Section IV

The Scientific Basis for the Elimination of Brain Damage due to Iodine Deficiency

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1. Introduction

As indicated in Section I of this volume, the term Iodine Deficiency Disorders (IDD) refers to all the ill effects of iodine deficiency in a population that can be prevented by ensuring that the population has an adequate intake of iodine (Hetzel 1983, WHO/UNICEF/ICCIDD 2001). These effects are listed in **Table 1**. The presently recommended daily intake of iodine is shown in **Table 2**.

Brain damage and irreversible mental retardation are the most important disorders induced by iodine deficiency. Extensive studies throughout the world over the last 20 years have revealed that 130 countries are affected by iodine deficiency, with a total population of 2.2 billion at risk of the occurrence of varying degrees of brain damage (WHO/UNICEF/ICCIDD 1999). Iodine deficiency is the leading cause of preventable mental retardation (WHO 1994).

Table 1. *Spectrum of Iodine Deficiency Disorders (IDD)*

Foetus	Abortions
	Stillbirths
	Congenital anomalies
	Neurological cretinism:
	mental deficiency
	deaf mutism, spastic diplegia, squint
	Hypothyroid cretinism:
	mental deficiency, dwarfism, hypothyroidism
	Psychomotor defects
Neonate	Increased perinatal mortality
	Neonatal hypothyroidism
	Retarded mental and physical development
Child and Adolescent	Increased infant mortality
	Retarded mental and physical development
Adult	Goitre with its complications
	Iodine induced hyperthyroidism (IIH)
All Ages	Goitre
	Hypothyroidism
	Impaired mental function
	Increased susceptibility to nuclear radiation

From: Hetzel (1983); WHO/UNICEF/ICCIDD (2001)

Table 2. *Recommended daily intake of iodine*

90 µg for pre-school children (0 to 59 months) ;
120 µg for schoolchildren (6 to 12 years);
150 µg for adults (above 12 years); and
200 µg for pregnant and lactating women

From WHO/UNICEF/ICCIDD (2001)

This Section IV will provide a global overview of the disorders induced by iodine deficiency. Special emphasis will be put on recent developments in the concept of IDD such as the role of iodine deficiency in the development of brain damage and mental retardation; goitre seen as a sign of maladaptation to iodine deficiency rather than as the adaptative process to the deficiency; assessment of the iodine status of a population; and control of IDD including present achievements, monitoring and side effects.

Extensive and recent global reviews of the different aspects of IDD are available elsewhere (Stanbury and Hetzel 1980; Hetzel et al 1990; Delange 1994; Hetzel and Pandav 1996; Hollowell and Hannon 1997 and Hetzel 1999).

2. The Iodine Deficiency Disorders in the Life Cycle

The effects of iodine deficiency on growth and development can be considered at the various stages of life as follows:

2.1 Iodine Deficiency in the Foetus

Iodine deficiency in the foetus is the result of iodine deficiency in the mother. The consequence of iodine deficiency during pregnancy is impaired synthesis of thyroid hormones by the mother and the foetus. The reduction of blood thyroid hormones is associated with a greater incidence of abortions, still births, and congenital anomalies, which can be reduced by correction of the iodine deficiency. The effects are similar to those observed in maternal hypothyroidism, which can be reduced by thyroid hormone replacement therapy (McMichael et al 1980).

An insufficient supply of thyroid hormones to the developing foetal brain results in mental retardation (Pharoah et al 1971; Hetzel et al 1990; Stanbury 1994; Bernal and Nunez 1995; Chan and Kilby 2000; Glinoer and Delange 2000). This vulnerability extends to the end of the second year of life by which time the brain has achieved an adult weight. There

is therefore a very rapid period of growth during pregnancy and the first two years of life during which time the brain is very vulnerable to thyroid hormone deprivation with the likelihood of irreversible damage. For this reason a check of thyroxine levels is made at the fourth day of life as a routine screening procedure carried out in most industrialised countries with the aim of detecting congenital abnormalities of the thyroid. So that immediate correction with thyroid hormone replacement can be initiated. Congenital abnormalities occur in approximately 1 in 4000 births. In areas of severe iodine deficiency such neonatal hypothyroidism may occur in up to 10% of births. So there is a very large increase in iodine deficient populations, which indicates the massive dimension of the problem (Hetzel and Pandav 1996) and the urgency for correction of the iodine deficiency.

2.1.1 Brain development in humans

Brain growth is characterized by two periods of maximal growth velocity (Dobbing and Sands 1973). The first one occurs during the first and second trimesters between the third and the fifth months of gestation. This phase corresponds to neuronal multiplication, migration and organization. The second phase takes place from the third trimester onwards up to the second and third years postnatally. It corresponds to glial cell multiplication, migration and myelination. The first phase occurs before the foetal thyroid has reached its functional capacity. It is now agreed that during this phase, the supply of thyroid hormones to the growing foetus is almost exclusively of maternal origin while during the second phase, the supply of thyroid hormones to the foetus is essentially of foetal origin (Vulsma et al 1989; Morreale de Escobar et al 2000).

2.1.2 Experimental studies in animals

Studies of the effects of iodine deficiency in animals have confirmed the morphological and biochemical modifications seen in the hyperplastic goitre of man (Bernal and Pekonen 1984; Pandav and Rao 1997). More recently the effects of iodine deficiency on development, particularly those relating to the foetus have been investigated. These studies on the sheep, marmoset (Callithrix jacchus jacchus) and the rat have been particularly concerned with foetal brain development because of its relevance to the human problem of endemic cretinism and brain damage resulting from foetal iodine deficiency.

i) Iodine Deficiency and the Sheep

Severe iodine deficiency has been produced in sheep (Potter et al 1982) with a low iodine diet of crushed maize and pelleted pea pollard (8-15µg iodine/kg) which provided 5-8µg iodine per day for sheep weighing 40-50 kg. The iodine deficient foetuses at 140 days were grossly different in physical appearance in comparison to the control foetuses. There was reduced weight, absence of wool growth, goitre, varying degrees of subluxation of the foot joints, and deformation of the skull **(fig. 1)**. There was also delayed bone maturation as indicated by delayed appearance of epiphyses in the limbs. Goitre was evident from 70 days in the iodine deficient foetuses and thyroid histology revealed hyperplasia from 56 days gestation associated with a great reduction in foetal thyroid iodine content and reduced plasma T_4 values. There was a lowered brain weight and DNA content as early as 70 days, indicating a reduction in cell number probably due to delayed neuroblast multiplication, which normally occurs from 40-80 days in the sheep. Findings in the cerebellum indicated arrested development (Potter et al 1982).

A single intramuscular injection of iodized oil (1 ml = 480 mg iodine) given to the iodine deficient mother at 100 days gestation was followed by partial restoration of the lamb brain weight and body weight with restoration of maternal and foetal plasma T_4 values to normal (Potter et al 1984).

Studies of the mechanisms involved in the sheep revealed significant effects of foetal thyroidectomy in late gestation and a significant effect of maternal thyroidectomy on brain development at mid-gestation. The combination of maternal thyroidectomy (carried out 6 weeks before pregnancy) and foetal thyroidectomy produced more severe effects on the brain than that of iodine deficiency associated with greater reduction in both maternal and foetal thyroid hormone levels (McIntosh et al 1983; Hetzel 1999). These findings confirm the importance of both maternal and foetal thyroid hormones in foetal brain development.

ii) Iodine Deficiency in the Marmoset

Severe iodine deficiency has been produced in the marmoset (Callithrix jacchus jacchus) with a mixed diet of maize (60%), peas (15%), torula yeast (10%) and dried iodine deficient mutton (10%) derived from the iodine deficient sheep already described above. The newborn iodine deficient marmosets showed some sparsity of hair growth (Mano et al 1987). The thyroid gland was enlarged with gross reduction in plasma T_4

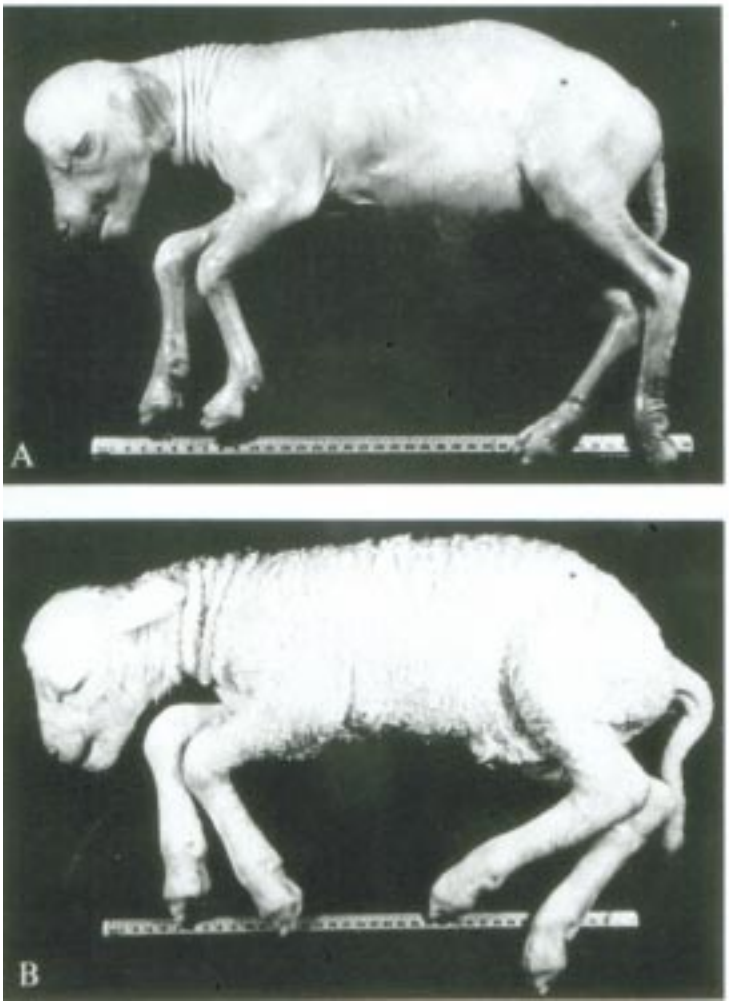

Fig.1 *Effect of severe iodine deficiency during pregnancy on lamb development. A 140 day old lamb foetus (normal gestation period 150 days) was subjected to severe iodine deficiency through feeding the mother an iodine deficient diet (5-8µg per day) for 6 months prior to and during pregnancy, compared to a control lamb of the same age fed the same diet with the addition of an iodine supplement. The iodine deficient lamb shows absence of wool coat, subluxation of the leg joints and a dome-like appearance of the head due to skeletal retardation. The brain was smaller and contained a reduced number of cells, compared to the control. From: Potter et al (1982)*

in both mothers and newborns, greater in the second pregnancy than in the first, suggesting a greater severity of iodine deficiency. There was a significant reduction in brain weight in the newborns from the second pregnancy but not from the first. The findings were more striking in the cerebellum with reduction in weight and cell number evident and histological changes indicating as in the sheep, impaired cell maturation. These findings demonstrate the significant effects of iodine deficiency on the primate brain.

iii) Iodine Deficiency in the Rat

Studies in rats have been carried out using the diet consumed by the people of Jixian village in China (Li et al 1985) (see Section I). This village was severely iodine deficient with 11% endemic cretinism. The diet included available main crops (maize, wheat), vegetables, and water from the area with an iodine content of 4.5µg/kg. After the rats had received the diet for 4 months, the newborn showed obvious goitre, foetal serum T4 was 3.6µg% compared to controls of 10.4µg% and they had higher I^{125} uptake and reduced brain weight. The density of brain cells was increased in the cerebral hemispheres. The cerebellum showed delayed maturation as in the other species.

2.1.3 Epidemiological and clinical aspects of brain damage and mental retardation in iodine deficiency

These aspects are developed in the section "Specific Iodine Deficiency Disorders".

2.2 Iodine Deficiency in the Neonate

An increased perinatal mortality due to iodine deficiency has been shown in Zaire (Zaire now the Republic of the Congo) from the results of a controlled trial of iodized oil injections alternating with a control injection both given in the latter half of pregnancy (Thilly et al 1980). There was a substantial fall in infant mortality with improved birth weight following the iodized oil injection. Low birth weight of any cause is generally associated with a higher rate of congenital anomalies and higher risk through childhood. This has been demonstrated in the longer term follow up of the controlled trial in Papua New Guinea in children up to the age of 12 years (Pharoah et al 1971; Pharoah and Connolly 1987) and in Indonesia (Cobra et al 1997).

A reduction of infant mortality has also been reported from China following iodine supplementation of irrigation water in areas of severe iodine deficiency. Iodine replacement has probably been an important factor in the national decrease in infant mortality in this country (Delong et al 1997).

Apart from mortality, 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 (Dobbing 1974). The thyroid hormone, dependent on an adequate supply of iodine, is essential for normal brain development as has been confirmed by the animal studies already cited.

Studies on iodine nutrition and neonatal thyroid function in Europe confirm the continuing presence of iodine deficiency affecting neonatal thyroid function and hence a threat to early brain development (Delange et al 1986). A series of 1076 urine samples were collected from 16 centres from 10 different countries in Europe along with an additional series from Toronto, Canada and analyzed for their iodine content. The results of these determinations are shown in **Table 3**. The distribution was skewed so that arithmetic means were not used, but the results were expressed in percentiles. Some very high values were seen which could be attributed to the use of iodinated contrast media for radiological investigation of the mother during pregnancy. There was a marked difference in the results from the various cities. The high levels in Rotterdam, Helsinki and Stockholm differed from the low levels in Gottingen, Heidelberg, Freiburg and Jena by a factor of more than 10. Intermediate levels were seen in Catania, Zurich and Lille.

Data on neonatal thyroid function was analysed for four cities where enough newborns (30,000-102,000) had been tested. The incidence of permanent congenital hypothyroidism was very similar in the four cities but the rate of transient hypothyroidism was much greater in Freiburg, associated with the lowest level of urine iodine excretion, than in Stockholm, with intermediate findings from Rome and Brussels. These data confirm the significance of iodine intake for neonatal thyroid function.

In developing countries with more severe iodine deficiency, observations have now been made using blood taken from the umbilical vein just after birth. Neonatal chemical hypothyroidism was defined by serum levels of T_4 less than 3µg/dL and TSH greater than 100µU/ml). In the most severely iodine deficient environments in Northern India, where

Table 3. *Frequency distributions of urinary iodine concentrations in healthy full - term infants in 14 cities in Europe and Toronto, Canada*

	Urinary Iodine Concentration				
City	**Number of Infants**	**10th Percentile**	**50th Percentile**	**90th Percentile**	**Frequency (%) of values Below 5µg/dL**
Toronto	81	4.3	14.8	37.5	11.9
Rotterdam	64	4.5	16.2	33.2	15.3
Helsinki	39	4.8	11.2	31.8	12.8
Stockholm	52	5.1	11.0	25.3	5.9
Catania	14	2.2	7.1	11.0	38.4
Zurich	62	2.6	6.2	12.9	34.4
Lille	82	2.0	5.8	15.2	37.2
Brussels	196	1.7	4.8	16.7	53.2
Rome	114	1.5	4.7	13.8	53.5
Toulouse	37	1.2	2.9	9.4	69.4
Berlin	87	1.3	2.8	13.6	69.7
Gottingen	81	0.9	1.5	4.7	91.3
Heidelberg	39	1.1	1.3	4.0	89.8
Freiburg	41	1.1	1.2	2.3	100.0
Jena	54	0.4	0.8	2.2	100.0

The European cities are listed according to decreasing values (50^{th} percentile)
From: Delange et al (1986)

more than 50% of the population has urinary iodine levels below 25ug per gram creatinine, the incidence of neonatal hypothyroidism was 75 to 115 per thousand births (Kochupillai and Pandav 1987). By contrast in Delhi, where only mild iodine deficiency is present with low prevalence of goitre and no cretinism, the incidence drops to 6 per thousand. In control areas without goitre the level was only one per thousand.

There is similar evidence from neonatal observations in neonates in the Congo in Africa where a rate of 10% of chemical hypothyroidism has been found (Delange et al 1982). This hypothyroidism persists into infancy and childhood if the deficiency is not corrected, and results in retardation of physical and mental development (Vanderpas et al 1984). These observations indicate a much greater risk of mental defect in severely iodine deficient populations than is indicated by the presence of cretinism. They provide strong evidence for the need to correct the iodine deficiency in Europe as well as in developing countries.

Another important aspect of iodine deficiency in the neonate and child is an increased susceptibility of the thyroid gland to radioactive fall-out. Delange (1990) has shown that the thyroidal uptake of radioiodine reaches its maximum value in the earliest years of life and then declines progressively into adult life. The apparent thyroidal iodine turnover rate was much higher in young infants than in adults and decreased progressively with age. In order to provide the normal rate of T_4 secretion, Delange has estimated that the turnover rate for intra-thyroidal iodine must be 25-30 times higher in young infants than in adolescents and adults. In iodine deficiency a further increase in turnover rate is required to maintain normal thyroid hormone levels. This is the reason for the greatly increased susceptibility of the neonate and foetus to iodine deficiency. Iodine deficiency also causes an increased uptake of radioiodide, resulting from exposure to nuclear radiation. Protection against this increased uptake can only be provided by correction of iodine deficiency, which constitutes a further urgent indicator for the correction of iodine deficiency in Europe as well as in developing countries.

2.3 Iodine Deficiency in the Child

Recent work has demonstrated the effects of mild and moderate iodine deficiency on brain function. Aghini-Lombardi et al (1995) reported that in children aged 6-10 years in an area in Tuscany who had mild iodine deficiency (64µg iodine/day), the reaction time was delayed compared

with matched controls from an iodine sufficient area (142µg iodine/day). The cognitive abilities of the children were not affected.

Additional investigations conducted in areas with moderate iodine deficiency have also demonstrated the presence of definite abnormalities in the psycho-neuromotor and intellectual development of children and adults who are clinically euthyroid but who do not exhibit the other signs and symptoms of endemic cretinism, that is the most severe form of brain damage caused by iodine deficiency. These studies are summarized in **Table 4**.

The impairment of intellectual development in these conditions represents the long-term consequence of transient neonatal hypothyroidism (Calaciura et al 1995).

In more severe iodine deficiency, the anomalies found in the population are of the same type, although more frequent and more severe than those found in moderate iodine deficiency. The frequency distribution of IQ in apparently normal children in such conditions is shifted towards low values as compared to matched controls who were not exposed to iodine deficiency during the critical period of brain development because of correction of the deficiency in the mothers before or during early gestation (Fierro-Benitez et al 1974; Kochupillai et al 1986; Huda et al 1999). More globally, in their meta-analysis of 18 studies on neuromotor and cognitive functions in conditions of moderate to severe iodine deficiency, Bleichrodt and Born (1994) concluded that iodine deficiency resulted in a mean loss of 13.5 IQ points in the total population.

2.4 Iodine Deficiency in the Adult

A high degree of apathy has been noted in populations living in severely iodine deficient areas. This may even affect domestic animals such as, dogs (Pandav and Rao 1997). It is apparent that reduced mental function due to cerebral hypothyroidism (reduced brain T_3) is widely prevalent in iodine deficient communities with effects on their capacity for initiative and decision making. This indicates that iodine deficiency can be a major block to the human and social development of communities living in an iodine deficient environment which can be reversed by correction of the iodine deficiency. This is particularly striking following iodized oil injections as in Sengi village in Indonesia (see Section I).

In addition to this impact on brain and neuro psychological intellectual development, iodine deficiency at any period in life, including during adulthood can induce the development of goitre with mechanical complications and/or thyroid insufficiency.

Table 4. *Neuropsychointellectual Deficits in Infants and Children in conditions of Mild to Moderate Iodine Deficiency*

Regions	Tests	Findings	Authors
Spain	Locally adapted Bayley Mccarthy Cattell	Lower psychomotor and mental development than controls	Bleichrodt et al 1989
Italy Sicily	Bender-Gestalt	Low perceptual integrative motor ability. Neuromuscular and neurosensorial abnormalities	Vermigilio et al 1990
Tuscany	Wechsler Raven	Low verbal IQ, perception, motor and attentive functions	Fenzi et al 1990
Tuscany	Wisc	Lower velocity of motor response to visual stimuli	Vitti et al 1992
	Reaction time		Aghini-Lombardi et al 1995
India	Verbal, pictorial Learning tests Tests of motivation	Lower learning capacities	Tiwari et al 1996
Iran	Bender-Gestalt Raven	Retardation in psychomotor development	Azizi et al 1993
Malawi	Psychometric tests inclusing verbal fluency	Los of 10 IQ points as compared to iodine-supplemented controls	Shrestha 1994
Benin	Battery of 8 non verbal tests exploring fluid intelligence and 2 psychomotor tests	Loss of 5 IQ points as compared to controls supplemented with iodine for one year	Van den Briel et al 2000

Another consequence of longstanding iodine deficiency is the development of hyperthyroidism in the adult (Vanderpump et al 1995; Aghini-Lombardi et al 1999) but also in the child (Garcia-Mayor et al 1999). This is accompanied by multinodular goitres with autonomous nodules. The pathogenesis of this syndrome is discussed later in this chapter (side effects of iodine supplementation). It is now accepted that such hyperthyroidism is one of the disorders induced by iodine deficiency.

3. Specific Iodine Deficiency Disorders

3.1 Endemic Goitre

3.1.1 Epidemiology

The term endemic goitre is a descriptive diagnosis and reserved for a disorder characterised by enlargement of the thyroid gland in a significantly large fraction of a population group, and is generally considered to be due to insufficient iodine in the daily diet. Since nontoxic goitre also exists when there is abundant iodine in the diet, the distinction between endemic and non-endemic goitre is necessarily arbitrary. Endemic goitre may be said to exist in a population when more than 5% of the preadolescent (aged 6-12) school age children have enlarged thyroid glands, as assessed by the clinical criterion of the thyroid lobes being each larger than the distal phalanx of the subject's thumb (WHO/UNICEF/ ICCIDD 2001). Detailed criteria are discussed further below.

Most of the mountainous districts in the world have been or still are endemic goitre regions. The disease may be seen throughout the Andes, in the whole sweep of the Himalayas, in the European Alps where iodide prophylaxis has not yet reached the entire population, in Greece and the Middle Eastern countries, in many foci in the People's Republic of China, and in the highlands of New Guinea. There are or were also important endemias in non-mountainous regions, as for example, the belt extending from the Cameroon grasslands across northern Zaire and the Central African Republic to the borders of Uganda and Rwanda, Central Europe and the interior of Brazil. An endemic existed in the Great Lakes region in North America two generations ago. Measurements have indicated that these regions have in common a low concentration of environmental iodine. The iodine content of cereals and the drinking water is low, as is the quantity of iodide excreted each day by residents of these districts.

Goitre maps of various countries have been repeatedly drawn, requiring modification as successful prophylactic measures have been introduced. Although goitre was an important problem in many regions of the United States of America in the past (Clesen 1929), more recent USA surveys have shown it in no more than 4-11% of schoolchildren, and with almost no evidence of iodine deficiency (Hollowell et al 1998). This finding is a testimony to the effectiveness of iodine prophylaxis in preventing endemic goitre.

The great arc of the Himalayas from West Pakistan across India and Nepal, into Northern Thailand and Vietnam and into Indonesia, is one of the most highly endemic regions of the world. The disease used to be a major problem throughout the Andes. It has been reported from Australia and New Zealand and from different places in Europe. The world and regional distribution of goitre was exhaustively reviewed by Kelly and Snedden in 1960 and subsequently by others (Stanbury and Hetzel 1980); (Delange et al 1993); (Hetzel and Pandav 1996); (Delange et al 1998) and (WHO/UNICEF/ICCIDD 1999).

These surveys reveal striking differences in the rate of goitre in different endemic regions and even in adjacent districts. The geographic unevenness of an endemic undoubtedly has much to do with the habits of the population and their economic resources for the importation of foods. In attempting to account for the variability in the expression of endemic goitre from one locality to the next, the availability of iodine should be investigated before searching for some other subtle dietary or genetic factor. The key to the problem almost always lies in the availability of iodine. One must also consider the possibility that an observed goitre rate may not reflect current conditions, but rather may be a legacy of pre existing iodine deficiency that has not yet been entirely resolved by an improvement in the supply of iodine. The assessment of goitre in a population is further discussed below in the section on assessment of the IDD status of the population.

3.1.2 Causes

i) Iodine Deficiency

The arguments supporting iodine deficiency as the cause of endemic goitre are four:

a) the close association between a low iodine content in food and water and the appearance of the disease in the population;
b) the sharp reduction in incidence when iodine is added to the diet;

c) the demonstration that the metabolism of iodine by patients with endemic goitre fits the pattern that would be expected from iodine deficiency and is reversed by iodine repletion.;
d) finally, iodine deficiency causes changes in the thyroid glands of animals that are similar to those seen in humans (Hetzel and Pandav 1996; Delange and Hetzel 1998).

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. Most reports place the mean intake between 10 and 50µg/24 hour. Severe iodine deficiency is still encountered up to the present. From two endemic goitre areas of Zimbabwe mean iodine urinary excretion from adults was reported to vary between 10µg/L and 20µg/L (Todd and Bourdoux 1991). In Senegal a mean iodine excretion of 17µg/g creatinine (roughly equivalent to 24hour) was also reported in 1992 (Lazarus et al 1992). In the Eastern part of Germany, a 24 hour iodine excretion of 16µg has been reported in 1989 (Delange and Burgi 1989). This is only a small sample of many reports indicating that iodine deficiency, even in its severe form, is still present in many parts of the world.

ii) Goitrogenic factors

Although the relation of iodine deficiency to endemic goitre is well established, other factors may be involved. A whole variety of naturally occurring agents has been identified that might be goitrogenic in man (Gaitan 1980; 1989). Most of these have only been tested in animals and/or have been shown to possess anti-thyroid effects in vitro. These compounds belong to the following chemical groups: Sulfurated organics (like thiocyanate, isothiocyanate, goitrin and disulphides), flavonoids (polyphenols), polyhydroxyphenols and phenol derivatives, pyridines, phalate esters and metabolites, polychlorinated (PCB) and polybrominated (PBB) biphenyls, other organochlorines (like DDT), polycyclic aromatic hydrocarbons (PAH), inorganic iodine (in excess), and lithium. Gaitan (1980) divides goitrogens into agents acting directly on the thyroid gland and those causing goitre by indirect action. The former group is subdivided into those inhibiting transport of iodide into the thyroid (like thiocyanate and isothiocyanate), those acting on the intrathyroidal oxidation and organic binding process of iodide and/or the coupling reaction (like phenolic compounds) some phalate derivatives (disulfides

and goitrin) and those interfering with proteolysis, dehalogenation and hormone release (like iodide and lithium).

Indirect goitrogens increase the rate of thyroid hormone metabolism (like 2,4 dinitrophenol, PCB's and PBB's). Soyabean, an important protein source in many third world countries interrupts the enterohepatic cycle of thyroid hormone (Van Wyk et al 1959) and may cause goitre when iodine intake is limited. It should be recognized that goitrogens are usually active only if iodine supply is limited and/or goitrogen intake is of long duration.

Goitre and especially large colloid goitres in endemic iodine deficiency represents maladaptation to iodine deficiency because it leads to a vicious cycle of iodine loss and defective thyroid hormone synthesis (Dumont et al 1995).

3.2 Endemic Cretinism

3.2.1 Epidemiology

When Sir Robert McCarrison described cretinism in north western India during the first decade of this century (McCarrison 1908) he delineated a **neurologic form**, with predominantly neuromotor defects, including strabismus, deaf mutism, spastic diplegia, and other disorders of gait and coordination. The other form, which he called the **myxedematous form**, showed evidence of severe hypothyroidism, short stature, and markedly delayed bone and sexual maturation.

3.2.2 Neurological Cretinism

The three characteristic features of neurological endemic cretinism in its fully developed form are extremely severe mental deficiency together with squint, deaf mutism and motor spasticity with disorders of the arms and legs of a characteristic nature. **(fig. 2)**. As would be expected with a deficiency disease there is a wide range in the severity of the clinical features in the population affected. Recent studies by De Long et al (1985), Boyages et al. (1988) and by Halpern et al (1991) have provided new observations and insights.

i) The three characteristic features of neurological endemic cretinism are:

a) **Mental deficiency** is characterised by a marked impairment of the capacity for abstract thought but vision is unaffected. Autonomic, vegetative, personal, social functions and memory appear to be relatively well preserved except in the most severe cases.

Fig. 2 *Male from Ecuador about 40 years old, deaf-mute, unable to stand or walk. Use of the hands was strikingly spared, despite proximal upper-extremity spasticity.*
From: Delong et al (1985)

b) **Deafness** is the striking feature. This may be complete in as many as 50% cretins. It has been confirmed by auditory brain stem evoked potential studies, which showed no cochlear or brain stem responses even at the highest sound frequencies. These findings suggest a cochlear lesion. In subjects with reduced hearing a high tone defect is apparent. Deafness is sometimes absent in subjects with other signs of cretinism. All totally deaf cretins were mute and many with some hearing were found to have no intelligible speech.

c) **The motor disorder** shows a characteristic proximal rigidity of both lower and upper extremities and the trunk. There is a corresponding proximal spasticity with markedly exaggerated deep tendon reflexes at the knees, adductors and biceps. Spastic involvement of the feet and hands is unusual or, if present, is much milder than that of the proximal limbs. Function of the hands and feet is characteristically preserved so that most cretins can walk. This observation is very useful in differentiating cretinism from other forms of cerebral palsy commonly encountered in endemic areas, such as cerebral palsy from birth injury or meningitis.

In addition to frank cretinism, a larger proportion of the population (estimated to be 3-5 times as great) suffers from some degree of mental retardation and coordination defect. Comparative population based neuropsychological assessments of children in areas of iodine deficiency compared with areas with adequate iodine intake confirm a shift of the intelligence curve to the left in the iodine deficient areas. Careful examination of affected individuals in such areas, reveals a pattern of neurological involvement similar to that seen in frank cretins, although of milder degree. In assessing these less severe defects, nonverbal tests are most helpful and school progress is a good indicator. After the age of 3 years drawings are very useful, indicating a defect in visual motor integration (Delong et al 1985).

On the basis of his clinical observations, De Long (1987) suggests that the neuropathological basis of the clinical picture includes underdevelopment of the cochlea for deafness; maldevelopment of the cerebral neocortex for mental retardation; and maldevelopment of the corpus striatum (especially putamen and globus pallidus) for the motor disorder. The cerebellum, hypothalamus, visual system, and hippocampus are relatively spared. Studies of human cretin brains by modern techniques would provide further insight.

The frequency of goitre and thyroid dysfunction in these defectives is similar to the ones observed in the general population.

ii) Pathophysiology of neurological cretinism

Developmental neuropathology and available epidemiologic data suggest that the period from about 12-14 weeks until 20-30 weeks of gestation may be the critical period during which damage occurs. Cochlear development occurs at the same time. These data correlate well with the data from the Papua New Guinea trial, which indicated that iodine repletion, must occur before pregnancy to prevent cretinism (Pharoah et al 1971; Pharoah and Connolly 1987).

Studies already cited above on the effect of iodine deficiency on brain cell development in the newborn rat, sheep and marmoset suggest that iodine deficiency has an early effect on neuroblast multiplication. Brain weight is reduced with a reduced number of cells as indicated by lowered DNA, a greater density of cells in the cerebral cortex and reduced cell maturation in the cerebellum. In the light of the evidence summarized above that maternal thyroxine crosses the placenta, it is now concluded that neurological cretinism is caused by maternal hypothyroidism due to iodine deficiency in view of the fact that correction of maternal iodine deficiency before pregnancy will prevent cretinism in the infant (Pharoah et al 1971).

3.2.3 Hypothyroid (Myxedematous) Cretinism

The typical hypothyroid cretin **(fig. 3)** has a less severe degree of mental retardation than the neurological cretin. All the features of severe hypothyroidism are present from early life, As occurs with sporadic congenital hypothyroidism (Dumont et al 1963; Delange et al 1972) there is severe growth retardation, incomplete maturation of the features including the naso-orbital configuration, atrophy of the mandibles, puffy features, myxedematous, thickened and dry skin, dry and sparse hair, eyelashes and eyebrows and much delayed sexual maturation.

Contrasting with the general population and with neurological cretinism, goitre is usually absent and the thyroid is often not palpable, suggesting thyroid atrophy. This diagnosis is confirmed by thyroid scans which show thyroids in normal location but of small volume with a very heterogeneous and patchy distribution of the tracer (Delange 1974). Thyroidal uptake of radioiodine is much lower than in the general population. The serum levels of T_4 and T_3 are extremely low, often undetectable and TSH is dramatically high. Markedly enlarged sella turcicae have been demonstrated, suggesting pituitary adenomas (Melot et al 1962).

Fig. 3 *A group of hypothyroid cretins and adults from the Democratic Republic of the Congo in the age range 16-30 years. Clinically normal adults are shown at the back. There is severe longstanding hypothyroidism with dwarfism, puffy features, dry skin and severe mental retardation (Delange et al 1972).*

Hypothyroid cretinism used to be particularly common in Zaire. The early reports by the Belgian teams indicated limited neurological abnormalities in the cretins in this country (Delange et al 1972). The movements are slow and the reflex relaxation is usually much prolonged. However hyper reflexia and Babinski signs were occasionally reported while knocked knees, flat feet were obvious from the photographs of these patients reported in the literature. However, subsequent neurological examination of some of these patients (De Long et al 1985) revealed in some of them the neurological signs reported in the neurological type of cretinism, partly obscured by the features of severe hypothyroidism.

Iodine deficiency is, as for the neurologic type, a prerequisite for hypothyroid (myxedematous) cretinism. Its role is demonstrated by:

- the correlation between the degree of iodine deficiency and the frequency of the condition,
- the preventive action of iodine supplementation on its incidence (Thilly et al 1980; 1983; Hetzel and Pandav 1996).
- the reemergence of cases in previously affected populations following cessation of salt iodization programs as recently reported from Central Asia. (Delange et al 1998).

4. Assessment of the IDD Status of the Population

The assessment of the status of iodine nutrition constitutes the basis for the development of a national IDD control program. Three major components are required for the assessment and, later, monitoring of IDD in an iodine deficient population. They are in order of importance from a public health point of view:

- the determination of the excretion of iodine in the urine;
- the determination of thyroid size and the estimation of the prevalence of goitre;
- the determination of the serum levels of TSH, thyroid hormones and thyroglobulin.

Updated recommendations regarding these three variables have been recently published in a WHO/UNICEF/ICCIDD Handbook (2001).

Apart from the techniques involved in these procedures, selection and sampling of the population has to be carried out using accepted criteria to provide valid indicators of the status of the population being studied. In general, observations have often been made on school children as one of the most vulnerable groups. A total sample of 200 children in the age range 10-14 years will suffice. Randomization is required to cover the variable distribution of goitre, which is related to hilly or mountainous terrain. This and other epidemiological aspects are discussed more fully elsewhere (WHO/UNICEF/ICCIDD 2001).

4.1 Urinary Iodine

Urinary iodine excretion is a good marker of the very recent dietary intake of iodine and, therefore, is the index of choice for evaluating the degree of iodine deficiency and of its correction. Iodine concentrations in casual urine specimens of children or adults provide an adequate assessment of the population iodine nutrition, provided a sufficient number of specimens is collected. Twenty four hours samples are difficult to obtain and are not necessary. Relating urinary iodine to creatinine is expensive and unnecessary.

Several methods of determination of urinary iodine have been reported (Dunn et al 1993; Rendl et al 1998; Ohashi et al 2000). The most commonly used is called Method A (WHO/UNICEF/ICCIDD 2001). Small samples of urine are digested with ammonium persulfate at 90-110^{o}c. The iodine content is then determined with the sensitive colorimetry of the Sandell-Kolthoff reaction in which iodine is determined from its catalytic reduction

Table 5. *Epidemiological criteria for assessing iodine nutrition based on median urinary iodine concentrations in school-aged children*

Median urinary iodine (µg/L)	**Iodine Intake**	**Iodine Nutrition**
< 20	Insufficient	Severe Iodine Deficiency
20-49	Insufficient	Moderate Iodine Deficiency
50-90	Insufficient	Mild Iodine Deficiency
100-199	Adequate	Optimal
200-299	More than adequate	Risk of iodine-induced Hyperthyroidism within 5-10 years following introduction of iodized salt in susceptible groups
>300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)

From WHO/UNICEF/ICCIDD (2001)

of cerium ammonium sulfate in the presence of arsenious acid. This method detects urinary iodine concentration in the range 0-100µg/L (0-1.19µmol/L).

For epidemiological studies, the population distribution of urinary iodine is required rather than individual levels. Because the frequency distribution of urinary iodine is usually skewed towards elevated values, the median is used instead of the mean as indicating the status of iodine nutrition. **Table 5** shows the epidemiological criteria presently recommended for assessing iodine nutrition based on median urinary iodine concentrations.

The need for samples to be taken from pregnant women has become apparent in the light of recent studies (Glinoer and Delange 2000).

Casual urine samples from school children can be collected at the same time as the goitre is assessed.

The values of urinary iodine can be most conveniently expressed as a range with a median or by the proportions at a series of cut off points,<20µg per litre, <50µg per litre and <100µg per litre.

4.2 Prevalence of Goitre

The size of the thyroid gland changes inversely in response to alterations in iodine intake, with a lag interval that varies from a few months to several years. The prevalence of goitre is an index of the degree of longstanding iodine deficiency and, therefore, is less sensitive than urinary iodine in the evaluation of a recent change in the status of iodine nutrition (WHO/UNICEF/ICCIDD 2001).

Thyroid size is traditionally determined by inspection and palpation but ultrasonography of the thyroid provides a more precise and objective method. **Table 6** shows the revised and simplified classification of goitre.

Table 6. *Revised classification of goitre*

Classification	Description
Grade 0	No palpable or visible goitre
Grade 1	A goitre that is palpable but not visible when the neck is in the normal position (ie the thyroid is not visibly enlarged). Thyroid nodules in a thyroid which is otherwise not enlarged fall into this category
Grade 2	A swelling in the neck that is visible when the neck is in a normal position and is consistent with an enlarged thyroid when the neck is palpated

From WHO/UNICEF/ICCIDD (2001)

However, the evaluation of the prevalence of goitre based on palpation has been questioned because the reproducibility of assessment by palpation is low, especially with the size estimation of smaller glands, particularly in children (WHO/UNICEF/ICCIDD 1994).

Therefore, the method of choice is now ultrasonography which is reproducible with a maximum deviation of 10%. Normative values for thyroid volume measured by ultrasonography as a function of age, sex and body surface area have been proposed (Delange et al 1997). However, these normative values might have been overevaluated by some 30% due to interobserver variability in thyroid ultrasonography (Zimmermann et al 2001). Updated normative values are presently being reevaluated. By definition, a thyroid is considered as goitrous when its volume is above the percentile 97 established for sex, age and body surface area in iodine replete populations (WHO/ICCIDD 1997).

As already stated the prevalence of goitre in iodine replete populations is below 5 percent.

4.3 Measurement of the Serum Concentrations of TSH, Thyroid Hormones and Thyroglobulin

The serum thyroid hormone levels are a further index of the effects of iodine deficiency.

However, difficulties are often encountered in obtaining venous blood samples in populations due to apprehension about blood collection and operational difficulties. Therefore, these measurements are not recommended in routine assessment and monitoring (WHO/UNICEF/ ICCIDD 2001).

5. Technology of Iodine Supplementation

5.1 Iodized Salt

Iodized salt is considered as the most appropriate measure for iodine supplementation (WHO/UNICEF/ICCIDD 2001).

The advantage of supplementing with iodized salt is that it is used by all sections of a community irrespective of social and economic status. It is consumed as a condiment at roughly the same level throughout the year. Its production is often confined to a few centres, which means that processing can occur on a larger scale and with better controlled conditions. However, this is often not the case in developing countries.

There are two forms of iodine, which can be used to iodize salt: "iodide" and "iodate" usually as the potassium salt. Iodate is less soluble and more stable than iodide and is therefore preferred for tropical moist conditions. Both are generally referred to as "iodized" salt.

The daily requirement of iodine is 150µg per person for adults as already mentioned. The level of iodination of salt has to be sufficient to cover this requirement together with losses from the point of production to the point of consumption including the expected shelf life. It also has to take into account the per capita salt consumption in an area. Previously, generally accepted levels of salt consumption in the range 10-15g per day are now regarded as excessive because of the increased liability to hypertension. However, it is important to state here that a Joint WHO/ FAO Expert Consultation on, "Diet Nutrition and the Prevention of Chronic Diseases" (WHO Technical Report Series, 916, 2003) Clearly stated the following with respect to salt intake while suggesting ranges of population nutrient intake goals. To quote, "Salt should be iodized

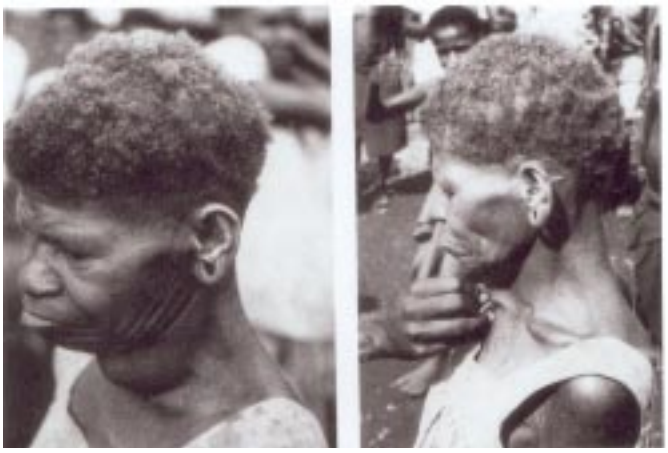

Fig. 4: *Nodular goitre in a New Guinea woman (a) before and (b) three months after injection of iodized oil. The photos demonstrate the subsidence of goitre following the injection of iodized oil. This is associated with improved energy and well being due to correction of hypothyroidism. (From: Buttfield and Hetzel (1967).*

appropriately. The need to adjust salt iodization depending on observed sodium intake and surveillance of iodine status of the population should be recognized" Iodized salt is also needed as a feed supplement for cattle and other livestock in iodine deficient areas. Allowing for these factors, the level of iodine as iodate being used at present to provide 150µg of iodine by day is in the range of 20-40mg per kg (WHO/UNICEF/ICCIDD 1996). If salt intake falls, the level of iodine supplementation can readily be increased to maintain the required intake of 150µg per day.

The other aspects of the use of iodized salt in the prevention of IDD, including the implementation and monitoring of programs of universal salt iodization (USI) are discussed in Section V.

5.2 Iodized Oil

Iodized oil ("lipiodol") was first used for the correction of iodine deficiency in Papua New Guinea. In a controlled trial in the Boana area of the Huon Peninsula of New Guinea, McCullagh carried out a double blind follow-up over 3 years which revealed successful prevention of goitre (McCullagh 1963). In subsequent laboratory studies on the same population, Buttfield and Hetzel (1967) demonstrated both severe iodine

deficiency and the effectiveness of the single iodized oil injection (4ml) in correcting iodine deficiency for a period of up to $4^{1/2}$ years. A further controlled trial in the Western Highlands of Papua New Guinea revealed the prevention of endemic cretinism provided the injection was given before pregnancy. There was also a reduction in recorded foetal and neonatal deaths in the treated group (Pharoah et al 1971; Pharoah and Connolly 1987).

A further advantage of iodized oil has been the subsidence of established goitre within one to three months of the injection. **(fig. 4)** This is much appreciated by the goitrous subjects. When coupled with increased energy and well being consequent on the correction of hypothyroidism, there has been continued demand for the measure, originally in Papua New Guinea, and in many other countries since.

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 (Dunn 1996).

The physiology and pharmacology of iodized oil in goitre prophylaxis has recently been extensively reviewed (Wolff 2001).

In excess of 100 million injections of iodized oil have been given since 1974 with very little in the way of side effects apart from a rare abscess at the site of injection. Refrigeration is not required, which is a great advantage. Iodized oil is certainly an effective means for the correction of iodine deficiency and has opened up the possibility of elimination of IDD as a public health problem in the next decade. However the necessity for an injection has 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 are readily available through the primary health care system, then the costs are comparable to those of iodated salt: 5-10 US cents per person per year. On the other hand, if the oil can 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 has confirmed the convenience of the oral administration of iodized oil at yearly intervals through the primary health care system at a village level. In general the effect of oral administration lasts half the time of the same dose given by injection (Delange 1994).

5.2.1 Target Groups

An iodized oil supplementation program is necessary when other methods have been found ineffective or can be considered to be inapplicable. Iodized 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 iodized oil in reducing goitre can be important in demonstrating the benefits of iodization, which can lead to community demand for iodized salt. In general iodized oil administration should be avoided over the age of 45 because of the possibility of precipitating hyperthyroidism in subjects with longstanding goitre (see further below). Pregnancy is not regarded as a contra-indication (WHO 1996; Delange 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 iodized oil administration is that it can be carried out without the legislation required for iodized salt.

The possibility of linking up an iodized oil program with other preventive programs including the Child Immunization Program, has been investigated (WHO 1987). Great progress has been made with child immunization programs in Africa and Asia. A series of injections are given covering diphtheria, tetanus toxoid and whooping cough (3 injections), polio (usually double oral administration) and measles (single injection). The target group is young children (0-2 years). Tetanus toxoid is recommended for pregnant women as a preventive measure against tetanus in the neonate.

To this series of measures, iodized 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 Organization.

5.3 Other Methods

Iodized bread was used in Tasmania in preference to both iodized salt and iodide tablets distributed through the schools, and shown to be effective (Clements et al 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 has now reversed the situation and increased the likelihood of iodine deficiency in the population. Successful use of iodized bread has been reported from Russia when bread became a staple (Gerasimov et al 1997).

Iodized 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 (Maberly et al 1981).

Similar results have been obtained from further studies in Thailand, in Sicily, Mali, Central African Republic and China. They have been recently reviewed (ICCIDD 1997).

6. Control of IDD

6.1 Current Status of IDD Control Programs

Seaweed has been used to prevent goitre in China for centuries but it is only in the years 1910 to 1920 that systematic programs of salt fortification with iodine were introduced as a strategy for the elimination of IDD in Switzerland (Burgi et al 1990) and in the United States of America (Marine and Kimball 1920).

Starting in the late 1950s with pioneering studies in New Guinea (McCullagh 1963; Buttfield and Hetzel 1967), supplementation with iodized oil was introduced in severely affected populations in Asia, Africa and Latin America. Initially, iodized oil was administered intramuscularly, more recently by the oral route. Follow-up studies of these programs are reported and summarized elsewhere (Dunn 1996). As indicated earlier in this chapter, iodized oil appeared as a particularly effective procedure for the elimination of IDD: goitre prevalence decreased rapidly and thyroid function reverted to normal and remained normal up to 5 years after injection of iodized oil and for 1 to 2 years after oral administration (Buttfield and Hetzel 1967). A further controlled trial in the Western Highlands of Papua New Guinea revealed the prevention of endemic cretinism provided the injection was given before pregnancy (Pharoah et al 1971). The trial also revealed a reduction in recorded foetal and neonatal

deaths in the treated group. As indicated earlier, mental development was markedly improved and the frequency of stillbirths and the perinatal mortality decreased while the birthweight increased (Pharoah et al 1971 ; Pharoah and Connolly 1987).

In summary, the studies using iodized oil unquestionably demonstrated that correction of iodine deficiency, greatly reduced or eliminated its consequences: brain damage, mental retardation, goitre, impaired thyroid function and perinatal morbidity.

Similar but less dramatic effects occur with iodized salt depending on the rapidity of the correction of iodine deficiency.

The justification, technology and organization of programs of universal salt iodization are described in Section V.

As described in Section II following the World Summit for Children of 1990 to assist the joint efforts and action of the 130 IDD affected countries and their governments, there has now developed an informal Global Partnership. This Partnership includes major agencies of the United Nations, namely UNICEF, WHO, and the World Bank; the bilateral aid agencies, especially Australia, Canada and the Netherlands; international technical NGOs such as ICCIDD and the Micronutrient Initiative (MI); The Program Against Microntrient Malnutrition (PAMM), funding by Kiwanis International through UNICEF and the salt industry. Great progress has been achieved during the last decade in ensuring access to iodized salt for iodine deficient populations (see further Sections II and V).

6.2 Monitoring and Impact of the Programs of Salt Iodization

The social process for successful implementation a national IDD control program includes the following components (see Section II): situation assessment; communication of results to health professionals, political authorities and the public; development of an action plan; implementation of the plan and finally, evaluation of its impact at population level. This last phase, monitoring, is often neglected not only because it is the last phase in the process but because it may be over shadowed by other components of the program such as implementation, which is considered as the main or occasionally even the single component to be considered. In addition, many countries affected by IDD belong to the group of countries with low income that therefore do not have the financial or technical resources for the laboratory facilities necessary to

carry out proper monitoring of salt quality and iodine status. And yet, monitoring is crucial because IDD is a disease and its prevention and therapy require trained professionals to supervise the program and verify its effects.

As indicated in Section V the most cost-effective way to achieve the virtual elimination of IDD is through Universal Salt Iodization, (USI). Therefore, the indicators used in monitoring and evaluating IDD control programs include:

- Indicators to monitor and evaluate the salt iodization process (Process indicators);
- Indicators to monitor the impact of salt iodization on the target populations (Impact indicators).

The process indicators are discussed in detail in Section V.

The impact indicators have been recently reevaluated and discussed (WHO/UNICEF/ICCIDD 2001). They are described in detail earlier in this Chapter. As indicated, they include especially the determination of urine iodine.

It is now considered that iodine deficiency has been eliminated from a particular country when the access to iodized salt at household level is at least 90%, together with a median urinary iodine of at least 100µg/L and with less than 20% of the samples below 50µg/L.

Currently, we have much less information about the impact of the salt iodization programs on IDD than on the implementation of the programs themselves. The monitoring data of all countries affected by IDD with a program of iodine supplementation are summarized country by country on the websites of ICCIDD (http://www.iccidd.org) and WHO (http://www.who.int.nut) (See Section VIII, IX and Appendix I).

As assessed by measurements of urinary iodine, many countries have achieved the elimination of iodine deficiency, e.g. Algeria, Kenya, Cameroon, Tanzania (Africa), Iran, Lebanon, Tunisia (Eastern Mediterranean), Bhutan, China, Indonesia, India, Thailand (Asia), Venezuela, Peru, Ecuador (Latin America) and Switzerland, Austria, Great Britain, Finland, Norway, Sweden, Poland, Macedonia and Serbia in Europe.

So far few longitudinal or case control studies address the influence of USI on the other main disorders induced by iodine deficiency, such as impairment of thyroid function, low birth weight, perinatal mortality and morbidity and the prevention of mental retardation. The statement that correction of iodine deficiency protects 85 million neonates from the risk of brain damage and mental retardation annually is politically attractive

but scientifically questionable as it results simply from a multiplication of the birth rate of the affected countries by the percentage of access to iodized salt at household level. Both figures lack precision.

Finally, partnership evaluation of country programs using for example the ThyroMobil model (Delange et al 1997) indicated that in some countries, poorly monitored programs of salt iodization resulted in excessive iodine intake associated with risks of adverse health consequences such as iodine-induced hyperthyroidism (IIH).

6.3 Side Effects of Iodine Supplementation

As discussed so far in this chapter, iodine deficiency is associated with the development of thyroid function abnormalities. Similarly, iodine excess, including following overcorrection of a previous state of iodine deficiency, can also impair thyroid function. The effect of iodine on the thyroid gland is complex with a U shaped relation between iodine intake and risk of thyroid diseases as both low and high iodine intake are associated with an increased risk. It is stated that normal adults can tolerate up to about 1000µg iodine/day without any side effects (WHO 1994). However this upper limit of normal is much lower in a population which was exposed to iodine deficiency in the past. The optimal level of iodine intake to prevent any thyroid disease may be a relatively narrow range around the recommended daily intake at 150µg (Knudsen et al 2000).

The possible side effects of iodine excess are as follows:

6.3.1 Iodide goitre and iodine-induced hypothyroidism

When the iodine intake is chronically high, as for example in coastal areas of Japan (Suzuki et al 1965) and China (Ma et al 1982) due to the chronic intake of seaweeds rich in iodine such as laminaria or in Eastern China because of the high iodine content of the drinking water from shallow wells (Zhao et al 2000), the prevalence of thyroid enlargement and goitre is high as compared to normal populations and the prevalence of subclinical hypothyroidism is elevated. The mechanisms behind this impairment of thyroid function are probably both iodine enhancement of thyroid autoimmunity and reversible inhibition of thyroid function by excess iodine (Wolff-Chaikoff effect) in susceptible subjects (Roti and Vagenakis 2000). However, this type of thyroid failure has not been observed after correction of iodine deficiency, including in neonates after the administration of huge doses of iodized oil to their mothers during pregnancy (Delange 1996).

6.3.2 Iodine-induced hyperthyroidism (IIH)

Iodine-induced hyperthyroidism (IIH) is the main complication of iodine prophylaxis. It has been reported in almost all iodine supplementation programs (Stanbury et al 1998). The outbreak most extensively investigated occurred in Tasmania in the late 1960s following iodine supplementation simultaneously by iodized bread and the use of iodophors by the milk industry (Connolly et al 1970; Stewart et al 1971). The incidence of hyperthyroidism increased from 24 per 100,000 in 1963 to 125 per 100,000 in 1967. The disease occurred most frequently in individuals over 40 years of age with multinodular goitres (Vidor et al 1973) The most severe manifestations were cardiovascular and were occasionally fatal. The epidemic lasted for some 10 to 12 years and was followed by an incidence of hyperthyroidism somewhat below that existing prior to the epidemic.

The problem of IIH was recently reactivated when it was reported that the introduction of iodized salt in Zimbabwe resulted in a sharp increase in the incidence of IIH from 3/100,000 to 7/100,000 over 18 months (Todd et al 1995). A high risk of IIH was also reported from Eastern Congo following the introduction of iodized salt (Bourdoux et al 1996). A multicentre study conducted in seven African countries, including Zimbabwe and Congo (WHO/UNICEF/ICCIDD 1997) showed that the occurrence of IIH in the last two countries was due to the sudden introduction of poorly monitored and excessively iodized salt in populations which had been severely iodine deficient for very long periods in the past. The conclusion of the multicentre study was that the risk of IIH was related to a rapid increment of iodine intake resulting in a state of acute iodine overload. On the contrary as already mentioned an increased incidence of hyperthyroidism was not reported in populations which could adjust their thyroid function and regulation to a chronically high iodine intake.

IIH following iodine supplementation cannot be entirely avoided even when supplementation uses only physiological amounts of iodine. In a well controlled longitudinal study in Switzerland the incidence of hyperthyroidism increased by 27% during the year after the iodine supply was increased from 90µg/day to the recommended value of 150µg/day (Baltisberger et al 1995). Subsequently there was a steady decrease in the incidence of the disorder.

The reason for the development of iodine-induced hyperthyroidism after iodine supplementation has now been explained (Dremier et al 1996). Iodine deficiency increases thyroid cell proliferation and mutation rates

which, in turn, trigger the development of multifocal autonomous growth with scattered cell clones harbouring activated mutations of the TSH receptors. Measurement of total intrathyroidal iodine by means of X-ray fluorescence scanning showed that only some nodules keep their capacity to store iodine, others become autonomous and can cause hyperthyroidism after iodine supplementation (Jonckheer et al 1992).

It thus appears that IIH is one of the Iodine Deficiency Disorders. It appears to be inevitable in the early phase of iodine supplementation. It is important that clinical facilities are available for diagnosis and treatment of these patients. They are usually over the age of 40 so that radioactive iodine is the treatment of choice.

6.3.3 Iodine-induced thyroiditis

Another possibility is the aggravation or even the induction of autoimmune thyroiditis by iodine supplementation. In experimental conditions, excessive iodine intake can precipitate spontaneous thyroiditis in genetically predisposed strains of beagles, rats or chickens. The mechanism involved in iodine-induced thyroiditis in animal models could be that elevated dietary iodine triggers thyroid autoimmune reactivity by increasing the immunogenecity of thyroglobulin or by inducing damage of the thyroid by cell injury by free radicals.

Attention was drawn to the possibility of iodine-induced thyroiditis in humans when studies conducted in the United States of America following the implementation of salt iodization showed an increased frequency of Hashimoto's thyroiditis seen in goitres removed by surgery (McConahey et al 1962).

However, to the best of our knowledge, although cross sectional studies have associated endemic goitre with the presence of thyroid autoantibodies for example in Sri Lanka (Premawardhana et al 2000) no large epidemiological metabolic or clinical surveys have been performed which have analyzed the impact of large scale programs of iodine supplementation on the occurrence of clinically significant iodine-induced thyroiditis with public health consequences on thyroid function. The longterm prospective study presently organized in Denmark (Laurberg et al 1998) could provide an adequate answer to the question as to whether correction of iodine deficiency results in clinically significant development of thyroid autoantibodies and thyroid failure. For the Danish authors, thyroid autoantibodies appear as markers but not inducers of thyroid disease, i.e. they are the consequence of the goitre rather than its cause.

6.3.4 Thyroid cancer

In animals, the chronic stimulation of the thyroid by TSH is known to produce thyroid neoplasms (Money and Rawson 1950). There is a tendency for higher incidence rates of thyroid cancers in autopsy material from endemic goitre areas although the relationship of thyroid cancer and endemic goitre has often been debated without agreement being reached on many aspects, including causal relationship (Harach et al 1985).

Iodine supplementation is accompanied by a change in the epidemiological pattern of thyroid cancer with an increased prevalence of papillary cancer discovered at autopsy (Vigneri et al 1998). However, the prognosis of thyroid cancer is significantly improved following iodine supplementation due to a shift towards differentiated forms of thyroid cancer that are diagnosed at earlier stages.

Moreover, careful monitoring of the incidence of thyroid cancer in Switzerland following iodine supplementation showed that the incidence of thyroid cancers steadily decreased from 2 to 3 per 100,000 in 1950 to 1 to 2 per 100,000 in 1988, i.e. during a period when iodine intake increased and reached an optimal value (Levi et al 1991).

Finally, fine-needle aspiration biopsies were performed in Poland between 1985 and 1999 in 3,572 patients treated by thyroidectomy and were compared to the results of postoperative histopathological examinations. The particular interest of this study is that Poland used to be an endemic goitre area and that iodine deficiency was progressively corrected during the study period 1985-1999. The frequency of neoplastic lesions significantly decreased throughout the examined period and the ratio of the papillary/follicular carcinomas increased. However, the frequency of cytologically diagnosed chronic thyroiditis increased from 1.5 to 5.7% (Slowinska-Klencka et al 2002).

7. Conclusion

In conclusion, it appears that the benefits of correcting iodine deficiency far outweigh its risks (Braverman 1998; Delange 1998). Iodine-induced hyperthyroidism and other adverse effects can be almost entirely avoided by adequate and sustained quality assurance and monitoring of iodine supplementation which should also confirm adequate iodine intake.

We conclude that the progress towards correction of iodine deficiency globally in the past decade is a public health success unprecedented with a non-infectious disease and that sustainable elimination of this Ancient Scourge is within reach.

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