a cretin but a wide spectrum of clinical symptomatology was concluded (Rosch and Maffei, 1844).

King Carlo (1848) appointed a special Commission to study the extent of goitre throughout his Kingdom and to recommend the means of controlling it. Ten year later the Commission submitted its report, which recorded that 3,70,403 persons in France above the age of 20 had goitre and 1,20,000 were cretins out of 36 millions.

There was a great diversity in opinion on the cause of goitre. The concept that a deficiency disorder was the prime cause of endemic goitre was generally not accepted until 1850. The vital role of the thyroid gland was established from thyroidectomies on various animals (Maurice Schiff, 1854). It

was believed that the "initiative process" responsible for the development of goitre must have been due to the effects of a positive substance (Virchow, 1863). He was essentially correct, TSH is the major stimulus for thyroid growth, but failed to recognise the significance of iodine deficiency in this process. Virchow was well aware of iodine deficiency theory, but unfortunately his rejection of this theory set back attempts to institute iodine prophylaxis by many years.

The disease was attributed to properties of water, atmosphere and faulty nutrition, poverty, unsanitary living conditions, alcoholism, consanguinity in marriage. Sporadic cretinism was recognised and its similarities to endemic cretinism were noted (Fagge, 1871). Fagge's observations were extended (Gull, 1871) and hypothyroidism in the child that continued to the adult (*"a cretinoid state supervening in adult life."*) was described (Gull, 1873). Primary atrophic hypothyroidism was later termed *myxoedema* (Ord, 1878).

Many observers in 19$^{th}$ century were influenced by the amusing opinions concerning the function of the thyroid gland mainly due to its liberal blood supply and believed that it provided a shunt for the brain. This function was the basis for the belief that the larger size of the gland in women was necessary to guard the female system from the influence of the more numerous causes of irritation and vexation of mind to which they are exposed than the male sex (Rush, 1820).

This theory was opposed and it was pointed out that "if it were indeed true that the thyroid contains more blood at some times than at others, this effect would be visible to the naked eye; in this case women would certainly have long ceased to go about with bare necks, for husbands would have learned to recognise the swelling of this gland as a danger signal of threatening trouble from their better halves." (Hofrichter, 1920).

These beliefs and theories of early 19th century led to a conclusion that thyroid gland did not have an important physiological role.

The thyroid was recognised as an organ of importance when its enlargement was observed to be associated with changes in the eyes and heart. This condition is now called hyperthyroidism. The condition escaped description as the first case was seen (Parry, 1786) but was published in 1825. The description of hyperthyroidism followed (Graves, 1835 and Basedow, 1840). Atrophy of thyroid gland was first associated with the symptoms of hypothyroidism much later than hyperthyroidism (Gull, 1874).

Before 1890, the relationship between goitre and iodine was suspected. The concept that a deficiency disorder was the prime cause of endemic goitre was generally not accepted even by the middle of the 19th century. It was not until the discovery of iodine in the thyroid gland (Baumann, 1896), that iodine prophylaxis gained credibility.

## *2.2. IDD IN THE 20th AND THE 21st CENTURIES*

The 20th century found that goitre was present in 96% of the mothers who had given birth to cretins (McCarrison, 1908) and it was declared that "endemic goitre is the easiest known disease to prevent" (David Marine, 1915). Iodised salt was proposed for goitre control in Switzerland based on an explanation from a "Natural Experiment". Low prevalence of goitre in one area named Vaud canton was noted due to the presence of a trace of iodine in salt whereas the other cantons had high prevalence of goitre due to the consumption of salt without iodine (Hunziger, 1915). Thyroxine was isolated as the active component of the thyroid, and was shown to contain 65% iodine by weight (Kendall, 1915). Tri-iodothyronine was identified in the thyroid gland (1952).

The link between iodine content of food and goitre prevalence was confirmed and the first large-scale trials with iodine were carried out in USA on 5000 girls between 11-18 years. The results of prophylactic and therapeutic effects were impressive (Felleberger, 1916-1920). Until the 1920s iodine prophylaxis of goitre was not contemplated on any scale but its efficacy was demonstrated in field trials (Marine and Kimball, 1921) and was proved to be safe (Klinger, 1921). The Goitre Commission in Switzerland investigated the natural occurrence of iodine and then decided on goitre prophylaxis for the 25 autonomous cantonal states of the country (Von Fellenberg, 1922).

Between 1924 to 1975, surveys were conducted for goitre rate simultaneously in Michigan, Switzerland, Austria, Italy and many other countries and it was estimated that over 200 million persons were afflicted with goitre (Kelly and Sneddon, 1960). Goitre was treated with iodised salt and a mass community scale prophylaxis of goitre with iodised salt was introduced (Kimball, 1964). Goitre rates among schoolchildren were reassessed after introduction of iodised table salt (1 part of KI in 5000 parts of salt) and significant fall in goitre rate from 38 to 9% was reported.

By the second half of the last century knowledge for successful prevention and control of the problem had been acquired. The theoretical basis for human adaptation to iodine deficiency was enunciated (Riggs, 1952) and confirmed elegantly by classical field studies in Mendozoa (Stanbury, 1954).

Goitre was regarded as an obligatory response to prolonged and severe iodine deficiency, and an increase in thyroidal iodine clearance was shown to be the basic mechanism of conservation. The subsequent demonstration of a qualitative alteration in favour of triiodothyronine indicated an additional mechanism (Querido, Schut and Terostra, 1956).

Hyperplasia of thyroid gland in man was shown to be largely due to an increase in the levels of TSH as a result of either a fall in the circulating levels

of thyroid hormones (Studder and Greer, 1965) or consumption of antithyroid drugs (Utiger, 1965) or excessive iodine intake (Murray and stewart, 1967). However, the relative efficiency of these adaptive processes had been questioned since precise measurement of serum thyroid hormones became possible because it was shown that serum TSH may be elevated in over 50% of persons in an endemic population despite maintenance of T3 levels (Ibbertson, 1974). The doubts were also raised about the significance of TSH elevation when thyroid synthetic capacity is reduced because many individuals with such biochemical abnormalities appeared clinically euthyroid on the other hand (Oppenheimer and Surks, 1975).

Though the first preventive measures against goitre were introduced in 1920 in USA and Switzerland, there is a little achievement in the satisfactory control of endemic goitre in India, Indonesia, Thailand, Vietnam, and Burma where millions of people are still affected by goitre (Hetzel BS, 1976).

The term Iodine Deficiency Disorders (IDD) was suggested to denote all the effects of iodine deficiency on growth and development instead of the term "goitre" that had been used in the past. Goitre was indeed the obvious and familiar feature, but the knowledge had expanded in last 25 years and a new term was needed. This reconceptualization of the problem – "packaged" in the acronym IDD – had been one factor in securing more attention to the problem. The term IDD is in fact adopted in the field of international health and nutrition (Hetzel BS, 1983).

The aetiology, epidemiology and treatment of endemic goitre and iodine deficiency disorders were described in detail for the first time (Eastman CJ, 1988). Pathological goitre was difficult to quantify because of the continuous variations undergone for age, sex and iodine deficiency. It was believed that grading of endemic goitre by palpation (a traditional method) was subjective and with an interobserver variability of 20%. Ultrasonography supplemented the traditional clinical methods for epidemiological and interventional studies

and provided a tool to determine the nature and structural changes within the goitre. The aetiological factors were determined to be iodine nutrition and goitrogens. Dietary iodine deficiency was clearly the major aetiological factor in both endemic goitre and cretinism but various cofactors greatly modified the expression of these iodine deficiency disorders. These confounders were goitrogens, micronutrient deficiencies and immunological mechanisms. The major physiological compensatory response to iodine deficiency is decrease in serum thyroxine level that decreases cerebral conversion of thyroxine to triiodothyronine especially in pituitary gland leading to increase in thyroid stimulating hormone. The compensatory mechanisms prevent biochemical hypothyroidism in cerebral tissues. Iodine supplementation programmes form the basis of the public health strategy in combating these disorders. Salt, water and bread could be iodised for iodine supplementation programmes. Where the iodisation of foodstuffs was not feasible, oral or intramuscular iodised oil could act as an alternative for iodine supplementation.

With the development of the technique to measure thyroid volume by ultrasonography (Brunn, 1981), many scientists first described the thyroid size by palpation and then used ultrasonography for confirmation of various goitre grades. The importance of ultrasonography over traditional thyroid palpation was well established.

The thyroid volumes of schoolchildren (13 years in age) were compared in the Federal Republic of Germany (2224 schoolchildren) and Sweden (224 children) (Gutekunst R, 1988).

Thyroid volumes of German and Swedish adults were estimated by sonography. The thyroid size of 6-16 year old German was also determined by palpation and ultrasonography for comparison of two methods. This study supported the goitrogenic effect of iodine deficiency by the comparison of thyroid volume and iodine excretion between Germans and Swedes. The study found no relation between thyroid volume and iodine excretion in iodine

deficient area. Effective iodine prophylaxis was suggested (Gutekunst R, 1986).

In few areas, despite adequate supply of iodine endemic goitre was noted and possible cause reported was the presence of environmental goitrogenic agents (Lamberg BA, 1991).

Evaluation of thyroid size by ultrasonography in healthy iodine sufficient children and adolescents from Sweden showed a continuous rise in thyroid gland volume from the age of 5 years to 15-16 years. There was no gender difference in the thyroid volumes (Ivarsson, 1989).

Normal values of thyroid gland volume in children were established and correlated with height, weight, and body surface areas that did not find a significant difference between male and females in each height group as mean thyroid volume for height function was obtained (Ueda D, 1990).

The prevalence of endemic goitre was evaluated by measuring thyroid volume on the basis of rotation ellipsoid model formula (Thyroid volume = width x length x thickness x 0.52) in schoolchildren living in a moderately iodine deficient area. This became borderline iodine sufficient in 1996 due to the implementation of voluntary iodised salt consumption. It was concluded that iodised salt prophylaxis was able to increase urinary excretion, to keep the progression of goitre endemia in the children born prior to the implementation of prophylaxis, and to prevent the development of goitre in the children born after prophylaxis. However thyroid size did not decrease in the children born prior to 1985 because they were previously exposed to iodine deficiency (Aghini-Lombardi F, 1997).

The thyroid volume and urinary iodine values were standardised for the assessment of IDD by studying European schoolchildren in the age range of 6 to 15 years. Medians and 97$^{th}$ percentiles for thyroid volume in each age

and BSA by gender were estimated. An inverse relation between median urine iodine levels and percentage prevalence of goitre was shown (Delange F, 1997). This European reference was accepted and adopted by WHO as an international normative reference for comparisons.

Many comparative studies of local and international universal normative WHO/ICCIDD, 1997, thyroid volume reference had been done in different parts of the world. The suitability of this normative thyroid volume reference remained questionable as shown in the next few year studies below in the year 1999 to 2001. At last, a factór was derived in 2001 that decreased the International WHO thyroid volume reference valuës of 1997.

The possible need for regional evaluative scales remained open and intercalibration for the methods used for ultrasonography remained an important issue (Delange F, 1999).

Thyroid volume were measured by ultrasonography in Bangladeshi and United States school children and were compared with WHO/ICCIDD normative reference adopted from thyroid volume measured by ultrasonography in European school children. The upper normal limits of thyroid volume for age and BSA for United States school children were lower than that of WHO/ICCIDD normative adopted reference. It was concluded that thyroid volume for BSA should be preferred over thyroid volume for age reference in areas with prevalent malnutrition (developing countries). Thyroid volume for weight as well as thyroid volume for BSA alone would perform in the developed countries. Thyroid volumes of European children were larger in comparison to US children because of residual effect of IDD in recent past in some areas of Europe (Xu F, 1999).

A study was conducted in non-iodine-deficient areas of Malaysia to obtain local thyroid volume reference data in the children. These thyroid volumes were compared with 1997 WHO/ICCIDD reference for the assessment of IDD

in Malaysia. It was concluded that local Malaysia thyroid volume established from this study should be used in the screening of children for thyroid enlargement in preference to 1997 WHO/ICCIDD reference because WHO values were found to be was too high (Foo L C, 1999).

The interobserver and intraobserver variations were determined for sonographic measurements of thyroid volume in children. Mean intraobserver variation was 8% and interobserver variation was 13% thereby showing a significant variation in sonographic measurements of thyroid volume in children (Özgen A, 1999).

Ultrasonographic thyroid volumes were described in a representative sample of iodine sufficient Swiss school children and compared with the 1997 WHO/ICCIDD reference data. It was concluded that Swiss children had smaller thyroids than the WHO/ICCIDD reference. As the IDD was a known problem in Europe and WHO/ICCIDD reference was based on data from this population, they had bigger volumes. The reason suggested was either a residual effect of IDD or an interobserver and inter equipment variability in thyroid volume measurements because their values differed from earlier similar study (Hess SY, 2000).

Normal thyroid volumes values were established for school children having sufficient iodine intake through out their lifetime but the consumed iodised salt was supplied by different salt manufacturers. It was concluded that children got sufficient iodine consumption in different cities served by different salt manufacturers. Also the superimposition was evident between the thyroid volume in this study and WHO/ICCIDD normative reference (Bürgi H, 1999).

The suitability of indicators of iodine status was evaluated from thyroid function, (thyroglobulin, TSH and free thyroxine in serum, thyroid volume and urinary iodine concentration) in iodine-deficient schoolchildren under conditions of increasing iodine supply. Thyroid volume and thyroglobulin

decreased and urinary iodine increased in iodised oil- supplemented group whereas the other group that consumed only iodised salt for some period of the study had limited thyroid volume alterations but their urinary iodine increased and thyroglobulin decreased to the same extent. Hence urine iodine and thyroglobulin were considered to be the appropriate indicators of iodine supply (van den Briel T, 2001).

Iodine intake and thyroid size was evaluated in Dutch schoolchildren contrasting those living in iodine deficient region with those living in iodine sufficient region. It was concluded that there was no IDD in the Netherlands as iodine intake was sufficient from bread but not from sea fish or table salt. It was also shown that the girls had larger thyroid volumes at the age of 12 - 13 years due to the effect of earlier puberty. After the age of 14 boys had larger thyroids (Wiersinga WM, 2001).

Thyroid volumes and urinary iodine was measured in German school children and compared with original Gutekunst normative data and WHO/ICCIDD normative reference. It was concluded that there was no IDD in Germany any more when thyroid volumes were compared to both thyroid volume references. Although WHO reference was too high for comparison (Rendl J, 2001).

Thyroid volume was measured by ultrasonography in 6-11 years old schoolchildren living in an iodine deficient area for 5 years and correlated with age, height, and weight, BSA, BMI. The most significant correlation was found between the thyroid volume and the age (Semiz S, 2001).

The contribution of inter-observer and/or inter-equipment variability was determined for the disagreement in sonographic thyroid volumes reported from different iodine sufficient areas of Europe, USA, Switzerland and Malaysia. The WHO/ICCIDD 1997, normative thyroid volume reference adopted from European children was considered to be too high. The results

of 2-day workshop showed that inter-equipment error contributed minimally to reported differences in the thyroid volume. However, inter-observer variability in sonographic thyroid volumes in children was high. These authors argued for the Standardization of methods used for sonographic thyroid volumes in children (Zimmermann MB, 2001).

The IDD was measured in Europe and mild to moderate iodine deficiency was still characterised in most European countries (Vitti P, 2001).

In 1990 at the World Summit for Children, Heads of State and Government from most nations of the world had agreed on the global goal for virtual elimination of iodine deficiency disorders (IDD) by the year 2000.

In 1992 at the International Conference on Nutrition, multi-sector country delegations from all over the world developed the prototype framework for national action.

Following a special recommendation of the United Nations Joint Committee on Health Policy, universal salt iodization (USI) was applied in almost all countries with an IDD problem recognized as being of public health significance (van der Haar F, 1997).

Young farm animals were affected by functional disorders of the thyroid gland. The health status of cattle could consequently affect iodine deficiency in human population as the major source of iodine in child's food is milk and milk products (Herzig I, 1996).

A unifying hypothesis that "severe iodine deficiency causing maternal and fetal hypothyroxinemia results in neurological defects in all cretins" was put forward. The clinical picture of endemic cretinism resulted from an interaction of two pathophysiological events, both resulting from iodine deficiency, but occurring at different times in the development of the fetus and neonate. The

first event followed a lack of thyroid hormones *in utero*, resulting in the neurological manifestation of the condition. The second event determined the duration and severity of continuing hypothyroidism after birth that results in thyroid hormone deficiency. Both components played a role and explain the frequent overlap of clinical signs (Steven Boyages, 1997).

The validity of support for the hypothesis was agreed and the hypothesis "that neurological features are present in all cretins" was accepted (Rajatanavin R, 1997).

The dispersion was reduced to 24% when urinary iodine excretion per day was estimated rather than urinary iodine concentration from a sample. Moderate iodine deficiency participants showed clear signs of substrate deficiency for thyroid hormone synthesis while mild iodine deficiency participants did not show clear signs (Anderson, 2001).

## 2.3. Definition of IDD

" A diet deficient in iodine may cause a wide spectrum of illness collectively termed IDD which affects people of all ages, but particularly pregnant women, developing fetus and the neonate" (Hetzel BS).

"IDD is the inclusive term used to refer to various effects of iodine deficiency on growth and development due to defective production of thyroid hormones. These effects are apparent at the individual, social and national levels and are completely prevented by correction of iodine deficiency" (Hetzel BS, 1993).

IDD refers to all ill effects of iodine deficiency in a population, that can be prevented by ensuring that the population has an adequate intake of iodine (WHO/ICCIDD/UNICEF, 2001)

"Thyroid hormone production and metabolism is influenced by a range of other goitrogenic substances found naturally in the environment and by other micronutrient deficiencies, notably selenium deficiency. Thus iodine deficiency may act alone or in concert with other environmental influences to produce a spectrum of conditions. These clinical manifestations reflect either the direct consequences of iodine deficiency on the thyroid or the secondary consequences of hypothyroidism on thyroid hormone sensitive target tissues (Steven C Boyages, 2000).

## 2.4. AETIOLOGY OF IODINE DEFICIENCY DISORDERS

The aetiology of simple goitre, affecting up to 5% of a population in iodine-sufficient areas and over 10% in endemic areas, is incompletely understood. It is generally believed that the development of simple goitre, whether endemic or sporadic, depends on complex interactions between genetic, environmental and endogenous factors. Suggested risk factors include iodine deficiency, naturally occurring goitrogens, protein energy malnutrition and many other factors. However, the possibility that simple goitre is a heterogeneous disease, should be left open (Brix TH, 2000)

### 2.4.1. IODINE DEFICIENCY:

Iodine deficiency was considered as the principal aetiological factor for endemic goitre in the past (Marine, 1923) and; it is accepted till today (Smyth PP et al, 1999). Iodine deficiency is also considered to play a primary role in goitrogenesis for euthyroid endemic goitre (Neumann S et al, 1999) or hypothyroid endemic goitre (decrease in total and free thyroxine with increase in TSH levels) (Konde M, 1994).

The important role of iodine deficiency in the etiopathogenesis of endemic goitre is indicated in Turkey where moderate iodine deficiency exists in control subjects as well as in endemic goitre subjects (Ozata M, 1999).

Various reviews (Stanbury, 1954; Hetzel, 1970; Studer, 1974; Roche and Lissitsky, 1960 and Kelly and Snedden, 1960) point to an epidemiological link between insufficient intake of iodine through food and drinking water and the development of endemic goitre. Correction of iodine deficiency is followed by the disappearance of endemic goitre in most areas, though in some areas goitre disappeared gradually or vanished completely before any systematic iodine prophylaxis had been started (Koenig, 1968, Maisterrena, 1969). This

change in the prevalence of goitre was due to the so-called "silent" prophylaxis, leading to an increase in dietary iodine intake through improved social and economic conditions and specifically a more varied diet.

Almost invariably, careful assessment of the iodine intake of a goitrous population reveals levels considerably below the average in regions where the disease does not exist. Severe iodine deficiency is still encountered up to the present indicating that it is still present in many parts of the world. Most reports place the mean intake between 10 and 50 µg/24 hour. From two endemic goitre areas of Zimbabwe mean iodine urinary excretion from adults was reported to vary between 10 and 21 µg/L (Todd CH et al, 1991). In Senegal a mean iodine excretion of 17 µg/g creatinine (roughly equivalent to 24h) was also reported (Lazarus JH, 1992). In the Eastern part of Germany, a 24h iodine excretion of 16 µg has been reported in 1989 (Delange F, 1989).

In certain regions iodine deficiency appears to act as a permissive factor in the onset of endemic goitre. Several investigators have described a situation, where in spite of severe iodine deficiency, endemic goitre is not found (Roche, 1959; Choufoer et al., 1965; Delange et al., 1968; Fierro-Benitez et al., 1969). Conversely, endemic goitre may persist despite adequate iodine supplementation and is found in some regions where there is no apparent shortage of iodine. Other factors that act in concert with iodine deficiency to produce thyroid enlargement are important in the full clinical expression of the iodine deficiency disorders. These are environmental goitrogenic factors and in their presence iodine deficiency results in the highest incidence of endemic goitre. The prevalence rates sometimes may reach as high as 50% in some communities (Choufoer, 1965; Delange, 1968; Fierro-Benitez, 1969; Malamos, 1971)

Severe iodine deficiency as indicated by very low levels of urine iodine excretion was the cause of goitre in New Guinea population (Buttfield, 1965).

The thyroid hormones in blood were lowest in the subjects having biggest goitres. These subjects were treated with iodised oil that led to subsidence of goitre with rise in their thyroid hormone levels. This work resulted in the use of iodized oil in Zaire, Ecuador, Peru and West New Guinea.

Rats when fed iodine free diet for 6 months, become hypothyroid (Nolan LA, 2000). These rats were studied for stress induction and corticosterone diurnal variation. It was demonstrated that the diurnal rhythm of corticosterone is lost in chronic hypothyroidism. There was attenuation of corticosterone secretion in response to stress. Restoration of iodine containing diet for one month restores the thyroid hormones but the diurnal rhythm of corticosterone and its response to stress remain reduced. Thus chronic hypothyroidism due to iodine deficiency attenuates hypothalamo- pituitary- adrenal axis activity that persists after functional recovery of thyroid axis.

The association between severe iodine deficiency and endemic goitre is well established, but little information is available on the relation between milder degrees of iodine deficiency and goitre prevalence. Marked differences in the prevalence of thyroid abnormalities mainly the goitre prevalence were found in moderate IDD and mild IDD regions with modest differences in iodine excretion (Knudsen N, 2000).

Even mild iodine deficiency leads to clinical hypothyroidism and moderate myxoedema with significantly reduced intellectual performance. Prevention of endemic goitre depends mainly on increasing the iodine intake of people in endemic areas. When iodine intake reaches the estimated adult minimum requirement (100 to 150 micrograms per day), the prevalence of goitre decreases. Management strategies for endemic goitre in developing countries should have two approaches to increase iodine intake. The first consists of adding iodine to food staples such as table salt. The second consists of medical treatment using agents such as iodized oil. Iodization or iodination of salt is the most widespread and cost-effective method of prevention.

Administration of iodized oil has been used only in severely endemic areas and in regions where reliable provision of iodinated salt is prevented by geographical barriers or political factors. However, iodized oil has been helpful in the start-up phase of prevention programs using iodized salt, either as an emergency measure or as a mean of convincing officials of the efficacy of iodine prophylaxis (Kouame P, 1999)

Iodine deficiency was detected in the children living in the districts having low concentrations in the water and foodstuffs (Utenina VV, 1998).

An increased risk of iodine deficiency was seen with vegetarian nutrition as a markedly reduced iodine intake was confirmed analytically for the lactovegetarian diet. Iodine supply was higher with non-vegetarian than with vegetarian diets hence there was a potential danger of Iodine deficiency disorders due to strict forms of vegetarian nutrition, especially when fruits and vegetables grown in soils with low iodine levels were ingested (Remer T, 1999).

## *2.4.2. NATURALLY OCCURRING DIETARY GOITROGENS:*

Goitrogens may be defined as substances that increase the thyroid gland size by interfering with the normal production of thyroid hormone. Some occur naturally in certain widely used food plants such as cabbage. Others are synthetic and are used medicinally (Delange F, 1993).

The initial recognition of dietary goitrogens as an aetiological factor was established from findings of goitre development in rabbits fed on cabbage (Chesney, 1928).

Production of goitre was reported later in rats by feeding the seeds of several species of Brassica (rape, choumoellier, turnip, etc.) (Hercus and Purves,

1936). Later thioglucosides were shown in plants belonging to family Brassicaceae (Clement, 1960, Strong, 1974).

Thioglucosides could degrade to give rise to two sorts of goitrogens: (a) Thiocyanate or Isothiocyanates that block iodine uptake and their action can be controlled by supplemental iodine. (b) Progoitrin converted to goitrin by gut bacteria or crushing of the plant that blocks organic binding of iodine and this action could not be controlled by supplemental iodine (Clement, 1960).

Thiocyanate resulted in goitre when used in large doses to treat hypertension (Barker, 1936).

Cyanide producing glycoside in the cassava root while undergoing the routine detoxification processing in the body, produces thiocyanate and this induced goitrogenesis by blocking iodine uptake in the thyroid gland (Delange, 1971).

Thiocyanate and precursors of thiocyanate, such as the cyanogenic glycosides, have been found particularly in the widely used tuber cassava (manioc) (Delange F, 1989).

Cassava caused goitre when fed to rats (Gaitan E, 1989).

A striking difference was observed in incidence of goitre in two regions of an isolated island in the Kivu Lake in Eastern Democratic Republic of Congo, although the iodine intake of both groups of ethnically identical people was approximately the same. There was a major difference in use of cassava (Delange, 1980).

A strong case was developed for cassava and endemic goitre in Zaire from a study of several communities in the Ubangi region of Zaire. An interesting relationship between goitre, on the one hand, and thiocyanate and iodide excretion, on the other was found. The thiocyanate was derived from

intestinal breakdown of the Cyanogenic glycoside, linamarin, from cassava and its conversion to thiocyanate by the liver. The results indicated a reciprocal relationship between iodide and thiocyanate in that increasing amounts of iodide protected increasingly against the thiocyanate derived from the cassava (Delange F, 1982).

It was well established that cassava may contribute to the severity of endemic goitre and probably the incidence of endemic cretinism but there were many severe endemics where cassava was not eaten. In these regions, it was possible that other goitrogens in the local food may contribute to the effects of a prevailing iodine deficiency (Delange F, 1982).

In the Idjwi Island of the Congo, the goitre incidence was much higher in the north despite a severe iodine deficiency in the whole island and cassava grown in the north showed suppressed $^{131}I$ uptake, but the cassava from south of the island did not show this effect (Delange and Ermans, 1971).

The effects of thiocyanate in iodine-deprived rats have been shown. These effects are decreased thyroxine in blood, decrease in nucleic acid and protein content of various brain regions, lowered rate of microtubule assembly thereby influencing myelin deposition and synaptogenesis in developing brain. These investigations suggest that goitrogens play a significant role in influencing biochemical events unique to developing brain (Rao, 1995).

Hypothyroidism and decrease in 2-deoxy-D-glucose transport across the blood-brain-barrier was observed in the offspring whose mothers were fed with KSCN chronically for a month (Raghunath M, 1998).

Intracarotid injections of KSCN per se had no effect on the 2-deoxy-D-glucose transport but feeding decreased the transport of glucose through BBB by 23% thus suggesting secondary effect of KSCN by altered thyroid status (Bala TS, 1996)

Thiocyanate may cross the human placenta and affect the thyroid of the fetus. Feeding a synthetic goitrogen, potassium thiocyanate (KSCN) to rats through two generations produced more severe hypothyroidism in second-generation pup than the first generation pup (Morreale, 1993).

Thiocyanate overload contributed to goitre endemics areas in Turkey (Erdogan MF, 2001).

Recently an epidemiological study of IDD has shown that the consumption of cassava is not an aetiological factor responsible for the endemic goitre. This contradictory report was based on a finding that when Cassava was consumed on a regular basis, it neither caused nor increased goitre formation in rural area of Senegal (West Africa) (Dillon JC, 1999).

Dietary thiocyanate overload, as evidenced from plasma thiocyanate concentration, was seen to be associated with endemic goitre prevalence of greater than 20% in Tripura (India). A large number of Cyanogenic plants (SCN precursors) were used as common vegetables. Studied population had no biochemical iodine deficiency as evidenced by median urinary iodine excretion levels (Chandra AK, 2001).

The goitrogenic effect of edible nuts in rats was shown (Srinivasan, 1957). The goitrogenic substance was in the nut skin.

Goitres were reported in infants fed exclusively on a milk formula made from soya bean flour (Hydovitz, 1960). Later it was suggested that soya bean flour had a direct antithyroid action (Konjin, 1971). These goitres were prevented by the addition of iodine to the milk formula (Shephard, 1972).

A goitrogenic substance; isothiocyanate in milk; was described to be the cause for two seasonal epidemics of endemic goitre in Tasmania (Gibson, 1960).

Aliphatic hydrocarbons with thiourea-like antithyroid activity were identified in well water in an area of Colombia where goitre was prevalent, despite normal urine iodine values (Gaitan, 1973). A significant relationship between this goitre prevalence of Colombia and bacterial contaminations (gram negative bacteria) of water supplies was then suggested (Gaitan, 1983).

Certain sulfur-containing onion volatiles are also goitrogenic (Gaitan E, 1989). All of these substances interfere with the accumulation of thyroidal iodide, an effect that usually can be overcome by an increasing iodine intake.

Certain drugs such as thiourea and related compounds when administered to rats were seen to cause hyperplasia of the thyroid gland and this observation quickly led to the introduction of the thionamide series of antithyroid drugs, now so familiar in clinical therapeutics (Mackenzie and MacKenzie and Astwood, 1943).

The role of methimazole, a thionamide compound used to inhibit iodide organification by inhibiting peroxidase activity, on FRTL5 thyroid cell proliferation had been described (Peter Smerdely and Steven Boyages, 1993).

Potent goitrogens like methyl mercaptoimidazole when fed for a very short time to pregnant dams produced severe hypothyroidism in the offspring. Different mechanisms for the different goitrogen induced IDD were suggested.

A report on a goitre survey in the school children of Bombay was presented that concluded that there was no direct correlation between the iodine deficiency in the diet and the presence of goitre in children either from a lower socioeconomic or higher income group. The low iodine intake probably unmasked goitrogenic factors in a population so that a population with relatively less iodine in its diet showed a higher incidence of goitre in the

school children between the ages of 10 to 14 years when the requirement of iodine is increased (Shah DS, 1976).

Though there was no positive proof that hyperplasia was unlikely due to the action of goitrogens alone in man, it was believed that the goitrogens interacted with other factors like iodine deficiency or other types of goitrogens in an endemic goitre area (McLaren EH, 1979).

Impairment of thyroid status has been evaluated by an epidemiological survey where there was a long-term exposure to heavy environmental pollution of polychlorinated biphenyls (PCB). The results showed an increase in the thyroid volumes of iodine sufficient adults and adolescents and an increase in thyroid antibodies. These results were attributed to the immuno-modulatory effects due to long-term exposure to heavy environmental pollution with PCB (Langer P, 1998).

Hyperplasia of thyroid gland was largely due to increase in the levels of TSH as a result of the fall in the circulating levels of thyroid hormones (Studer and Greer, 1965).

In man with goitres, raised TSH levels had been reported induced by antithyroid drugs (Utiger, 1965), iodine (Murray and Stewart, 1967) and lithium (McLarty, 1975).

Earlier studies of other goitrogens such as resorcinol (Bull and Fraser 1950) or para-amino salicylic acid (PAS) (McGregor and Somner, 1954) had shown high radioiodine uptakes which can be taken as presumptive evidence of elevated TSH levels.

Thyroid enlargement was seen to occur in the presence of normal TSH levels in early iodine deficiency goitre in rats and an autonomous gland response to intrathyroidal iodine deficiency was postulated (Studer and Greer, 1965).

A similar phenomenon was seen in propylthiouracil induced goitres in rats. An initial sharp rise in TSH followed by a fall to normal level with a subsequent slow rise on continuous use of the drug was seen (Griessen, 1973).

The thyroid gland thus enlarges even when TSH is normal because a lack of correlation was seen between goitrogenesis and TSH levels in Lithium induced goitre (Berens, 1970).

Variations in goitre prevalence were found to correlate closely with the fluoride content and hardness of the water in the Himalayas (Day and Powell-Jackson, 1972).

Occurrence of goitre was attributed to contaminated drinking water (McCarrison, 1908).

Firm evidence for goitrogenic action in humans was shown for a few compounds: thiocyanate, goitrin, resorcinol, dinitrophenol, PBB's and its oxides, excess iodine and high doses of lithium. Final proof for a definite role in endemic goitre had only been provided for thiocyanate and sulfurated organics, although substantial and circumstantial evidence favours the view that natural goitrogens, acting in concert with iodine deficiency, may determine the pattern and severity of the condition (Gaitan E, 1989).

***FLAVONOIDS***

Flavonoids are polyphenolic compounds that occur ubiquitously in foods of plant origin. Over 4000 different flavonoids have been described in cereals, pulses, vegetables and fruits as an integral coloured part.
A possible role for the consumption of pearl millet in the aetiology of endemic goitre with iodine sufficiency had been postulated (Elnour A, 2000).

The distribution of red rice cultivation in Sri Lanka (A developing country with originally Indian population) was coincident with the very high prevalence of IDD in some villages. Varieties of red rice grown in other countries contain anthocyanins and procyanidins that are flavonoid compounds in other foodstuffs and known goitrogens. The potential goitrogenic properties of red rice in Sri Lanka remained unknown and required further investigation. The incidence of goitre in Sri Lanka was supposedly multi-factorial, involving trace element deficiencies and other factors such as poor nutrition and goitrogens in foodstuffs (Fordyce FM, 2000).

Flavonoids were determined by chemical analyses in 85 foodstuffs comprising of cereals, pulses, nuts, oilseeds, and vegetables, fruits and beverages that are commonly consumed in Indian foods. Flavonoids were measured as a sum of quercetin, kaempferol, luteolin and pelargonidin. High flavonoid content (> 100 mg/100 gm) was present in tea, coffee, apple, guava, terminalia bark, fenugreek seeds, mustard seeds, cinnamon, red chilli powder, cloves and turmeric. Medium levels (50-100 mg) were found in Indian gooseberry, omum, cumin, cardamom, betel leaf and brandy. Small but significant amounts were also present in food-items of large consumption such as kidney beans, soybeans, grapes, ginger, coriander powder, bajra (pearl millet) and brinjal or egg plant (Nair S, 1998).

Flavonoid intake of adults was evaluated in a Bavarian subgroup of the national food consumption survey in Germany because data on the flavonoid content of food are not considered in food composition tables, and human intake data are scarce (flavonols) or missing. Average intake of all flavonoids (calculated as aglycons) amounted to 54.0 mg/d (median) with a great range of variability. The most important flavonoid groups were flavonols (12.0 mg/d), catechins (8.3 mg/d), and flavanons (13.2 mg/d), followed by anthocyanidins (2.7 mg/d), proanthocyanins (3.7 mg/d) and phloretin (dihydrochalcone) (0.7 mg/d). Fruits, fruit products and fruit juices were the most important flavonoid sources. Vegetables and its products provided about half of the flavonol

intake. Compared to other countries, flavonol intake of the investigated group of persons was rather low. With the built database it was possible for the first time to calculate the intake of further flavonoids besides flavonols. In comparison to the intake of other antioxidants (e.g. vitamins C and E) the amount of flavonoids in the diet was considerably high (Linseisen J, 1997).

Some common foods used in Indian culinary practices were assessed for their plausible biological effects. Green leafy vegetables had the highest anti-oxidant activity followed by wheat and rice. Cooking decreased this activity. Eugenol, the active principle of clove, showed anti-peroxidative activity in addition to decrease in $O_2$ formation (Krishnaswamy K, 1998).

Catechin contents of foods that belong to the flavonoid compounds (Fruits, vegetables, staple foods, and processed foods) commonly consumed in The Netherlands were evaluated. Most fruits, chocolate, and some legumes contained catechins. Levels varied to a large extent: from 4.5 mg/kg in kiwi fruit to 610 mg/kg in black chocolate (Arts IC, 2000).

Catechins have been synthesised commercially and are available as polyphenon-60 (P-60) containing green tea extract catechins at 66.2%. This P-60 was used as a source of catechins in the diet of rats and when they constituted 5% of the diet for 13 weeks, marked thyroid hypertrophy was revealed in males. The results indicated that dietary administration of the green tea extract catechins at high doses induced goitres in rats, and this might be due to antithyroid effects of catechins. The goitre were 444% when compared to the control rats (Sakamoto Y, 2001).

The contribution of Mediterranean diet (vegetable, fruit or wine?) to plasma concentration of (+)-catechin (a naturally occurring flavonoid) was determined. Highest plasma concentration of (+)-catechin was observed in subjects consuming fruit, vegetable and wine (Ruidavets J, 2000).

Consumption of halleko (Moringa stenopetala), a leafy vegetable common in the south Ethiopia, of more than two times per day was significantly ($p < 0.005$) associated with causation of goitre (Abuye C, 1999).

The intake, health effects and bioavailability of dietary flavonoids in The Netherlands was studied An estimation of the total flavonoid intake was difficult, because only limited data on food contents were available. It was estimated that humans ingest a few hundreds of milligrams per day (Hollman PC, 1999).

In an area of sufficient iodine intake as a result of well-monitored iodine prophylaxis, the increased thyroid volume in the polluted area was a result of long-term exposure to toxic substances. Long-term exposure to heavy environmental pollution with polychlorinated biphenyls (PCB) was evaluated in an epidemiological field survey by measuring thyroid volume of factory employees. Thyroid volume was significantly higher in the polluted area due to long-term exposure. Iodine intake was sufficient due to prophylactic measures (Langer P, 2000).

The role of goitrogens had been postulated when there is a very high prevalence of goitre despite sufficient iodine consumption. It was also suggested that there might not be a relationship between goitre and iodine deficiency in the population. The possibility of autoimmune thyroid disease that resembles goitre in early stages was suspected because of iodine repletion (Aminorroaya A, 2001).

## 2.4.3. PROTEIN ENERGY MALNUTRITION (PEM):

The four most important deficiency diseases in developing countries are protein-energy malnutrition (PEM), xerophthalmia (vitamin A deficiency), nutritional anaemias, and iodine deficiency disorders. Of these, PEM is the most lethal and the most difficult to control. The immediate cause is usually insufficient intake. Underlying causes of nutritional problems in the developing countries are conditioned mainly by poverty, near exclusive reliance on plant sources of nutrients, and high rates of infections. Other possible causes are inequity, and lack of knowledge. Mild or moderate PEM can be best judged by anthropometry. Economic improvement in the Third World is essential if PEM is to be greatly reduced (Latham MC, 1990). Population subgroups at particularly high risk are the children and women of poor families.

The probability that factors other than iodine deficiency contribute to the production of endemic goitre was perceived as early as 1924 (anonymous) and role of malnutrition was hypothesised.

Subjects living in the goitrous regions of Greece exhibited clear evidence of calorie undernutrition; different body build characteristics and suffered from delayed skeletal developments. The possible potential effect and a great role of generalised malnutrition (PCM) in the pathogenesis of endemic goitre was suggested because endemic goitre was associated with evidence of generalised malnutrition (Koutras DA, 1973).

PCM was reported to result in alterations of thyroid gland structure and function (Medeiros-Neto G, 1980).

Decreased gastrointestinal absorption of iodine was evidenced in PCM (Ingenbleek, 1973).

Normal thyroid hormone and TSH had been documented in malnourished goitrous subjects (Chopra, 1975).

Low values of thyroid hormone and TSH in children were reported (Ingenbleek Y, 1972-75).

Exaggerated response to TSH releasing hormones was reported (Pimstone et al, 1973). Decreased radioactive thyroid iodine uptake and clearance was seen (Ingenbleek Y, 1978) and later a close relation between nutrition and endemic goitre was also suggested from measurement of prealbumin, thyroxine binding globulin as markers of PCM and thyroxine (free and total) hormone (Ingenbleek Y, 1980).

Thyroid dysfunction was studied in protein calorie malnutrition to study many epidemiological aspects that escaped the iodine deprivation theory observed as early as 1924, at the time the first prophylactic measures were undertaken in the US. Several plausible etiological factors were subsequently proposed as tentative approaches to fill the gap between the iodine deficit theory and the recorded public health data. Compilation of all known or suspected goitrogenic agents constitutes the basis of large reviews. Several human studies lend increasing credence to the concept that declining nutritional status, per se, could aggravate the goitrogenic process synergistically to iodine deprivation in countries such as Mexico, Lebanon and Bangladesh. Lower socioeconomic status of populations and insufficient dietary consumption levels have been associated with higher prevalence of endocrine dysfunction. Goitrous Spanish patients excrete lower concentrations of nitrogen catabolites in their urine output than controls (Ingenbleek Y, 1986).

Negative correlation was shown between hyperplasia of thyroid gland and thyroxine binding prealbumin- a marker of PCM. Essential and non-essential amino acids were reduced in plasma of goitrous patients (Malave I, 1998).

In short-term PCM, the main abnormalities of thyroid were confined to thyroid hormonal transport system, without significant changes in the Euthyroid State whereas long term PCM resulted in overwhelmed adaptive mechanisms leading to hypothyroidism. Both adults and children were vulnerable to the long term PCM (Ingenbleek Y, 1980).

Defective thyroid iodine concentration in human PCM was reported with adequate hormone secretion thereby leading to depletion of thyroid iodine stores. This alteration in its severe form caused hypothyroidism and when adequate protein-calorie intake made the person replete, the abnormalities reversed (Ingenbleek Y, 1983).

Endemic goitre was seen among undernourished and stunted iodine deficient schoolchildren in Namibia (Jooste PL, 1992).

Adult women living in an iodine deficient area and exposed to protein malnutrition alone indicated maintenance of their thyroid homeostasis and the normal thyroid-hypophysis feedback with a high carbohydrate diet, regardless of the protein deficiency (Centanni M, 1991).

Four accessions of a legume bean were analyzed for proximate composition, mineral profiles, the protein fractions and amino acid profiles. Profiles of aminoacids of seed proteins as in most legumes revealed higher levels of all essential amino acids except threonine, leucine and lysine in black-coloured seed coat accessions and phenylalanine and tyrosine in white coloured seed coat accession compared with FAO/WHO (1991) requirement pattern (Vadivel V, 2000).

Plasma amino acid concentrations in men and women with protein energy malnutrition in the age range of 80-100 years were measured that showed the decrease in plasma concentrations of essential and non-essential aminoacids

in underweight elderly patients. Metabolic disturbance was reflected (Polge A, 1997).

The study to establish a relation between thyroid homeostasis and biochemical markers of PEM was conducted in a moderately iodine deficient rural area of South Italy. The subjects were exposed to mild PEM. The results provided evidence of detrimental effects of mild PEM on thyroid homeostasis in an iodine deficient area (Centanni M, 1998).

Significant positive correlations were observed between the concentration of thyroxine binding prealbumin (TBPA) (that was used as a marker for protein energy malnutrition) and the Z scores of weight-for-age, height-for-age and weight-for-height in children (Malave I, 1998).

The effects of malnutrition (protein energy malnutrition) on thyroid gland weight and thyroid hormone levels were investigated. A decrease in serum thyroxine, triiodothyronine and free triiodothyronine and an increase in TSH levels in PEM subjects compared to controls were seen. Free thyroxine levels were not influenced by PEM. The thyroid gland weights evaluated scintigraphically were higher in PEM subjects than the controls (Orbak, 1998).

In an endemic area of Africa where despite iodine sufficiency goitre was highly prevalent, role of protein energy malnutrition as an aetiological factor was suggested (Elnour A, 2000).

The prevalence of PEM was estimated with various anthropometric indices and was correlated with family income, lower parental height by logistic regression analyses. The results showed that PEM was high in rural minority and the reason was chronic socioeconomic under-development and genetic effects rather than a severe lack of food (Li Y, 1999).

## 2.4.4. OTHER FACTORS

### 2.4.4.1. TRACE ELEMENTS DEFICIENCIES

Endemic goitre could result from dysbalance of trace elements according to the most important variants of human contact with the abnormal environment with regard to the content of trace elements. There is polymicroelementoses and anaemic biogeochemical nature (Avtsyn AP, 1983).

#### *SELENIUM DEFICIENCY*

The extreme severity of the selenium deficiency (Se) might intervene either on the central and/or peripheral deiodination of thyroxine, or on the synthesis of the thyroid hormones (Thilly CH, 1990).

Despite government-sponsored iodised salt programmes in developing countries, endemic goitre is still prevalent. In recent years, it has been suggested that Se deficiency may be an important factor in the onset of goitre and other iodine deficiency disorders (IDD). One study in Sri Lanka showed that though Se deficiency was not restricted to areas where goitre was prevalent, a combination of iodine and Se deficiency was involved in the pathogenesis of goitre in Sri Lanka (Fordyce FM, 2000).

Marginal selenium deficiency was seen in Ankara and three cities of Turkey having goitre endemia. No correlation was detected between serum selenium concentration and thyroid volume or urinary iodine or thyroid hormones or sensitive TSH (Erdogan MF, 2001)

The concentration of selenium in serum of goitrous children is significantly lower than the healthy controls and nongoitrous children with high iodine deficiency (Giray B, 2001).

Selenium deficiency together with thiocyanate overload might be the responsible factor for high frequency of myxoedematous cretins in Zaire. Selenium supplementation (and thus deficiency) has demonstrated an action on thyroid function in man from an iodine deficient area of Zaire (Thilly CH, 1991).

Selenium status was determined in a population living in the core of endemic and nonendemic goitre belt of Zaire along with cretins in the same area. Severe selenium deficiency was seen in endemic goitre belt (seven times lower). An association was described between endemic myxoedematous cretinism and selenium deficiency (Venderpas JB, 1990)

***COBALT DEFICIENCY***

An endemic goitre zone was characterised by normal iodine consumption in Kazakhstan. Biogeochemical conditions showed that the concentration of cuprum, cobalt, manganese and fluorine were low (No author, 1987).

The effect of the diets differing in macroelements and trace elements (excess silicon in association with moderate deficiency of iodine and cobalt) were studied on thyroid function in normal people living in the endemic regions with regard to goitre and Shifts in thyroid function were found (Semenov VD, 1983).

The role of natural cobalt content in food products was established in the aetiology of endemic goitre (Oparin IA, 1969).

***IODINE AND ZINC DEFICIENCY***

In one study iodine and zinc deficiency were seen to co-exist in a male Turkish population with endemic goitre, but there was no selenium and copper deficiency (Ozata M, 1999).

### *IRON DEFICIENCY*

Because in developing countries, many children are at high risk for both goitre and iron-deficiency anaemia and there is a possibility that iron deficiency may impair thyroid metabolism, a study was conducted to determine if iron supplementation improves the response to oral iodine in goitrous, iron-deficient anaemic children. It was concluded that iron supplementation may improve the efficacy of oral iodized oil in goitrous children with iron-deficiency anaemia (Zimmermann M, 2000).

Association between goitre and iron deficiency anaemia was also shown in another study (Elnour A, 2000).

## *2.4.4.2. VITAMIN DEFICIENCIES*
## *VITAMINS A AND E AND IDD*

The goitre prevalence was 29.8% in a study from school-children would point to alimentary iodine deficiency and moderate IDD but the goitre examinations suggested the iodine deficiency was not the only etiological factor of goitre on the island of Krk. The average plasmatic values of vitamins A and E in the children with enlarged thyroids were statistically significantly lower from the reference values and this fact suggested their role in aetiology of IDD (Mesaros-Kanjski E, 1999).

Children having goitre were having no iodine deficiency but they had Vitamin A deficiency in Sudan (Elnour A, 2000).

A new etiological approach to endemic goitre was suggested when the hypothesis that vitamin A-deficiency alters the structure of thyroglobulin (Tg) required validation. Vitamin A-deficiency impaired the normal mannosylation,

conformation and iodination of thyroglobulin. This conclusion was drawn from the findings that blood levels of retinol fell to one tenth of the control mean and circulating concentrations of total and free T4 and T3 increased significantly. This biochemical hyperthyroidism contrasted with the maintenance of normal TSH plasma values, suggesting a generalised peripheral refractoriness to thyroid hormones (Ingenbleek Y, 1983)

# 2.5. CORRLTION BETWEEN IDD AND VARIOUS FACTORS

### EXCESS SILICONE AND IDD

Shifts in thyroid function were found to correlate with the increased content of silicon and some other trace elements in the diets. The silicon subregion is marked by the incidence of dysthyrosis of the thyroid gland (Semenov VD, 1983).

### SUFFICIENT IODINE AND GOITRE

Recently many studies have shown that despite sufficient iodine intake (measured indirectly from UI levels) endemic goitre is seen.

In spite of adequate availability and consumption of iodized salt, IDD still exists and is endemic in the Tarai region of North India. This was concluded because overall estimated goitre prevalence was 38.18 per cent when 770 children between the ages of 10-12 years were examined by palpation. Families of 95.53 per cent of children consumed salt having 15 ppm or more of iodine as evidenced from analyses iodine content of salt samples. The median urinary iodine levels also proved sufficient iodine intake (Mittal M, 2000).

In Sudan despite iodine sufficiency goitre was highly prevalent and the possible etiological factors named were consumption of millet, vitamin A deficiency, and protein-energy malnutrition (Elnour A, 2000).

Endemic goitre was found to be prevalent in South Tripura, NorthEast India and its occurrence varied from 14% to 31%. This indicated mild to severe degree of iodine deficiency in the studied population clinically but the pattern of median urinary iodine level showed that there is no biochemical iodine

deficiency. However IDD continued to be prevalent in the region (Chandra AK, 1997).

The prevalence of goitre has been continued to endemic figures in Spain but the mean urinary iodine was in the normal range (Madueno C, 2001).

## *GEOGRAPHICAL PLACEMENT AND IDD:*

A deficiency of iodine is characteristic of mountainous regions of the world and the frequency of goitre in such areas has been recognised for centuries. The prevalence of goitre was measured in high (3150 meters above sea level) and low altitudes (500 meters above sea level) of Saudi Arabia that showed higher prevalence at high altitudes (Abu-Eshy SA, 2000).

There are mainly three ecological regions: Terai (flat region), Hilly region (300-3,000m altitude) and mountainous regions (>3,000m altitude). In the old times many scientists reported IDD in mountainous regions but recently various studies have shown that Terai region was more affected than either that Hilly or mountainous regions (Baral N, 1999).

The health status of children and adolescents residing in geographic endemic area of the Republic of Tatarstan showed a significant increase in the incidence of thyroid hyperplasia caused by iodine deficiency and other risk factors like biological, naturally ecological, and social were equally important (Sakharev AG, 1999).

An improvement in iodine deficiency is reported from The State of Himachal Pradesh in the Himalayan range that was known endemic region for the last 40 years. The state government was supplying iodised salt to the district since 1970. The area of study was located at an average altitude of 10,000 feet above sea level. The findings of the study indicated that iodine nutrition

was in the transition phase from iodine deficient to iodine sufficient (Kapil U, 1998).

### *SOCIOECOMIC STATUS AND IDD*

School children surveyed for goitre prevalence in Bombay showed that 8% from high and 21% in the low socioeconomic groups had goitres. This study also reported that iodine deficiency was not the sole cause for goitre as revealed by dietary survey and urinary iodine estimations (Desai MP, 1997).

### *ETHNICITY AND IDD*

Thyroid enlargement was not seen to be associated with ethnic origin, thiocyanate ingestion, HLA DR/DQ phenotype frequency, or thyroid growth-stimulating Immunoglobulin (TGI) positivity (Smyth PP, 1999).

### *GENETIC FACTORS AND IDD*

There is a possibility that genetic factors may be involved in iodine deficiency disorders. It was hypothesised that endemic goitre is a multifactorial disease in which the major factor would be of environmental nature (iodine deficiency) with a lesser role for genetic factors. Mutations, in a heterozygote state, of one of the genes involved in tiered hormonogenesis could lead to a less effective metabolic pathway in the iodine transport or hormonogenesis. It was postulated that the presence of some genetic variants in the population or the heterozygote status of individuals for thyroid hereditary disorders might influence the degree of the thyroid enlargement and/or hypothyroidism (De Braekeleer M, 1998)

In some endemic goitre areas of Nigeria there was no evidence of iodine deficiency; therefore, both environmental and non-environmental factors could be taken into account. Environmental factors could be the radioactivity

and electromagnetism, foodstuff, the hydro-geological and chemical composition of natural water and the non-environmental important factor could be of genetic factors. It was assumed that the endemic goitre could have a multifactorial pathogenesis (Paggi A, 1998).

### *THERAPEUTIC MEASURES AND IDD*

Prevention of goitre recurrence with L-thyroxine when compared with pure iodide substitution after thyroid surgery for nodular goitre in an iodine deficient area, showed that recurrences were seen with both L-thyroxine medication and iodide substitution. This proved that in an iodine deficient area, substitution with iodide was just as effective as medicating with L-thyroxine (Feldkamp J, 1997).

Administration of levothyroxine and/or iodide can effectively reduce the thyroid volume in endemic goitre. Combinations of levothyroxine and iodide in different dosages when given to subjects with diffuse euthyroid goitre, leads to reduction of thyroid volume, while the intrathyroid concentration of iodine remained unchanged (Kreissl M, 2001).

### *PREGNANCY AND IDD*

Pregnancy can be viewed as a prolonged physiological condition stimulating the thyroid gland. Among the factors that may influence thyroid size, pregnancy and its goitrogenic effect have been widely investigated. The physiological thyroid hormone's steady-state equilibrium is markedly modified during pregnancy because of high circulating levels of human Chorionic Gonadotropin with its thyrotropic action, increase in serum T4-binding globulin as a consequence of high oestrogen levels, and intense iodothyronine deiodination activity of the placenta. The pregnancy-induced changes in maternal thyroid function may be achieved easily if iodine supply is adequate. Instead, in areas with limited dietary iodine intake, pregnancy

may lead to a relative iodine-deficient state as assessed by more intense relative hypothyroxinemia, preferential triiodothyronine secretion with increased serum T3/T4-ratio, and elevated thyroglobulin levels (Burrow GN, and Glinoer D, 1990)

When a pregnancy takes place in iodine-sufficient conditions, the thyroid gland adapts easily to the challenge of pregnancy and goitre formation during gestation is not observed (Berghout A, 1994 and Glinoer D, 1999). On the contrary, pregnancies occurring in women with a restricted (or deficient) iodine intake are frequently accompanied by goitrogenesis, affecting both the mother and fetus (Berghout A, 1999, Rasmussen NG, 1989). Furthermore, changes in thyroid volume associated with gestation are directly correlated to the degree of iodine deficiency (Caron P, 1997). Most studies had concluded that pregnancy-induced thyroid volume alterations were reversible after the delivery (Pedersen KM, 1993).

Recently one study in healthy women showed a significant association between a larger thyroid size and the number of their previous pregnancies that was correlated with each other. This constituted the first clinical confirmation that the goitrogenic effect of pregnancy was maintained in the long term, and was related to the number of pregnancies. This confirmed the hypothesis that goitre formation during pregnancy was not fully reversible after parturition, and provided an additional strong argument to indicate the need to increase the iodine supply in pregnant women to an adequate level of 200 $\mu$g/day, as recommended by WHO (Mario Rotondi, 2000).

## *IODINE EXCESS AND THYROID STATUS*

The relationship between the iodine intake level of a population and the occurrence of thyroid diseases is U-shaped with an increase in risk from both low and high iodine intakes. The pathophysiology of endemic goitre caused by excessive iodine intake is not well defined. By interacting with the immune system, iodine excess may trigger the development of autoimmune thyroid disease such as Hashimoto's lymphocytic thyroiditis (LT) (Boyages S, 1989). It was concluded that endemic iodine goitre was not associated with Hashimoto's LT and autoimmune growth factors such as thyroid growth-stimulating activity might play a primary role in the pathogenesis of thyroid growth in this condition (Boyages S, 1989).

Severely excessive iodine intake (median urinary iodine excretion levels around 800 microgram per 24 hours) is associated with a higher prevalence of thyroid hypofunction and goitre in children. A number of studies indicate that moderate and mild iodine excess (median urinary iodine >220 microgram per 24 hours) are associated with a more frequent occurrence of hypothyroidism, especially in elderly subjects. The exact mechanism leading to this has not been clarified, and the limits of excessive iodine intake are not defined precisely (Laurberg P, 2001)

Government of India had implemented compulsory use of iodized salt all over the nation since1985 as a prophylactic measure. But the programme was criticised through various channels of publications, stating that the long term consumption of iodised salt may result in toxic effects of iodine, such as thyrotoxicosis and other thyroid related complications. A survey was carried out therefore to study the effects of prophylaxis programme in a non-endemic area and ill effects if any, due to prolonged use of iodised salt were studied. The study concluded that use of iodised salt had beneficial effects towards prophylactic measures against goitre. Also prolonged consumption of iodised

salt in non-endemic area had not resulted in any ill effects due to extra iodine (Bhasin SK, 2001).

Excess iodine in household water was considered as the likely cause of endemic goitre as evidenced from estimation of thyroid size. Elevated urinary iodine levels in the China was reported (Zhao J, 2000). These authors did not consider goitrogens as an aetiological factor.

There was evidence to suggest that elevated levels of iodine in the diet were associated with autoimmune thyroid disease (ATD) in susceptible individuals and that autoimmune thyroiditis (Hashimoto's disease) was less common in susceptible individuals who lived in regions with dietary iodine deficiency. There were epidemiological studies in endemic goitre areas that reported an increase in ATD, particularly thyroiditis, after the therapeutic administration of iodized salt, bread and oil. Lymphocytic infiltration of the thyroid was rarely found in-patients from severe endemic goitre regions, yet there was a reversal of this observation after dietary iodine supplementation. Although these mechanisms related to the onset of autoimmune thyroiditis on exposure to excessive amounts of iodide, the relationship of iodide intake and autoimmune hyperthyroidism was less clear (Foley TP Jr, 1992).

An autoregulatory mechanism within the thyroid served as the first line of defence against fluctuations in the supply of iodine and also permitted escape from the inhibition of hormone synthesis that a very large quantity of iodine induced (Wolff-Chaikoff effect and escape therefrom). Iodine excess could result principally from the use of iodine-containing medicinal preparations or radiographic contrast media. The pathologic consequences of iodine excess would ensue only when thyroid Autoregulation was defective, in that escape from the Wolff-Chaikoff effect could not occur, or when Autoregulation was absent. In defective Autoregulation circumstance, the provision of excess iodine might lead to iodide goitre with or without hypothyroidism. Absent Autoregulation might be a feature of longstanding multinodular goitre, and the

provision of excess iodine in this circumstance might induce thyrotoxicosis (Jod-Basedow disease). The pathologic consequences of iodine excess would resolve when the source of iodine had been dissipated (Woeber KA, 1991).

### *COGNITIVE PERFORMANCE AND IDD*

The influence of inadequate iodine intake on the thyroid status and cognitive performance of school children was assessed in a town within the goitre belt of Southwestern Nigeria with known environmental iodine deficiency. The cognitive function tests, Draw-A-Person (DAP) test and the Standard Progressive Matrices (SPM) were administered simultaneously to all the pupils in the class. The results showed that maintained euthyroidism with mild degree of iodine deficiency did not seem to have adversely affected their cognitive performance (Ojule AC, 1998).

### *LEARNING AND MOTIVATION AND IDD*

Administering maze, verbal and pictorial learning tasks and motivation test, the effect of prolonged iodine deficiency on learning and motivation were studied. The results showed that severely iodine deficient children were slow learners compared to mild iodine deficient ones. The learning disability and poor motivation were attributed to neural impairment and poor sociopsychologic stimulation (Tiwari BD, 1996).

### *THYROID SIZE AND URINARY IODINE*

Iodine deficiency of moderate degree from the point of goitre prevalence of 34% and mild degree from urinary iodine excretion levels was revealed in a region but no significant correlation was observed between urinary iodine excretion levels and thyroid volumes.

### *ELECTROENCEPHALOGRAM (EEG) AND IDD*

The EEG abnormalities were seen in 34% of studied Ecuador schoolchildren with higher rate among girls and the best predictor was found to be a diagnosis of goitre (Levav M, 1995).

### *URINARY IODINE AND BREAST MILK IODINE*

The risk of women with low iodine excretion was 15 fold higher in comparison to women with sufficient iodine excretion to provide breast milk for their babies with insufficient iodine content. It is concluded that urinary iodine excretion can be used as a predictor to monitor the IDD in lactating mothers (Pongpaew P, 1999).

### *CARCINOMA AND IDD*

Patients of carcinoma of the thyroid gland residing in the Mountaineous-Altai endemic goitre region had nodular and diffuse-nodular goitre as an important etiological factor in the development of malignant tumour. There was a deficiency of trace elements (iodine, copper, and cobalt) in the surrounding environment of the endemic regions of the Mountaneous-Altai that permitted to refer this disease to geographical pathology (Neimark II, 1978).

### *CLASSIFICATION OF GOITRE BY PALPATION (1960 VERSUS 1994) AND ULTRASONOGRAPHY*

Goitre surveys are used to assess the degree of iodine deficiency in a population. The change of goitre classification made by WHO in 1994 implied that a smaller thyroid size should be regarded as goitre. Furthermore, the acceptable goitre prevalence was lowered from 10% to 5%, and ultrasonography was recommended as a more precise method for diagnosis of goitre. The effects of the change of palpation system were studied and the

precision of the old and new systems was compared with that of ultrasonographic examination (Peterson S, 2000). It was advised that a return to the old (1960) palpation criterion for goitre: "lobes larger than the terminal phalanxes of thumbs" and to an accepted palpation goitre prevalence of 10% can allow affordable monitoring of thyroid size through palpation in field surveys.

***PALPATION IS INACCURATE***

Palpation of thyroid in children was said to be unreliable and inadequate for distinguishing mild thyroid enlargement from normal (Gutekunst R, 1986).

Clinical evaluation by palpation was usually inaccurate but ultrasonography was an excellent and objective method for assessing thyroid volume in children (Lupoli G, 1999).

***PREFERENCE OF ULTRASONOGRAPHY IN MILD IODINE DEFICIENCY:***

Ultrasound was the most reliable method to determine thyroid volume (Brunn J, 1981, Gutekunst R, 1986, Hegedüs I, 1983).

In areas of mild endemicity, an ultrasonographic measurement of thyroid volume was preferable to inspection and palpation for determination of goitre (WHO/ ICCIDD, 1997).

A study was conducted in Val Sarmento, (a mountain area of Basilicata, Italy), an area with mild-moderate grade (Grade I) of iodine deficiency in 1996. Thyroid size was measured by palpation and ultrasonography and the results proved that the measurement of thyroid volume by ultrasonography was an essential instrumental method for a correct epidemiological study of endemic goitre, particularly in areas where there is mild iodine deficiency (Lupoli G, 1999).

### *LOW IODINE IN WATER AND IDD*

Low iodine concentration in drinking water (mean iodine concentration in drinking water was 2.04 mg/l) was associated with the iodine deficiency in an area of Cerdanya (Pyrenees) (Vila Ballester LL, 1999).

## *MILD IODINE DEFICIENCY AND THYROID STATUS*

The association between severe iodine deficiency and endemic goitre was well established, but little information was available on the relation between milder degrees of iodine deficiency and goitre prevalence.

Recently a comparative epidemiological study was performed in two regions of mild and moderate IDD regions in Denmark, where ultrasonography and palpation of the thyroid was performed in all participants and iodine excretion was measured in casual urine samples. The results showed that goitre prevalence increased in both regions with age to the age group 40-45 years, but not after that age. The study concluded that marked differences in the prevalence of thyroid abnormalities were found in these regions with modest differences in iodine excretion (Knudsen N, 2001).

Serum levels of thyroid hormones (thyroxine and TSH) were in the normal range with different grades of goitre. Thyroid hormones do not differ with respect to urinary iodine. The only hormone affected is triiodothyronine that may increase in few subjects due to compensations (Semiz S, 2001).

### *CIRCADIAN RHYTHM AND URINARY IODINE*

The existence of a universal circadian rhythm of urinary iodine level was shown from a study of 3023 spot urine samples from adults and children. The rhythm was independent of the individual subject, age, gender and season and showed lowest UI levels between 8-11 AM. UI peaks occurred 4-5 hours after main meals (Claudine A, 2000).

## *2.6. URINARY IODINE ESTIMATION METHODS*

### *SPECTROPHOTOMETRIC METHOD*

This method to determine iodide is based on the inverse colorimetric method in which iodide catalyzes the reduction of ceric ions by arsenous acid in a reaction (Sandell-Kolthoff, 1937). The decrease in absorbance of the yellow ceric ion at 420 nm is proportional to iodide concentration.

$$As^{3+} + I_2 \rightarrow As^{5+} + 2\,I^-$$

$$Ce^{5+} + 2\,I^- \rightarrow 2\,Ce^{3+} + I_2$$

### *AUTOANALYZER METHOD (AAII, TECHNICON)*

The method used dialysis for urine samples rather than digestion prior to colorimetric determination of iodine. In this method mineralisation takes place in a continuous flow manner. The method is reliable for iodine sufficient samples that means when the urinary iodine is above 50 µg/l. The results would be essentially the same as the digested samples in iodine sufficiency but iodine deficient samples give artificially high iodine values due to interference from goitrogens (Garry PJ, 1973).

## ELECTROCHEMICAL METHOD

This method used a crystalline membrane specific electrode and was a simple and reliable one (Mura P, 1986). Current electrodes are not sensitive enough to recognise the low levels encountered in areas of iodine deficiency, and determination is not rapid.

## X-RAY FLUORESCENCE

Urinary iodide measurement has been carried out by X-ray-fluorescence, either directly on urinary solution, or after matrix concentration. Proportionality between emitted XK alpha rays of iodine and iodide mass in standards has been observed on a large scale, ranging up to 400 micrograms. With an exciting-1.11 GBq (241(95) Am)-radioactive source, 0.44 microgram are detected for solid matrix, and 0.9 microgram/ml for iodide in solution for 10 mn measuring time. So direct measurement on solution can be applied only to high-excreted iodide. For normal range iodide determination is performed after anionic resin concentration (on 100 ml or 200 ml). For tracing, Na $I^{131}$ is employed. The binding ratio is strongly depending on flow, resin weight, and associate urinary anionic components (Turzo A, 1990).

## ASHING OR DIGESTION METHODS:

### CHLORIC ACID METHOD

The chloric acid method was most commonly used to obtain accurate and reproducible measurements of iodine and it removed interfering substances. Two adaptations of the Sandell-Kolthoff reaction were described in which urine was first digested with chloric acid and iodine was then determined from its catalytic reduction of ceric ammonium sulfate in the presence of Arsenious acid. Both methods used gentle digestion by chloric acid in a heating block. Method A detected iodine in a colorimeter, method B by the indicator ferroin

and a stopwatch (Dunn J, 1993). Unfortunately, chloric acid was a potential hazard requiring an explosion proof hood among other precautions.

## *AMMONIUM PERSULPHATE METHOD*

### *MICROPLATE METHOD (METHOD L, HITACHI)*

Photometric determination of iodine concentrations in urine was using a modified ceric arsenite method with ammonium persulphate as an oxidant. In this method, both the reaction and the digestion process took place into a microplate format. A specially designed sealing cassette was used to prevent loss of vapour and cross-contamination among wells. The digestion process was performed in a microplate with ammonium persulphate that was covered and kept in sealing cassette and then in an oven at 110 degrees C for 60 min. After the digestion, mixture was transferred to a transparent microplate and the Sandell-Kolthoff reaction was performed at 25 degrees C for 30 min, urinary iodine is measured by a microplate reader at 405 nm (Ohashi T, 2000).

Bioclone Kits to measure urinary iodine are based on this method but there are some changes in timings and oven temperature for digestion process i.e. the plate is kept for 90 minutes and temperature is 90 degrees C.

This simple, convenient, and economic method was adapted from Pino et al and is "Method H", currently recommended. Method requires a heating block and a spectrophotometer, both inexpensive instruments. This method is the same as "Method A". Ammonium persulphate, is a non-explosive, non-hazardous chemical, as the oxidising reagent for chloric acid in the digestion step, thus avoiding toxicity from the chloric acid, and gives comparable results. The oxidation procedure can be completed in 30 minutes at a temperature of 91-95 degrees C (Pino, 1998).

## INDUCTIVELY COUPLED PLASMA MASS SPECTROMETRY (ICPMS)

An inductively coupled mass spectrometric method was developed for the direct determination of iodine in urine and is considered as Gold method. The application of isotope dilution analysis with added $^{129}I$ offers new possibilities for automatic and accurate determinations. The sample preparation consists of dilution with an ammonia solution containing $^{129}I$ (Haldimann M, 1998).

## ISOTOPE DILUTION ANALYSIS

The method was based on substochiometric isotope dilution analysis. Iodide was precipitated by substoichiometric amounts of AgNO3. Iodide-$^{131}$ was used as a tracer. Electrophoresis was performed to separate Ag131I from excess $^{131}I$-. The $Ag^{131}I$ zone was cut off the electrophoresis paper and counted with a NaI (Tl) scintillation counter. Count rates were plotted versus added KI concentrations. The unknown iodide amount was found by using these linear plots (Unak P, 1999).

## PAIRED-ION REVERSED-PHASE HPLC WITH ELECTROCHEMICAL DETECTION

This is an automated method for the routine analysis of urinary iodide, using paired-ion reversed-phase HPLC with electrochemical detection and a silver working electrode. Sample preparation is semiautomated by use of a reduced-pressure manifold. The average recovery of added iodine was 94%. The method is comparable to Technicon Autoanalyzer acid digestion method and there is a high correlation with it. After removal of organically bound iodine, the results for unbound urinary iodide determined by the two methods

were nearly identical because iodine is excreted in urine mainly as iodide (Rendl J, 1994).

## *PAIRED-ION REVERSED PHASE HPLC*

Paired-Ion Reversed Phase HPLC was used despite the high cost of instrumentation. The cost was outweighed by the benefits of processing a large number of samples with high accuracy and minimal technician time. For determining serum inorganic iodide (SII) the HPLC assay was the method of choice, because contaminations from the protein bound iodine fraction did not interfere with the detection process. The clinical relevance of the measurement of SII was limited, but allowed the calculation of the absolute iodine uptake that had great value in pathophysiologic studies (Rendl J, 1998).

## *RAPID URINARY IODINE TEST: METHOD J*

The method is also called the Rendl or Merck method. This was based on the iodide-catalyzed oxidation of 3,3',5,5'-tetramethylbenzidine by peracetic acid/$H_2O_2$ to yield coloured products. The color of the chemical reaction was compared with color categories of a pictogram corresponding to three ranges (<100, 100-300, and >300 μg/l) of iodide concentrations. The test was very easy to perform and did not require any instrumentation or apparatus. Sample preparation was simple and consisted in the removal of interfering substances by disposable columns, 65x10.5 mm, packed with specifically prepared activated charcoal (Rendl J, 1998).

## FLOW-INJECTION ANALYSIS

A flow-injection technique involves on-line catalytic digestion and spectrophotometry. Urine samples are digested by $KMnO_4$-$K_2Cr_2O_7$-$H_2SO_4$ solution and the iodine in the urine catalyzes the reaction of Arsenic (III) with ceric (IV). The remaining ceric (IV) is then reacted with brucine and the product is detected with a spectrophotometer at 480 nm. Analytical recovery ranges between 92% and 104% (mean 99%). The sampling frequency of the flow-injection technique was 70/h. The method can measure the iodine concentration in a freeze-dried urine reference sample and collected urine samples. This technique has the advantages of being simple, rapid, precise, accurate, and sensitive (Yaping Z, 1996).

## AUTOMATED ULTRAVIOLET IRRADIATION ASSAY METHOD

An automated measurement system of urinary iodine was modified and a sensitive assay system was established using ultraviolet (UV) digestion. The automated system is sensitive. The theoretical values were recovered when UV irradiation was used but not in its absence. High (supraphysiological) doses of thiocyanate or ascorbic acid, which are major interfering substances to the ceric-arsenious acid reaction, did not interfere with this system. This modified automated assay system is useful and applicable for screening UI in inhabitants of iodine-deficient areas (Tsuda K, 1995).

### METHOD K

This is Semi-quantitative, similar to Method A but uses the redox indicator ferroin and places samples in categories rather than giving precise numbers.

## 2.7. THE SPECTRUM OF IDD

***FETUS***

Fetus Abortions, Stillbirths

Congenital anomalies

Increased perinatal and infant mortality

Neurological cretinism (mental deficiency, deaf mutism,

Spastic diplegia, squint)

Myxoedematous cretinism (dwarfism, mental deficiency, hypothyroidism)

Psychomotor defects

Increased susceptibility of the thyroid gland to nuclear radiation (after 12 weeks)

***NEONATE***

Neonatal goitre

Neonatal hypothyroidism

Increased susceptibility of the thyroid gland to nuclear radiation

***CHILD AND ADOLESCENT***

Goitre

Juvenile hypothyroidism

Impaired mental function

Retarded physical development

Increased susceptibility of the thyroid gland to nuclear radiation

***ADULT***

Goitre and its complications

Hypothyroidism

Impaired mental function

Iodine induced hyperthyroidism

Increased susceptibility of the thyroid gland to nuclear radiation

***ALL AGES***

Goitre and Hypothyroidism

Impaired mental function

Increased susceptibility to nuclear radiation

## 2.8. IDD IN THE LIFE CYCLE

All these effects are totally preventable by correction of iodine deficiency (Hetzel BS, 1985, Dunn J and Delange F).

### IODINE DEFICIENCY IN THE FETUS

Iodine deficiency in the fetus is the result of iodine deficiency in the mother. Correction of iodine deficiency in the human mothers from iodine deficient areas reduces the rate of spontaneous abortions and stillbirths. Thyroid treatment of hypothyroid pregnant mother benefits in decreased risk of spontaneous abortions and stillbirths (McMichael 1980).

Iodized oil when given to women of Zaire and Papua New Guinea during latter half of pregnancy showed that there was a substantial fall in infant mortality with improved child weight and a development quotient (Thilly, 1981).

The consequence of iodine deficiency during pregnancy is impaired synthesis of thyroid hormones by the mother and the fetus. Thyroid hormones play an essential role in brain maturation and function. Their deficiency during fetal life results in irreversible brain damage and mental retardation. One important concept developed during recent years is that the thyroxine available to the fetal brain derives not only from the fetal thyroid but also from the mother.

### IODINE DEFICIENCY IN THE NEONATE

Neonatal goitre was once commonly seen in iodine deficient areas and its decrease was described in Austria in humans in 1954 following the use of potassium iodide from fourth month of pregnancy. There was a reduction of goitre rate in the new born from 47% to 5% in two years (Kopf, 1954).

Neonatal hypothyroidism is a well-recognised cause of mental defect. This is due to the fact that the development of the brain is dependent on adequate supply of thyroxine. The importance of the state of thyroid function in the neonate relates to the fact that the brain of the human infant at birth has only reached about one third of its full size and continues to grow rapidly until the end of the second year. An increased perinatal mortality due to iodine deficiency has been shown in Zaire from the results of a controlled trial of iodised oil injections alternating with a control injection given in the latter half of pregnancy. There was a substantial fall in infant mortality with improved birth weight following the iodised oil injection. The thyroid hormone, dependent on an adequate supply of iodine, is essential for normal brain development during and after pregnancy.

In many developed countries every newborn child is tested for thyroid stimulating hormone or thyroxine on $4^{th}$ or $5^{th}$ day. If the thyroxine level is low or TSH is high and thyroid function is abnormal, further check is made. In Western countries, the incidence of such an abnormality runs at 1 per 3500 live births. An incidence of 75-115 per 1000 live births for neonatal chronic hypothyroidism was shown in a severe iodine deficient area of India (Kochupillai, 1989). The incidence for neonatal chronic hypothyroidism was 6/1000 births in mildly iodine deficient area of Delhi.

## *IODINE DEFICIENCY IN THE CHILD*

Iodine deficiency in children is characteristically associated with goitre. The goitre rate increases with age, reaching a maximum with adolescence. Girls have a higher prevalence than boys do. Observation of goitre rate in 8-14 years can provide a convenient indication of community prevalence.

The prevention and control of goitre was first demonstrated in schoolchildren (and Kimball, 1917). It was then recognised that goitre was only a part of IDD

(Marine et al, 1921): "the prevention of goitre meant vastly more than cervical deformities. It meant in addition, the prevention of those forms of physical and mental degeneration such as cretinism, mutism, and idiocy that were dependent on thyroid insufficiency. Further it would prevent the development of thyroid adenomas which were an integral and essential part of endemic goitre in man due to the same stimulus."

Studies from a number of countries of school children living in iodine deficient areas indicated impaired school performance and Intelligence Quotients, in comparison with matched groups from non-iodine deficient areas (Stanbury, Bleichrodt, Ecuador, 1987).

## *IODINE DEFICIENCY IN THE ADULT*

The most common effect of iodine deficiency in adults is goitre. Characteristically there is an absence of classical clinical hypothyroidism in adults with endemic goitre. However, laboratory evidence of hypothyroidism with reduced thyroxine levels, normal triiodothyronine and raised TSH level is common.

Iodine administration, especially as injectable iodized oil, is effective in the prevention of goitre in adults.

A high degree of apathy had been noted in populations living in severely iodine deficient areas of Northern India. This even affected domestic animals such as dogs. It was apparent that reduced mental function due to cerebral hypothyroidism was widely prevalent in iodine deficient communities with effects on their capacity for initiative and decision-making (Li, 1987). This indicated that iodine deficiency could be a major block to the human and social development of communities living in an iodine deficient environment.

# 2.9. REGIONAL DESCRIPTIONS OF IDD

## DEVELOPED COUNTRIES

## AMERICAS

IDD has existed in the America since antiquity. In Canada and the USA, endemic goitre was widespread in the Great Lakes region, the northern Rockies, Appalachia but has been eradicated by increased dietary iodine. Noguera et al (1986) reported >40% prevalence of goitre in the countries Bolivia, Ecuador and Peru. Argentina had severe iodine deficiency and goitrous population was treated with iodized oil and all the salt for human and animal use was enriched with iodine. It is possible that IDD may not be a problem in Argentina anymore. Bolivia had severe iodine deficiency till 1983. Some of the areas in Chile (Pedregoso) had goitre prevalence rate of 84% due to iodine deficiency and ingestion of goitrogens in the pinon nuts but now it is iodine sufficient. Southeast Cuba had the goitre prevalence of 30% in the population that was attributed to calcium carbonate contributing to goitrogenesis. The goitre prevalence was described as 33% in Nicaragua and 13% in Panama The goitre prevalence in 1995 was 9% in Uruguay and 14% in Venezuela.

## AUSTRALIA

It is currently believed that iodine deficiency does not exist in Australia (Hetzel BS, 1993 and Mortimer RH, 1998). However, iodine status is seldom, if ever, measured in routine clinical care, and there are some reasons why iodine intake in Australia may be inadequate. It was a common perception that iodine deficiency is not a major public health concern in mainland Australia. Recent evidence, however, has shown that the consumption of iodine is declining in Australia and situation is similar to USA and it was suggested that

Australia no longer should be considered an iodine-replete country automatically. This study measured urinary iodine by ICPMS method and showed high frequency of iodine deficiency in participants that suggested insufficient dietary sources of iodine in this country (Gunton JE, 1999). In another study, urinary iodine excretion (UIE) was evaluated as the indicator of iodine nutrition, in various demographic groups (schoolchildren, healthy adult volunteers, pregnant women and patients with diabetes) in the Sydney metropolitan area. Urinary iodine in spot urine sample was measured in a Technicon II Autoanalyzer using an in-house, semiautomated method. The results showed that all four-study groups had the median UIE below 100 microg/L, the criteria set by the World Health Organization for iodine repletion, and confirm that iodine deficiency has remerged in Sydney, Australia. One of the major causes of the reduced iodine intake was the reduction of iodine in milk since the dairy industry replaced iodine-rich cleaning solutions with other sanitisers. Secondly, less than 10% of the population are currently using iodised salt.

## *DEVELOPING COUNTRIES*

## *AFRICA*

The overall incidence, location and severity of IDD are not known. Of an estimated population of 400 millions, perhaps 150 million people are severely at risk. They consist mostly of women of childbearing age and children. Another 8 million people in the population suffer from severe effects of iodine deficiency; they include 2 million cretins and 6 million mentally handicapped people. The burden imposed by IDD on the community contributes to economic underdevelopment of the continent that contains over 31 of the World's poorest countries. The scourge of IDD had continued unabated, leaving in its trail preventable social, economic, and nutritional disasters.

IDD is a major public health problem in over 60% of African countries. The etiological factors for this are iodine deficiency, goitrogens and malnutrition. Iodine excretion information is scanty. Iodized oil injections are used in Zaire and Tanzania. Goitrogen studies are mainly on the role of cassava in producing goitre by Ermans, Thilly, Delange and others. Ekpechi et al reported a vegetable used daily by a population in Benue State as goitrogenic. Millet, turnip and cabbage functioned as goitrogens was also reported. The possible role of malnutrition was examined and reported by Ingenbleek in Senegal.

## *SOUTH EAST ASIA*

### *BANGLADESH*

Goitre is found throughout all 21 districts. The regional surveys were conducted in 1960 and 1975 that showed a high prevalence rate of goitre. National survey was conducted in 1981-82 on 214,608 persons and overall goitre prevalence rate for the country was 10.5% with two districts affected severely (Rangpur 27.5% and Jamalpur 29.2%). The population at risk of IDD was 38%. A national IDD control program was decided in 1984 with iodised salt for long term and iodised oil injections as immediate measures.

A quantitative survey to determine the prevalence of use of iodized salt was conducted (Rasheed et al). The reasons behind non-use of iodised salt and its correlation with socioeconomic status was explored. The results revealed that only 1.9% of the households used iodised salt. The use of costly iodised salt was limited due to the availability of coarse non-iodised salt and lack of the knowledge about the link between iodised salt and IDD.

## BHUTAN

A WHO supported survey was conducted in 1975 in selected districts that indicated a goitre prevalence of 47-68% in schoolchildren and 50-53% in the community. The first national survey was conducted in 1983 that declared entire country at risk of IDD. Since 1982 several thousands iodised oil injections were given but the impact evaluation were never carried out. National iodization program started from 1985.

A proposal for more vigorous iodine deficiency control was developed under the Chairmanship of Dr. Eastman from Australia in May 1999. The short-term goals of the project were iodized salt in cities, townships, and villages along the main roads, and an iodized oil program elsewhere. The long-range goal is USI. The iodized oil programs are expected to end eventually except in villages or populations where iodized salt is still not available.

## MYANMAR

Goitre was recognised in Burma since 1896. Up to 1982 studies had indicated a goitre prevalence of 50% in 314 townships with northern hill states affected severely (75%). In 1969 the government established a pilot program of iodated salt program that led to decrease of goitre prevalence from 91 to 24% in Chin State. In 1983 awareness of IDD led to launching of iodised oil injection program for four years.

The salt iodization program was reviewed last year in the 1998 and the use of iodized water to correct iodine deficiency in ibid was proposed in 1999.

## *INDIA*

The National Iodine Deficiency Disorders Control Program (NIDDCP) is attempting to control the prevalence of IDD in India. High prevalence of endemic goitre and cretinism existed in Himalayan/sub Himalayan belt. The National Goitre Control Program began in 1962 with the establishment of salt iodization plants. Iodised salt is not available to about half the Indian population of about one billion. Iodised salt is made available to sub-Himalayan belt as a priority. The iodised oil pilot program was conducted in Gonda district in Uttar Pradesh that led to a fall in goitre prevalence from 63 to 10%.

Sixteen States and 4 union territories had endemic goitre foci reported by various surveys for 10 years between 1975-1985. The reasoning for this goitre endemicity was the various possibilities put forward by various scientists (Singh BS, 1994). These were:

1. The population did not perceive small and moderate goitres as a health problem.
2. Non-iodised salt was much cheaper and more acceptable to many Indian palate.
3. Non-iodised salt was still available in the banned States of India (ban for the sale of non-iodised salt existed in 17 States of India).
4. At the same time people were not aware of the national control programs for their welfare.

IDD are an important public health problem in India with an estimated 270 million people at risk of IDD. India has adopted the strategy of salt iodization for control of IDD and has the goal of "Universal iodization of salt by 1995 and elimination of IDD by 2000" (Pandav CS, 1995).

The prevalence of IDD was established in schoolchildren of Delhi that does not lie in the classical Himalayan goitre belt. The sale of uniodized salt had been banned in Delhi since 1989 and the study was done five years after the ban to see its impact. The study showed mild to moderate IDD, though the rates had fallen from the earlier study reports, IDD was not eliminated from Delhi (Pandav CS, 1996).

The overall prevalence of goitre in Sikkim was 54% and urinary iodine concentration as estimated from a representative sample of the population showed a mean value of 40 µg/l (SD 2.68). This survey showed the existence of severe iodine deficiency in Sikkim associated with endemic cretinism to the extent of 3.5% (Sankar R, 1998).

An overall goitre prevalence of 52 per cent and almost normal Urinary Iodine was found in Baramulla district of Kashmir valley (Zargar AH, 1997).

The predominantly tribal population of India involved in coconut plantations in Car Nicobar, (an island that was used to send criminals from India once upon a time) was once assessed for their knowledge, beliefs and practices regarding iodine deficiency disorders. It was reported that these Tribals were unaware about the cause for IDD (Mallik AK, 1998). It was concluded that the awareness about IDD needed reinforcement.

All states except Kerala had banned the sale of noniodized salt. Recently in year 2000, the ban to iodise all edible salt was lifted by the Indian Government.

## *INDONESIA*

Goitre was known for centuries and the prevalence was 18%. National iodine supplementation program began from 1974 with iodized oil injections and iodised salt consumption. Indonesia has the most developed IDD control program. Prior to 1974 eight percent cretins were born but after the iodine supplementation program not a single cretin was born.

In 1998, 65% of all families consumed iodized salt, and the figure was expected to reach 90% by the year 2000.

## *NEPAL*

The first government survey of the country in 1965-66 showed an overall goitre prevalence of 55%. Many studies were conducted thereafter by Delange et al, Ramalingaswami et al and Ibbertson et al. that showed a very high prevalence of goitre. From 1972 iodised salt was imported but later iodised salt plants were built. In 1977 mass iodized oil injections campaign covered most of the children and pregnant women. In 1986 the impact of iodised oil was studied that showed satisfactory results. Over 90% of households consume iodized salt.

## *SRI LANKA*

Goitre is a recent disease with earliest reports from late 19$^{th}$ century. The surveys from 1947-79 showed endemic goitre in rural parts. The problem was due to the leaching of iodine content from the soil as a result of heavy rainfall. A large national survey (Professor M. A. Fernando, 1987) found a prevalence of 18.8% among schoolchildren, the highest being in Kalutara (30%). Only 4 of 17 districts had less than 10%. Legislation for salt iodization became

effective in 1995. Studies of several families showed that the mean consumption of edible salt was 7 grams/person/day.

## PAKISTAN

IDD in Pakistan had been described frequently. Endemic goitre occurred particularly in the north, but also in most other parts of the country. The Iodized Salt Support Facility provides increased support to the private sector. A 1995 estimate was that 19% of households consume adequately iodized salt. Most salt is rock salt, iodized by dry mixing with KIO3.

## THAILAND

Ramalingaswami conducted various surveys in Thailand. First survey in 1955 demonstrated a goitre prevalence of 58% (30-90%) in two districts of Northern Thailand. Next survey in 1957 of 5 districts from same area showed a goitre prevalence of 24-49% in primary school children. National surveys were not done but it was known that environmental iodine deficiency existed with 4% cretinism. The iodated salt program was launched in 1962.

A current estimate reported that 50-90% of households was consuming iodized salt.

# CHINA AND FAR EAST

## CHINA

Iodine deficiency is widely scattered all over this country. Epidemiological surveys were conducted for most of the country that reported very high prevalence for goitre and cretinism. In 1961 an Organization was founded for the Endemic Disease Control that introduced preventive measures in 16

endemic goitre areas. These were mainly the salt iodination in most of the districts with iodised oil in some of the northern parts. The 1997 National Monitoring Plan Surveillance Study reported annual production of iodized salt as 6.2 million tons, covering 90% of the salt requirement, with 80% being of satisfactory quality. The total goitre rate was 10.9% and the median urinary iodine greater than 100 μg/L for the entire country. Excellent progress had occurred in all provinces.

## *QINGHAI*

The national monitoring results (1997) and preliminary data (1999) have shown that 80% of Chinese households are consuming effectively iodized salt (> 20 ppm), but more than 10% use salt containing > 60 ppm, and another 10% use noniodized salt. The average iodine concentration at the consumer level is around 40 ppm and the UI in children is about 300 mcg/L, but some are higher. Careful studies confirmed that iodine losses between production and consumption were very low, less than anticipated, when small waterproof packages were used.

## *MONGOLIA*

The total goitre rate in children in 1993 was 28%. Salt iodization is being undertaken. A national program exists but there is not yet legislation. Current problems are lack of effective implementation systems and labs. A study team (1998) found that the mean standard salt intake in Ulaan Baatar was 11 grams for women and 13.2 grams for men. Sixty-eight percent used only iodized salt, and 1% never used it. These figures were similar to those noted in a previous survey about a year before.

## LIBYA

Mildest goitre endemia was reported. Salt iodization has existed since 1980. A survey in 1993 reported 90% of households consuming adequately iodized salt. In 1997, WHO recommended using potassium iodate ($KIO_3$) and increasing the level of iodine used, and the Secretary of Health decreed in 1998 that $KIO_3$ should be added to salt at a level of 34-66 parts per million (ppm), with regular monitoring and follow-up. The source of salt was salt lakes.

## TUNISIA

Goitre prevalence of 50% was reported. A 1993 review reported that the iodization level in salt was too low, and the country has reinstated universal salt iodization at 40 ppm. Since March 1996, only iodized salt was allowed on the market. UNICEF reported that 98% of households consumed adequately iodized salt.

## JORDAN

No much information was available until recently. A 1993 national survey showed a total goitre prevalence of 37.7% and low mean urinary iodine level. A National Coordinating Committee was established in 1994 and a plan of action adopted in 1996, with salt iodization beginning in the same year. All salt produced was iodized with $KIO_3$ at 67-100 ppm or with potassium iodide (KI) at 58-72 ppm.

## SUDAN

IDD in Sudan had been described frequently due to a considerable interest in IDD problem. Salt iodization began in 1994 and currently one-third of all salt

produced is iodized at 40-50 ppm iodine. A national IDD committee was established in 1991 and legislation for salt iodization passed in 1994. A proposal for monitoring iodized salt had been prepared. Iodized oil was distributed to children and women, covering 7% of the population, between 1988 and 1995.

## *SYRIA*

Virtually no information was available until recently. A 1990 national survey reported a total goitre prevalence of 73%. Iodization was by spraying with $KIO_3$, but some salt was dry mixed automatically. An estimated 40% of households consumed adequately iodized salt.

## *KUWAIT*

Data are being obtained on IDD prevalence. The main salt producers have agreed to start salt iodization.

## *LEBANON*

A 1993 survey found a goitre prevalence of 26% and a median urinary iodine concentration of 60 μg/L. Governmental decree states that all salt imported or produced in the country should be iodized. A 1996 survey reported that 92% of households consume adequately iodized salt. Legislation requires 50 ppm. A recent survey of 15 households in each of 30 clusters found that 84% of 461 samples were adequately iodized with either iodate or iodide.

## MOROCCO

A 1993 survey showed a national goitre prevalence of 22%. A national coordinating committee was established in 1991 and a plan of action developed. Salt iodization began in 1995 with $KIO_3$ at a level of 80 ppm. Legislation in 1995 decreed salt iodization. A neonatal screening program with TSH and $T_4$ was planned. Between 1992 and 1996 iodized oil was distributed in six mountainous provinces that were hyper-endemic, and also in Azal, Taza, Chefchaoun, and Ouarzazate.

## OMAN

Mild IDD was found in a national survey in 1993. A national coordinating committee was established and a plan of action adopted in that year, with salt iodization beginning in 1995, backed by a law the same year. An estimated 65% of households consume iodized salt. The country also imported salt and a ministerial decree required that it be iodized. The only local producer has been iodising his salt after receiving technical advice from WHO/EMRO.

## PALESTINE

A 1997 survey of the West Bank and Gaza Strip showed a15% goitre prevalence. A national coordinating committee was established in 1994. A plan of action is currently being adopted and salt iodization will be initiated with the help of UNICEF.

## QATAR

A small 1996 preliminary survey found a mean urinary iodine excretion of 234 µg/L, with 70% of samples above 100 µg/L. No IDD control program currently exists. All salt is imported from neighbouring countries.

## SAUDI ARABIA

The first national survey, reported in March 1998, showed mild to moderate IDD prevalence, with the endemia in the south regarded as severe on the basis of goitre prevalence in schoolchildren. The national median urinary iodine excretion was180 µg/L, ranging from 110 µg/L in the south to 240 µg/L in the west. However, in the south 45% of samples were below 100 µg/L, compared with 19% in the north and 15% in the east. An official from the Ministry of Health has recommended universal salt iodization. Salt iodization began in 1980 with KIO3 at a level of 70-100 ppm. Enabling legislation dates from 1980 with modification in 1996.

## UNITED ARAB EMIRATES

A 1994 survey among schoolchildren reported a goitre prevalence of 40%. In October 1998 the Ministry of Health started planning for salt iodization.

## YEMEN

A rapid assessment reported 30% goitre prevalence among schoolchildren in the mountainous regions, where most of the population lived (Dr. Azizi, 1991). A national program was established by the Ministry of Health in 1993 and began activities in 1995. Iodized salt is the intervention method because salt is available locally (rock and sea salt). Small producing units were established

with iodization by spraying with $KIO_3$, the product containing 40-ppm iodine. A salt iodization law was passed in 1996. A film on the IDD problem in Yemeni village was produced, also four TV spots. The program uses radio and daily newspapers to increase awareness. Posters and educational pamphlets have been distributed to health centres. Boy scouts and girl guides were educated on IDD and how to use kits for monitoring iodine content of salt. Most people in the mountainous regions prefer noniodized salt because it is cheaper. They buy it in big quantities and then add it as rock salt to cereals before milling.

Preliminary results reported showed that 90% of households consumed adequately iodized salt in Yemen (UNICEF, 1998).

## 2.10. PRESENT STATUS OF IODISED SALT PROGRAMS

Iodised salt was first introduced in Switzerland and in the USA in the 1920s when it was shown to be a successful measure. New Zealand followed in 1941 but only very low levels were used in the first 20 years. Then in the 1950s and the 1960s a number of European countries followed with the expected benefits.

In general, iodination of salt was a simple procedure in these countries because the salt industries were large operations with automated refining plants. The addition of iodine was possible at very little extra cost and production could be readily achieved.

It was with confidence from this experience that salt iodination programs were initiated in several Central and South American countries. In Guatemala, Colombia, Argentina and Chile considerable progress was made with the control of IDD.

Iodine deficiency has recurred in Croatia, the Netherlands, and possibly other European countries. Moderate to severe iodine deficiency still persisted in all other European countries: Bulgaria, the Commonwealth of Independent States, Germany, Greece, Italy, Poland, Romania, Spain, and Turkey. In other words, except a few, in most European countries iodine deficiency had recurred or has persisted. Special recommendations were reached in order to try to eliminate iodine deficiency by the end of the century. Both the governments and the European community were called upon to initiate adequate legislation and other necessary measures to ensure the availability and use of iodised salt. It was especially recommended that in pregnant and lactating women daily iodine intake should be at least 200 mg/day and 90-120 mg/day in infants and children (Stanbury JB, 1998). To reach these objectives the mother's diet should be systematically supplemented with iodine whenever necessary, by vitamins/mineral tablets as prescribed by physicians. As breast milk is the best source of iodine for the infant, exclusive breast feeding for 4-6 months should be encouraged. When infants necessarily require formula, the iodine content of the formula milk should be increased to 100 mg/l for full term and 200 mg/l for premature babies.

A standardised evaluation of thyroid volume measured by ultrasonography and of urinary iodine in schoolchildren 6-14 years old was conducted in 1994-95 in 13 European countries (The ThyroMobil project). The study indicated a spectacular improvement of the status of iodine nutrition.

A recent review of the situation in 26 countries in the Commonwealth of Independent States, Central and Eastern Europe, the Baltic States, the former Yugoslavia and Turkey, indicated a dramatic recurrence of IDD in some of these countries. Especially, in the Central Asia Republics, after the interruption of the program of salt iodization implemented before the disruption of USSR.

More globally, the 71 heads of States and 80 other officials from 150 governments who attended the World Summit for Children held in New York in 1990 adopted the goal of virtual elimination of IDD by the year 2000. In response to this recommendation, most of the countries with IDD problems agreed to try to iodise 90 % of all edible salt by 1995 (Mid-decade goal).

A recent review of the progress published by the Sub-Committee of Nutrition of the United Nations evidenced major additional progress on a world scale with virtual elimination of the problem in countries where it used to be particularly severe such as Bolivia, Peru, and Cameroon. Outstanding progress has been recorded in China where there are no longer provinces with severe IDD, and even in the Democratic Republic of Congo in spite of its long history of severe IDD and recurrent political problems.

## TABLE 2.1. HOUSEHOLD CONSUMPTION OF IODIZED SALT IN VARIOUS COUNTRIES BY WHO REGION

| WHO region | Number of countries With IDD | Percentage of households consuming iodized salt |
|---|---|---|
| **Africa** | 44 | 63 |
| **Americas** | 19 | 90 |
| **South East Asia** | 9 | 70 |
| **Eastern Mediterranean** | 17 | 66 |
| **Europe** | 32 | 27 |
| **Western Pacific** | 9 | 76 |
| **Total** | 130 | 68 |

Source: WHO-UNICEF-ICCIDD. Progress towards the elimination of IDD. Geneva 1999

Universal Salt Iodization appears as a non-precedent public health triumph in the field of non-communicable diseases.

There is no doubt that the exposure to iodine deficiency causes an enlargement of thyroid volume in schoolchildren. The iodized salt prophylaxis is able to prevent the development of goitre in the children born after prophylaxis and to keep the further increase of thyroid volume in older children. (Antonangeli L et al, 1998). Selling iodized salt instead of common salt would be the most effective iodine prophylaxis method as suggested by Aghini-Lombardi F, 1998.

The usefulness of iodinated salt in the prophylaxis of endemic goitre was confirmed by many scientists (Franzellin F, 1998, Zini M, 1998).

## *2.11. MANDATORY IODIZATION AND IDD*

Mandatory iodization of salt virtually eradicated iodine deficiency within one year in South African schoolchildren, but the goitre rate in these children did not decline. It was suggested that measurement of goitres by palpation may not be appropriate in short-term evaluations of mandatory iodization programs (Jooste PL, 2000).

A significant improvement in iodine excretion only 12 months after introduction of a new mandatory salt iodination with 25 mg KI/kg of salt was seen in main geographic regions of Croatia (Kusic Z, 1999)

After promoting iodinated-food consumption, good results with a decrease in goitre prevalence and an increase in urinary iodine excretion were observed in the population of Pyrenees (Cerdanya-Girona) (Vila Ballester LL, 1999).

## 2.12. IODISED OIL

Iodised oil ("lipiodol") was first used for the correction of iodine deficiency in Papua New Guinea. This was based on the finding of a well-known delay in excretion of oil following its use for radiological investigation (Dr Douglas Jamieson, 1950).

A preliminary controlled trial study was conducted in a few subjects in Melbourne that indicated the effects of an intramuscular depot of iodised oil in the control of endemic goitre and on thyroid function persisted over 2 years (McCullagh, 1963).

After a period of three year a double blind follow-up study was carried out which revealed successful prevention of goitre (McCullagh, 1966).
Subsequent laboratory studies on the same population demonstrated both severe iodine deficiency and the effectiveness of the single iodised oil injection (4 ml) in correcting iodine deficiency for a period of up to 4 1/2 years (Buttfield IH and Hetzel BS, 1967).

A statement was released about the safe use of iodized oil to prevent iodine deficiency in pregnant women (WHO, 1996).

Lipidol was an expensive commodity hence an equipotent but cheaper vehicle was iodination of rapeseed oil that was known as Brassiodol. It can provide protection against iodine deficiency for 9 months (Ingenbleek Y, 1997).

It was shown that low dose (200 mg Iodine) oral iodized oil (Lipiodol, a poppy seed based iodinated oil) was safe and effective for treating goitre and maintaining normal Iodine status for at least 1 year. The oil was effective in controlling the iodine deficiency in goitrous iodine deficient children without

complications of Iodine induced hypo- or hyperthyroidism signs. UI remained significantly increased above baseline for the entire year (Zimmermann M, 2000).

The Physiological and pharmacological studies of goitre prophylaxis with iodized oil recently showed that thyroid complications resulting from excess iodide, such as thyrotoxicosis, thyroiditis, sialadenitis, or hypothyroidism, are much rarer after iodine supplementation with Lipiodol than with KI. They do not militate against its widespread use in endemic goitre populations, especially in pregnant women. When Lipiodol-induced thyrotoxicosis occurs it tends to be mild or even subclinical and self-limited. Iodide goitre or thyroiditis has not been seen after Lipiodol supplementation. Iodide derived from Lipiodol readily enters the fetus, possibly by active transport, and theoretically endangers the fetus because Autoregulation of the fetal thyroid occurs late during gestation. The use of locally produced iodized plant oils is recommended for financial reasons as well as for the benefits derived from local participation (Wolff J, 2001).

Extensive additional studies on the use of iodized oil in the correction and prevention of IDD have subsequently been conducted in Latin America, Africa, Asia and Eastern Europe (McCallagh SF, 1963, Dunn JT, 1996).

In excess of 20 million injections of iodised oil had been given since 1974 with very little in the way of side effects apart from a rare abscess at the site of injection. Refrigeration was not required, which was a great advantage. Iodised oil was certainly an effective means for the correction of iodine deficiency and had opened up the possibility of elimination of IDD as a public health problem in the next decade. However the necessity for an injection had been questioned, in view of the costs of the syringe and needles and the necessity to have specially trained staff to give the injections. If the staff were readily available through the primary health care system, then the costs were comparable to those of iodated salt: 5-10 US cents per person per year. On

the other hand, if the oil could be given orally it would be possible to use village health volunteers to supervise the administration of the oil. This would make it much more readily available to village communities with severe IDD problems. Another advantage of the oral preparation is the freedom from the risk of AIDS or hepatitis B infection from contaminated syringes, although this should be eliminated by proper sterilisation of needles or by using disposable syringes. Recent experience had confirmed the convenience of the oral administration of iodised oil at yearly intervals through the primary health care system at a village level (Bautista A, 1982). In general the effect of oral administration lasted half the time of the same dose given by injection.

## TABLE 2.2. RECOMMENDED WHO-UNICEF-ICCIDD DOSES OF IODIZED OIL IN THE PREVENTION OF THE IDD (DELANGE F, 1994).

| *Duration of Effect* | | | | |
|---|---|---|---|---|
| | Oral (mg Iodine) | | Intramuscular (mg Iodine) | |
| **Age Groups** | **3 Months** | **6 Months** | **12 Months** | **>1 year** |
| **Non-pregnant women of child bearing age** | 100 – 200 | 200 – 480 | 400 – 960 | 480 |
| **Pregnant women** | 50 – 100 | 100 – 300 | 300 – 480 | 80 |
| **Infants – Children** | | | | |
| **0 – 1 year** | 20 – 40 | 50 – 100 | 100 – 300 | 240 |
| **1 – 5 years** | 40 – 100 | 100 – 300 | 300 – 480 | 480 |
| **6 – 15 years** | 100 – 200 | 200–480 | 400 – 960 | 480 |
| **Males 16 – 45 years** | 100 – 20 | 200 – 480 | 400 – 960 | 480 |

# TARGET GROUPS

An iodised oil supplementation program is necessary when other methods have been found ineffective or can be considered to be inapplicable. Iodised oil can be regarded as an emergency measure for the control of severe IDD until an effective iodinated salt program can be introduced. The spectacular and rapid effects of iodised oil in reducing goitre can be important in demonstrating the benefits of iodisation, which can lead to community demand for iodised salt. In general iodised oil administration should be avoided over the age of 45 because of the possibility of precipitating hyperthyroidism in subjects with longstanding goitre.

Pregnancy is not regarded as a contra-indication (Delange F, 1996 and WHO, 1996). There is a considerable variation in the costs in various parts of the world as might be expected. One important factor is the availability of primary health care staff for the administration of the oil whether by mouth or by injection. The important feature of iodised oil administration is that it can be carried out without the legislation required for iodised salt.

The possibility of linking up an iodised oil program with other preventative programs including the Child Immunisation Program has been considered. Iodised oil administration (by injection or by mouth) could readily be added to cover young children over the first 2-5 years of life, the second most important target group. Women of reproductive age would require separate coverage through the primary health care system, especially the family planning health care system or in antenatal services at the same time as with tetanus toxoid. These measures have now been recommended by the World Health Organisation (EPI report, 1987).

## 2.13. OTHER METHODS OF IODINE SUPPLEMENTATION

Iodised bread was used in Tasmania in preference to both iodised salt and iodide tablets distributed through the schools, and shown to be effective (Clements FW, 1970). Its use was discontinued because of the availability of other sources of iodine, notably from milk consequent to the use of iodophors in the dairy industry. It is for this reason that milk has become a major adventitious source of iodine in many Western countries such as the USA, the United Kingdom, and in Northern Europe. A change in dairy practice would reverse the situation and increase the likelihood of iodine deficiency in the population (Steven Boyages, 2000). Successful use of iodized bread was also reported from Russia when bread became a staple diet (Gerasimov G, 1997).

Iodised water has been used in several countries. Reduction in goitre rate from 61 per cent to 30 per cent with 79 per cent of goitres showing visible reduction has been demonstrated following iodation of the water supply in Sarawak. Significant rises in serum T 4 and falls in TSH were also shown. Measurement of urinary iodine excretion indicated iodine repletion (Squatrito S, 1986).

Similar results have been obtained from studies in Thailand by Dr Romsai Suwanik and his group at the Siriraj Hospital, Bangkok and by Squatrito et al. in Sicily. In Mali, West Africa, silicone cylinders have been introduced especially designed to provide a depot source in village wells for a period of 12 months (Fisch A, 1993). This method is appropriate at village level if a specific source of drinking water can be identified; otherwise there is a heavy cost as less than 1 per cent of a general water supply is used for drinking purposes. More extensive use of the same procedure has subsequently been used in the Central Africa Republic (Yazipo D, 1995) and Sarawak, Malaysia (Foo LC, 1996).

## 2.14. CLINICAL FEATURES OF GOITROGEN-INDUCED GOITRES

In man goitrogen-induced goitres tend to be symmetrical and smooth or finely nodular. According to Begg and Hall (1963) goitres were of variable consistency. Generally there is an impression that goitre's firmness is directly proportional to the length of goitrogen intake. It is not known whether long term administration of goitrogen can lead to formation of a multinodular goitre. Clinically the subjects may appear euthyroid or hypothyroid, depending on the degree of inhibition of thyroid hormone synthesis induced by the goitrogen.

Histologically, these goitres usually show hyperplastic changes with disappearance of colloid, reduction in follicular lumen and increase in height of acinar cells. Such changes have been reported in goitres induced by iodide (Wolff, 1969), resorcinol (Bull and Fraser, 1950), PAS (McGregor and Sommer, 1954) and cobalt (Kriss, Carnes and Gross, 1955). Colloid goitres (Begg and Hall, 1963) and changes similar to those in Hashimoto's disease (Wolff, 1969) have, however, been seen in cases of iodide goitre.

## 2.15. RELEVANCE OF NATURALLY-OCCURRING GOITROGENS TO HUMAN GOITRE

It remains uncertain whether dietary goitrogens, other than iodine and soya flour, play any part in human goitrogenesis. Clements in 1960 concluded that it was unlikely that the thiocyanate content of food-stuffs contributed to goitrogenesis, since a study of the blood levels of thiocyanate, which produced goitre in men when this drug was used to treat hypertension, showed that an individual would have to consume at least 10 kg of cauliflower daily to attain similar levels. The progoitrin content of food vegetables is also very low (Altapura, 1959). It is possible that goitrogens could be concentrated in the milk of cows feeding on crops with a relatively low goitrogen content

(Arstila, 1969). The milk of cows from goitre-endemic districts of Finland (where pastures are contaminated with cruciferous weeds) had shown that it contains L-5-Vinyl-2-thio-oxazolidine, which is not present in the milk from other districts, and this milk produced goitre in rats (Peltola, 1960). Similar findings have been reported from parts of England with a high incidence of goitre (Kilpatrick, 1961). There is also epidemiological evidence linking a goitrogen present in milk with the seasonal enlargement seen in Tasmanian schoolchildren (Clements, 1960). It had been suggested that the Cyanogenic glycosides present in cassava may be responsible for the endemic goitre seen in Idjwi Island in Zaire (Delange, 1971).

Although it seems unlikely that dietary goitrogens acting alone can cause goitre in man, it is possible that these goitrogens interacting with other factors, such as iodine deficiency or other types of goitrogens, may contribute to the overall incidence of goitre in endemic areas. At present, however, there is no unequivocal proof that this is the case (McLaren EH, 1979).