IODINE DEFICIENCY DISORDERS IN INDONESIA: PAST, PRESENT AND FUTURE

Prof. DR. dr. R. Djokomoeljanto, SpD(KE)[1]
[1]Professor of Internal Medicine, Diponegoro University, Dr. Kariadi Semarang, Indonesia

ABSTRACT

Iodine Deficiency (ID) may cause a wide spectrum of abnormalities affecting fetus, neonates, children and adult population. The most severe form is endemic cretinism which is found in severely IDD areas. The pathophysiology of these are the inavailability of thyroid hormone during neurophysical development beginning in early pregnancy which are irreversible. In moderate and mild ID more subtle anomalies may be found, ranging from unsuccesful pregnancy outcomes (abortion, perinatal death, congenital abnormalities etc). Hypothyroxinemia not hypo-T_3 is crucial for brain development, since delicate regulation of T_3 can be done by local production of T_3 via 5'-DII deiodinase. Preterm babies are prone to hypothyroxinemia and inadequate iodine intake and this should be prevented. The highest burden of iodine deficiency *is not* goiter *but* psychoneurophysical development of men, which mostly are irreversible neurological damage. This problem is *easily prevented* by continuous supply of adequate iodine supply to high risk populations (pregnant and nursing mothers, children esp underthree's and child bearing age women). The recent International Thyroid Congress in Buenos Aires recently (Oct 31, 2005 – attached in this paper) isued a statement that all its members should help their government to overcome this global problem.

Keywords: iodine deficiency disorders, cretinism, thyroid

INTRODUCTION

The above mentioned declaration is worldwide agreement that iodine has major and tremendous role in the development of physical and mental development of children during pregnancy. It was also stated that the preventive treatment should begin as early as possible in the mother's womb. Iodine deficiency lowers the average IQ by 13.5 points, showing it as the main cause of potentially preventable mental retardation (IDD Newsletter 1996). Out of 1572 millions people at risk of IDD (of which 43 millions are affected by some degree of IDD-related brain damage), 27% residing in South East Asia (IDD News letter 1995).

IDD has been known in Indonesia for many years. The oldest information concerning the presence of goiter came from Javanese copper inscription found at Bangli, Bali. Later, data were compiled before the 2nd WW II and short after, which enable us to map only the widespread distribution of endemic goiter in Indonesia, but not the severity of the problem (Djokomoeljanto 1974). A national survey of primary schoolchildren from 1980-1982 in 26 provinces described a goiter prevalence of more than 10% in 68% sub-districts and a more than 30% in 40% sub-districts. Some villages had more than 80% prevalence of goiter. This survey estimated the presence of 75,000 cretins in the country since in some areas the incidence of endemic cretinism reached 10-15% of the population. It was estimated that 35 millions people are living endemic areas, and 3.5 millions were affected with goiter. (Benny Kodyat 1991). In 1988 a follow-up survey the total prevalence decreased by 37%. to 24.95% and further to 19.90% in 1990. The latest survey covering 27 provinces showed the decline of TGR to 9.8% (better than the targeted prevalence of 18%). There were 142.5 millions people living in non endemic area, 8.8 millions in severe endemic, 8.2 millions in moderate and 36.8 millions in mild endemic area. (Muhilal 1998)

The latest survey of 1998 showed the following results: TGR of schoolchildren was 9.8%, however TGR of pregnant women in the same village was 16.0%. The median UEI of pregnant women showed that 72% were ≥ 100 µg/l while 13% had UEI 50-99 µg/l. Median of TSH in pregnant women of 4,0 uU/ml was found and 30% of them had ≥ 5.0 uU/ml. Adequate iodine content (>30 ppm) of iodized salt was consumed only in 64.6% of households surveyed. There was a good correlation (r=0.8) between the proportion of salt that met the requirement for fortification and median value of UEI among pregnant women. It was estimated that there was 130.800.000 IQ points loss due to this problem. (Muhilal 1998) . We have shown that even with normal goiter and UEI in schoolchildren in areas once known to be endemic area, newly replete area, minimal brain dysfunction was found (Bambang-Hartono 1996). Neonates' TSH is closely correlated to mothers' TSH (Yasin 1989). Furthermore comparing the replete area and iodine deficient area, in replete area, mothers with TSH of ≥ 5uU/ml give birth to children with abnormal neurological development such as tone, primitive and postural reflex development from 0-2 years of age. Demographic data also shows serious problems. Among others are smaller birth weight, increased premature birth, spontaneous abortion were observed (Bambang Hartono 2001) Iodine capsule has been shown to improve infant survival in Indonesia (Cobra 1997).

The consequence of severe iodine deficiency to the population, beyond endemic goiter and endemic cretinism must be stressed. In severe iodine deficiency spectrum of abnormalities are seen

even in normal subjects. This phenomenon may be understood in the frame of the role of iodine in the development of an individual (physical, neuropyschological and mental). Within this context two components, e.g: *the mother* and *the fetus*, should be seen and discussed as a *single entity*. The accumulated studies show that mother's iodine nutrition may influence fetal iodine nutritional status and its development. Thyroid hormone is essential for fetal and neonatal development in particular the brain, but little is known about regulation of fetal thyroid hormone levels throughout human gestation (Hume 2004). The latest issue of iodine deficiency is whether mild iodine deficiency may result in abnormal human development. The prevention of *goiter* must be translated into the prevention of *the central nervous system deficits* that are very frequent and irreversible consequence. The role of iodine deficiency in mental development has not been clearly perveived until last third of the XXth century.

SPECIFIC REGULATION OF HORMONE REGULATION IN THE BRAIN

Deiodinase system

The active 'hormone' is T_3 and not T_4 hence it must be converted first to T_3 to be able to function properly. With the aid of *deiodinases* active hormone can be maintained to support the normal cycle of life and demands. There 3 main deiodinases : DI , DII and DIII They have their own specificities and functions.

Deiodinase system specific to the brain

Intracerebral thyroid hormone (TH) metabolism is responsible for maintenance of intracellular T_3 level. The intracerebral T_4 to T_3 conversion contributed 75-90% of the T_3 bound to brain cell nuclei, and only 10-25% comes from the circulation. This *local* T_3 production is the hallmark of brain, appears to be a consequence of the ability of brain to rapidly degrade T_3 derived from circulation and isolates the brain from environmentally influenced changes in thyroid hormone status. Two isoenzymes of the outer-ring deiodinase (ORD), type-I and II iodothyronine 5' deiodinase (5'D-I and 5'D-II) are found in the brain, 5'D-I is localized in the *glial* cells and 5'D-II in *neurons*. The inner-ring deiodinase (IRD) is found in the brain, placenta and fetal tissues. The last is called the D-3 (or 5D). The 5'D-II serves as the source of T_3 in the brain (Leonard 1992). The differences between D1, D2 and D3 are as follows: The main action of D1 is to convert T4 to circulating T3 (active hormone, not modified during pregnancy), D2 T4 → local T3 (in the placenta, brain, highest in the 1st trimester used for hemoeostatic mechanism), D3 to convert T4 → rT3 (reversed T3 – inactive) and T3 to T2, high in the placenta. It serves to inactivate maternal T4)

Selenium function

Selenium is essential constituent of glutathione peroxidase (GSH-Px) and 5'D-I. GSH-Px protects tissues from oxidative damage. Se in 5'D-I is responsible for bio-activating the prohormone T_4 by converting it to T_3 in peripheral tissues and thyroid . Whereas I (iodine) is needed for hormone synthesis, Se is needed for hormone activation , conversion and action. They work hand in hand (Meinhold 1992)

Present ideas of fetal developmental events are summarized in the Figure 1 that incorporates the new experimental findings regarding the migratory waves of cerebarl cells into the neocortex for human development. Taken as a whole, the indirect and direct evidence identify a relative iodine deficiency early in pregnancy as a cause of preventable neurodevelopmental deficits of the offspring (Escobar G 2000). Furthermore late second / early third trimester is regarded as critical transition period in fetal thyroid hormone metabolism, which may be interrupted by preterm birth and contribute to postnatal thyroid dysfunction (Hume 2004)

To study some difficult clinical aspects such as brain consequences of iodine deficiency, animal model (rats, marmoset, sheep) may give light to the pathogenesis of iodine deficiency on the brain. *In rats* T_4 and T_3 are present in embryonic tissues before the fetus has an active thyroidal secretion, and are of maternal origin. Once fetal-thyroid function (FTF) starts, intra- and extrathyroidal T_4 and T_3 pools increase rapidly, with 5'-D playing an important role in the availability of T_3 to different tissues. Transfer of thyroid hormones (TH) from mother to fetus continues until birth. If maternal contribution is missing (due to e.g.: in hypothyroid mothers) embyronic tissue is TH-deficient until fetal thyroid is compensating by increasing secretion. The maternal contribution of T_4 and T_3 mitigates the thyroid hormone deficiency *but* the effects are both tissue-dependent and iodothyronine-dependent. The fetal brain is totally protected from T_3 deficiency throughout gestation *if* maternal T_4 is normal and D2 activity increases in response to the low fetal T_4, while *normal maternal T_3 concentration are of no benefit to the fetal brain* if maternal hypothyroxinemia is not corrected (Obregon 1998).

IODINE DEFICIENCY AND CHILDREN'S NEUROPSYCHOPHYSICAL DEVELOPMENT

Fetal wastage is frequent in iodine deficiency, which is also associated with greater incidence of abortion, prematurity, stillbirth and congenital anomalies (McMichael 1980, Potter 1979). In the neonate, iodine deficiency causes an increased perinatal mortality, infant mortality and low birth weight babies (Thilly 1980, Bambang Hartono 2001, Delange 1986, Delange 1991). A brief review of he ontogeny of thyroid gland are as follows.Thyroid follicles undergo 3 stages of development: precolloid stage (7-13 weeks), the colloid stage (13-14 weeks) and follicular stage (14 weeks onwards). TG is detected as early as 5th gestational week, Active trapping of iodide detectable by 12th weeks during the precolloid stage, and the first indication of T_4 production occurs 2 weeks later, during the final stage of follicular lumen formation. In the hypothalamus TRH is detected by 8-9 weeks and TSH is present in the pituitary by 10-12 weeks. Fetal serum TSH and T_4 concentration remain at very low level until midgestation. At 18-20 weeks , both the fetal thyroid gland uptake and serum T_4 concentration begin to increase (Glinoer 2000)

In humans 3 stages can be identified: *phase I:* (0→12 weeks gestation, before the production of fetal thyroid hormone. The only source of TH is maternal. This is the period of brainstem development, cerebral neurogensis and migration), *phase II:* (12 weeks → to term, period in which brain is exposed to both maternal and fetal thyroid hormone. In this period neuronal differentiation, axonal outgrowth, dendritic ontogeny and synaptogenesis develop (continued in phase III) as well as cerebellar neurogenesis (predominantly prenatal) and gliogenesis (predominantly late fetal life to 6 months postnatal), and *phase III:* the postnatal period, where neonate depends on its own thyroid hormone production. In this phase the former processes go on combined with myelo-genesis (begin 2nd trimester → 2 years). Neonatal rat is an excellent model to study developmental events that occur 'in utero' in humans. (Porterfield and Hendrich 1993).

It should be remembered that *neurological development follows essential sequences* and , while there is eventual compensation of cell numbers in hypothyroidism, the cellular composition and architecture might remain abnormal. (Porterfield and Hendrich 1993). "All or none phenomenon" or "Once and the only opportunity" are sometimes referred to this period . It was previously thought that thyroxin could not pass the placenta, but Vulsma (1989), in congenital hypothyroidissm, showed that it does even a limited placental transfer, in small quantities, reaching 20-50% of the normal infants level. Due to in upregulation of the II 5'-deiodinase activity of the brain during the lowered T_4, these levels of T_4 might suffice a substrate to maintain normal or near normaln T_3 concentration in brain *but not for other tissues.*It seems that the most important issue for the CNS development abnormalities is the altered flow of nutrients or *substrate* to the fetus (in this context T_4) (Oppenheimer 1997) . When thyroid hormone is not adequate, some of the actions of thyroid hormones on brain development could be mediated through directly or indirectly increasing growth factors such as nerve growth factor, epidermal growth factor and the insulin-like growth factors. (Porterfield and Hendrich 1993). The importance of early transfer of thyroxin was also demonstrated clearly in rats experiments (Escobar 1993).

Impairment of the nervous system development and functions is the most important consequences of iodine deficiency. Three aspects are important: *first* the neurological insult, *second* timing of insult and *third* the pattern of CNS involvement. During nervous system development the damage is irreversible, while pyschomotor function impairment by hypothyroidism alone not affecting nerve development is regarded as reversible. The system mainly involved are : auditory (*cochlea*), motor and intellectual *(cortex and basal ganglia)*. The vulnerable window is the second and perhaps the third trimesters. This is the time of neuron generation and migration. This is still questionable to say that iodine treatment is not necessasry before the end of the first trimester (Obregon 1998) (Delong IDD Newletter 1990). Up to the end of the second trimester, iodine treatment protects the fetal brain from effects of iodine deficiency (Cao 1994). This is consistent with our observation that abnormal EEG was found only in children born from mothers who were injected with lipiodol after 16 weeks of gestation (Wijaya 1978).

The *critical period* for thyroid hormone action in the CNS development has been extended covering from late gestation to 1-2 years (in humans) or from postconceptional day 18 to postnatal day 27 (in rats). According to brain areas this period is characterized by " cell proliferation (gliogenesis) – neuronal migration and maturation – axon and dendritic proliferation – synapse formation and myelination". Thyroid deficiency prevent the correct set up of brain morphology. The damage caused by iodine deficiency in the complex organization of neuronal network *cannot be amended* by late administration of hormones, since thyroid hormones act on these processes as a regulating agent of cell proliferation and differentiation . The morphogenetic effects of thyroid hormones are the result of mRNA and protein synthesis. Some of the brain expressed proteins controlled by T_3 are MAPS (microtubule associated proteins), MBP (myelin basic protein), PCP2 (Purkinye cell protein2) , NGF, Synapsin 1 etc) (de Nayer 1994)

Concerning the effect of iodine deficiency on *cognitive* development, metaanalysis of 21 studies in iodine deficiency areas from all continets (excluding North America), a difference of 13.5 IQ points has been shown occurring in iodine deficient population (Bleichrodt 1987, 1994)

Severe Iodine deficiency. The typical consequences of severe IDD in human life are exemplified by endemic cretinism: neurological and myxedematous type, hypothyroidism and mental deficiency. (Choufoer 1965, Querido 1972, 1980, Pharoah 1980, Djokomoeljanto 1974, Delange 1986, Goslings 1975,1977). Similarities as well as differences were found in those areas. Myxedematous endemic cretins were prevalent in Zaire, Switzerland while neurological endemic cretins were prevalent in Papua New Guinea, Irian Barat and South America. In the Himalayan region , China, Indonesia both types were found. The exact pathogenesis of the difference is not fully understood, but possible explanations were available.(Delong 1989, Hetzel 1994, Halpern 1994, Boyages 1994). The inability of pregnant mothers to increase their low circulating T_4 (not of T_3!) during pregnancy was causally related to the birth of cretins (motor and cognitive impairment of the progeny was correlated with the degree of maternal *hypothyroxinemia*, and *not* with circulating T_3 or TSH level, those mothers were not clinically hypothyroid because of their relatively normal compensated circulating T_3 (Escobar GM 2000) . New development in the understanding of thyroid hormone effect is the presence of isoforms of thyroid hormone receptors: TRβ_2 that has unique role in photoreceptor development and TRβ_1 mediates actions in the brain and auditory system . However the exact mecahnism is still waiting for other findings (Heindel 2003). From the pathological point of view thyroid hormone that regulates axonal myelination may be controlled by (a) peripheral T_4 and T_3 production, (2) TH transport across blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCFFB) and (3) deiodination of the thyroid hormones. It is known the effect of hypothyroidism on axonal myelination is the reduced total number of axon, decreased number of oligodendrocytes and myelinated axons leading to reduced size of associated white matter tract and aberrant myelin structure (Jones 2005)

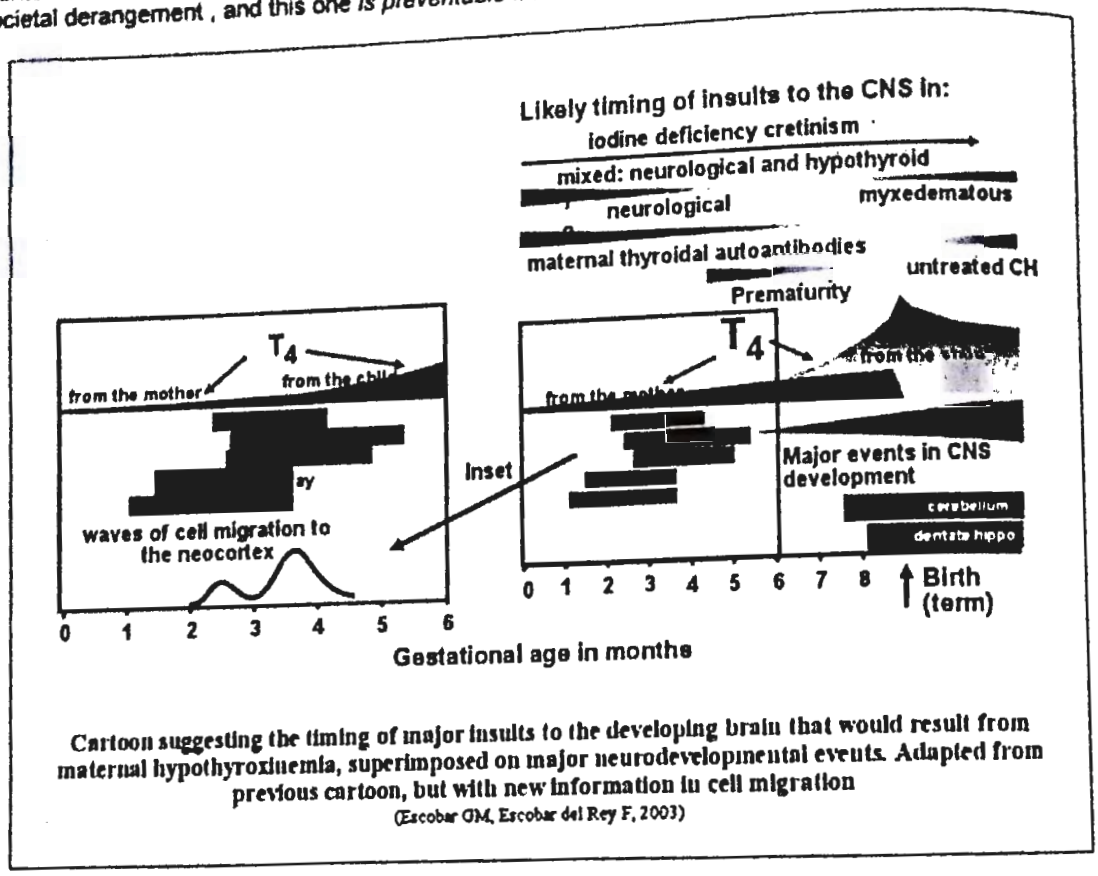
The known risk factors of abnormalities depends on : (1) the time, severity and duration of iodine deficiency insult during gestation, (2) the continuation of iodine deficiency postnatally, (3) the influence of and aggravation by other environmental factors such as selenium (Vanderpas 1990,Contempre et al.1994), thiocyanate (Thilly 1991), iron (Zimmerman 2002) or other factors. In those areas intervention studies were also done, that clearly showed endemic cretinism was prevented when iodine was introduced prior to gestation. Recently biphenolic compouns (BPAs), including PCB (polychlorinated biphenyls) are suspected to lower thyroid hormone levels. It blocks the TR action on oligodendrocyte differentiation (Zoeller 2005). The first epidemiological study was conducted by Australian scientist when for the first time controlled trial on the use of lipiodol injection in the prevention of endemic cretinism was done in the Highland of Papua New Guinea, involving a population of approximately 8000.(Pharoah 1971).

In severe endemias subjects which are not-cretins are also suffering from abnormal developments such as hypothyroidism, mental retardation, physical retardation etc. Our own study support those observations and we could say that *in severe iodine deficiency 'normals are not normal'.* (Djokomoeljanto 1974). The abnormality forms a continuum both in the cretins and in the non cretinous population (Querido 1978, Boyages 1994, Bleichrodt 1987,1994). In severe iodine deficiency, the concomitant iron, selenium and zinc deficiency should also be considered. Coexisting deficiencies of these elements can impair thyroid function. Iron deficiency impairs thyroid hormones synthesis by reducing activity of heme-dependent *thyroid peroxidase.* Iron deficiency blunts and irone supplementation improves the efficacy of iodine supplementation. Combined selenium and iodine deficiency leads to 'myxedematous cretinism' Among the seleno-cysteine-containing proteins are glutathione peroxidase, deiodinase and thioredoxine reductase families. Therefore adequate selenium nutrition supports efficient thyroid hormone synthesis and metabolism and protects the thyroid gland from damage by excessive iodide expsore or oxidant stress. Normalisation of *iodine* nutrition must *precede selenium* intervention to prevent hypothyroidism and thyroid damage (Zimmermann 2002).

The most important factor is mother's *hypothyroxinemia early in gestation*, (whether or not TSH is increased), because local T_3 generated from T_4 by D2 deiodinase to supply the temporal and spatial needs for thyroid hormone action in different brain structures is independent of circulating maternal or fetal T_3. These machanism can operate successfully *only* when there is adequate substrate of T_4. Persistence of maternal hypothyroxinemia later in pregnancy, further decrease the availability of T_4 to the brain would aggravate the neurodevelopmental damage. (Moreale de Escobar 2000, 2003)

Moderate Iodine deficiency. The clinical abnormalities related to IDD in such area is less prominent and difficult to assess. Besides biochemical laboratory data, sophisticated examinations are mostly needed. This is so due to the fact that neuropsychological development defects are specific for this abnormality. In those areas, mothers exposed to mild or moderate IDD may give birth to offspring with attention deficits and hyperactivity disorders (ADHD). So far this had been reported only in children with generalized resistance to thyroid hormones. This might suggest the common mechanism may be

either reduced sensitivity of nuclear receptor to thyroid hormones or reduced availability of intranuclear T_3 for nuclear receptor binding. Study in Italy : ADHD was found in 68.7% in area A (moderate IDD) and none in area B (mild IDD), IQ score in A was 92 compared to 110 in area B . Sixty percent (63,6%) of ADHD in area A were born from mothers who became *hypothyroxinemic* at early gestation, where only 20% non ADHD children was born to woman who was hypothyroxinemic at 20 weeks of gestation (Vermiglio 2004) This area of research attracts many scientists in the field of 'thyroidology ' since mental retardation which many believe to be associated with mild iodine deficiency poses population to societal derangement , and this one *is preventable* if iodine is administered in due time.



Cartoon suggesting the timing of major insults to the developing brain that would result from maternal hypothyroxinemia, superimposed on major neurodevelopmental events. Adapted from previous cartoon, but with new information in cell migration

(Escobar GM, Escobar del Rey F, 2003)

IODINE DEFICIENCY DISORDERS IN INDONESIA AT PRESENT

Since the main cause of IDD is environmental lack of iodine, which will not improve by itself, the adequacy of iodine nutrition will depend on the availability of external iodine through several sources. One of the main sources is Iodized salt. Without this intervention it is unlikely that adequacy can be met. *IDD monitoring* is therefore imperative. WHO has published manual on the *Assessment of IDD and monitoring their elimination* in 2001. Identification of IDD and its monitoring has to be done anywhere where resident population are goitrous. In this case palpation is adequate. However with the availability of urinary iodine estimation and other methods for assessing iodine deficiency, IDD can be seen in the non-classical places like in coastal areas, where goiter based on palpation is normal, in large cities, in highly developed cities or in places where IDD have been considered to have been eliminated, either by prophylactic program or general dietary changes. (WHO 2001) The monitoring system is to check the sustainability of program

There are 2 recent reports concerning the status of IDD in Indonesia. One is the National IDD Research published by the Department of Health (1998), which showed the *overall improvement* of IDD status in Indonesia. The summary are as follows: TGR of schoolchildren 9.8%, pregnant women 16.0%, median UEI in pregnant women was good (147,0 ug/l), however 13% were < 100 ug/l, median TSH was good (4.0 uU/ml) but 40% were still higher than 5 uU/ml. From this data it was estimated the loss of IQ was 130.793.313 points. For the sake of comparison the goiter prevalence was 22.8% in 1993.This must be due to the tremendous effort in the prevention program launched by the Government of Indonesia in recent years (Dini Latief 1999, Rahmi Untoro 2003).

Intervention programs

Intervention program in Indonesia was designed following the *social process model* put forward by Hetzel at the First Seminar on Endemic Goiter and Cretinism in Indonesia, Semarang 1978.(Hetzel 1978). This was based on the epidemiological studies on the wide distribution of IDD that almost no island is exempted from the problem and the understanding of the effect of iodine deficiency on the population especially in the severely iodine deficient areas. Theoretically iodine deficiency is one of the simplest micronutrient deficiencies to address. By periodical supplementing target population with iodine the problem can be solved *theoretically*. In our case iodized salt was the intended ideal solution. Intermediate actions with iodinated oil, injection or capsules were given in moderate and severe iodine deficient areas. Although effective other methods are not practical for national program.

To attain the goal that no cretin will be born in 2000 (it is changed to 2010), a national IDD Committee was established by Minister of Health Decree in 1990 and the national IDD country program thus consisted of three strategies : (1) iodized salt for human consumption as *permanent long-term* strategy, (2) iodinated oil injection or capsule for severely endemic areas, as *a short time measure* and (3) iodinated water as an appropriate technology in special high risk areas. (Benny Kodyat 1991)

Iodized salt

Salt iodization began under the Dutch regulation in 1927, but stopped in 1945 when salt monopoly was disbanded. It is understandable that good quality iodized salt and its distribution throughout Indonesia, an archipelago with more than 13000 islands, needs well established infrastructure. To make the problem simple the *blanket approach* with 40 ppm KIO_3 (±25%) was adopted. Preliminary intervention trial using this concentration was carried out in Central Java, which proved that 40ppm of iodized salt was effective in reducing goiter and increasing urinary iodine (Djokomoeljanto 1976, not published). The combat against IDD was initiated with the UNICEF support in 1976. At the beginning of the program, responsibility and accountability for enforcement was unclear within the government, and there was no mechanism for coordination among involved ministries and private sector. In 1990, the Indonesian Government (GoI) resumed a nationwide IDD control program with the assistance of the World Bank, UNICEF and other agencies. The goal of the program was to reduce the prevalence of IDD through monitoring the iodine status of the community, increasing the supply of iodized salt consumption while improving inter-sectoral coordination.

The World Bank supported GoI with Intensified IDD Control (IIIDC) Project started in 1997, however progress has been slower than expected because unresolved problem of poor accountability and weak enforcement. National coverage of iodized salt consumed at household level increased from 78.2% in 1995 to 81.5% in 1999. However iodized salt adequacy (containing > 30ppm) rose only from 50% in 1996 to 65.5%, 63.5%, 64.6%, 65.5% and 68.6% in 1998, 1999, 2000, 2001 and 2002 respectively.

According to the assessment of Susenas (*National Health Survey*), from 27 provinces only 4 provinces reached the expected > 90% iodized salt household consumption.; provinces in Java and Bali still at the level of 40 – 70%, while 2 provinces (NTB and NTT) were classified as very low (<40%) and some provinces stayed at the same level. Based on the district variations, from 1998 to 2002, 57.5% districts were at the same level, 14,6% became worse and 19.6% showed improvement of iodized salt consumption.

The salt industry is relying on more than 25,000 small salt farmers that produce about 80% salt. PT Garam, a government enterprise, produces only 20% of Indonesia's salt. The salt farmers are concentrated in the north coast of Java, Madura, Bali, South Sulawesi and East Nusa Tenggara. Higher capacity of salt production is concentrated in Java and Madura, while it is very low in other provinces. Small farmers produce their salt with basic traditional technology that renders salt with low quality, and not suitable for iodization.

Table 1. Percentage of household using adequate iodized salt (>30ppm) according to province and some districts.

	WSm	WJv	CJv	Pati	Rbg	Ejv	Pb	NTB	NTT	SS	SES	Mlk	Mgl
1998	93.7	59.2	61.9	55.7	31.5	60.5	35.5	12.1	15.4	27.3	58.7	33.4	65.8
1999	90.3	54.3	55.7	49.1	31.9	63.6	28.4	12.5	23.0	36.6	52.9	34.9	57.8
2000	90.5	57.7	51.8	57.5	30.1	63.3	26.4	13,7	29.2	43.4	59.0	60.5	47.9
2001	86.1	62.7	55.7	53.9	22.9	63.2	35.8	18.8	32.4	54.7	60.7	-	73.8
2002	92.9	67.8	54.6	44.0	36.1	67.8	35.4	18.0	32.6	59.8	58.7	-	63.8

Source Technical Monitoring Mid Term Evaluation. Pati & Rbg , Pb are subdistrict with huge production of people's salt.

From the report of the Mid Term Evaluation of the IIDC Project (2000) it was shown that coverage for household is far from satisfactory. Two issues may arise. From this study we can see that in Java, districts with plenty of people's salt producers (Indramayu, Cirebon, Pati, Rembang, Probolingga) has low coverage of consumption of iodized salt.. This may be due to the infiltration of iodized salt to the community, and public awareness is lacking. The other issue is in NTT, NTB, Maluku which could be due to the logistic problems. For both issues law enforcement is the key success. (Table 1).

Other observation from BPS showed that the concentration of iodine in salt is influenced by the method they keep salt at home (Table 2).

Table 2. Methods of storing iodized-salt at households and their iodine content

Method	Iodine content		
	Satisfactory (S)	Unsatisfactory (US)	Nil (0)
Closed	75.2 %	12.5 %	12.2 %
Open	49.9 %	23.5 %	26.6 %
Near oven / stove	59.6 %	19,3 %	21,2 %
In the cupboard	81.7 %	11.1 %	7.2 %
On the rack	70.1 %	14.8 %	15,1 %

BPS 2002 S=>30ppm, US < 30 ppm

Iodinated oil capsules

In the early phase of intervention when severe and mild IDD were simultaneously found, the blanket approach with 40ppm iodized salt *and* iodinated oil injection ('lipiodol') was introduced later was directed to areas with moderate to severe IDD, and in remote areas, as judged by the T school children and based on the results of our national survey. Injection was given every 4 years – 0,4 ml lipiodol for children age 0-6 months, 0,3-0,6 ml age 6-12months, 05-1,0 ml for 6mo-6 and 1-2ml for 6-45 years (Hetzel 1978). The target and realization of injection in 25 provinces period of from 1974 – 1989 (Five Year Development Plan II through IV) are presented in next Ta All together 11.462.192 injections out of the 13.193.455 target (86.8%) was achieved. (Country R New Delhi 1989). Evaluation showed that this approach was not efficient as a national pr although effective for special purpose. Some reasons made GoI to stop this approach. Among are the failure to reach the *same person* in the next 4 years, difficult guarantee for *safe injection* to high prevalence of hepatitis, injection has to be imported, and high delivery costs

Table 3. Number of iodinated oil injection *(lipiodol)* distributed and its coverage (Benny K, 1991)

Plan (years)	Target	Total injections	% coverage
II (1974-1979)	1.036.828	1.036.828	100
III (1979-1984)	6.484.262	5.928.915	91.0
IV (1984 – 1989)	5.672.365	4.496.359	79.0
Total	13.193.455	11.462.192	86.68

PT Kimia Farma with the help of CSIRO (endorsed by Dr Hetzel) produces *yodiol*® ca ('iodized-peanut-oil' Kimia Farma Indonesia) which was then used for national intervention prog overcome the above mentioned problems. This capsule was effective to prevent and treat IDD given once a year. Field studies had been carried out since, and showed that peanut iodized oil is efficacious than iodized poppyseed oil containing the same amount of iodine in controlling deficiency (Untoro 1999). The capsule can be distributed following the same existing channel us the distribution of vitamin A. Again the criterion for receiving iodinated capsule *yodiol* is based TGR of schoolchildren children. Earlier study, before IDD intervention program, there was correlation between schoolchildren and population TGR (r=0.93) (Tarwotjo 1982) , which wa confirmed by the latest survey (Muhilal 1998). The 1995/96 – 1997/98 surveys revealed the cover *yodiol capsule* distribution was high in pregnant women with high TGR, but not in low TGR p 1998). Each *yodiol capsule* contains 200 mg I /ml.(± 12 drops). The dose depends on the a gender. Dose is given once a year: infant (<1yr) 100 mg (6 drops), preschool children (1-5 capsule, women 6-35yrs 2 capsules, pregnant / nursing women 1 capsules and male 6-20 2 cap (Dept Health 1992).

In the year 2000 the iodinated capsule target was 7.0177.519 for CBW (child bearing age women), 870.273 for pregnant women, 914.640 for nursing women and 676.661 for primary schoolchildren. However, compared to the target the coverage achieved only 60.8.4% target for CBW, 86.9 % target for pregnant and 61.3 % target nursing women and 83.9% targets for schoolchildren (Directorate of Nutrition, 2001)

Table 4 . Coverage of iodinated oil capsules *(Yodiol ^{R})* in the year 2000

Item	Child Bearing AW	Pregnant women	Nursing Mothers	Prim School Child
Target	7.177.519	870.273	914.470	678.661
Distributed	4.365.509	756.693	560.720	569.444
Covarage	60.8 %	86.9 %	61.3 %	83.9 %

Source: Directorate of Nutrtion, MoH, Nov, 2001.

Monitoring and evaluation

When we did our recent national survey (reported earlier) the goiter rate was done by palpation method. We know that palpation method brings inter-observer even the intraobserver variation which is not small. To check this, we undertook study, using ThyroMobil method (initiated by Delange in Europe) in 5 provinces in Indonesia. The aim of the study was to evaluate the present IDD status (using the standardized method of USG for thyroid grading and urinary iodine) and to compare the two accepted methods for goiter grading estimating goiter prevalence in the community, e.g.: palpation and that using ultrasonography. In large parts of Indonesia, IDD has been eliminated but in many places it had been repalced by iodine excess. In Java and Sumatra the median UEI was 195 µg/l. Frequency below 100 µg/l was 17.2% but 18.2% above 300 µg/l and 0.7% even above 1000 µg/l!. The exteremely high value (>3000 µg/l) was only found in Central Java, in the district of Sukohardjo. We did not check yet the *iodine-induced hyperthyroidism.* It was found that with the exception of Bali, other studied provinces (West Sumatra, West Java, Central Java, Yogjakarta) were good (Djokomoeljanto 2001). This data supported the previous national survey (Muhilal et al 1998) that IDD had been eliminated in large part of Indonesia. Further more a very good correlation exist between both prevalence based on palpation method (9%) or ultrasonography (8,6% based on age, or 6.8% based on BSA *body surface area*) (Djokomoeljanto 2001).

The program and impact evaluation is now being done in Indonesia and will be finished the end of December 2003. From the preliminary data in Central Java we can conclude that community iodine status are mostly good. However substantial percentage are in excess (more than 300 µg/l). From my private patients, originating from Central Java who came for other thyroid diseases and UEI were checked , I had the impression that their iodine status were also good, and around 20% showed UEI more than the accepted standard, which raised question whether we have to consider the standard iodized concentration of 40 ppm or not. If we look at the present data of 2003, school children from Sukohardjo have still very high UEI. This had been mentioned also in the above mentioned ThyroMobil study. The UEI should be checked regularly.

However we must still be aware that improvement in TGR and biochemical status in former iodine-deficient areas may still have impact on the brain pathology. An example of this came from our study of schoolchildren from 2 adjacent villages in Central Java, one was formerly severe IDD area (Sengi). (Bambang Hartono 1996) Despite 'normal' iodine biochemical markers (UEI and TSH) and physical development, the IQs (full scale, performance and verbal) are different between the two groups by about 10 IQ points apart, while minimal brain damage (MBD) was prevalent in the ex – severe group (Bambang Hartono 1996). This is in accordance with observation by Dr Connolly and Pharoah (1981) concerning the behavioural sequeallae of fetal iodine deficiency.

In iodine deficient areas mothers are at risk of abortion, increased perinatal death etc (Thilly et al (1980) in Zaire, and Bambang Hartono (2001) observed also in Ngantang East Java). This may bear consequences since preterm neonates besides show negative iodine balance and neonatal hypothyroxinemia are in the 'in the critical period' where if untreated will results in neurodevelopment abnormalities. Care should be taken to avoid iodine deficiency in preterm babies (Ares 1997, Porterfield 1993)

Evaluation of iodine deficiency in Central Java and other 4 provinces in 1996 showed that despite normal iodine nutrition in children, considerable percentage of pregnant mothers were still suffering from mild IDD . This means that the risk to give birth abnormal babies were still there. This can be seen from examples shown in Table.3. It shows that: (a) In the same area the TGR of mothers is significantly greater than the corresponding TGR of schoolchildren. (b) Despite normal TGR and UEI in children considerable number of pregnant women still show TSH more than 5µU/ml which point to risk condition for the offspring. (Djokomoeljanto 1997, Djokomoeljanto 2001, Djumadias 1996).

It is obvious from Table.3. considerable number of pregnant women had high TSH (> 5 uU/ml). They were at the risk of impaired *neurological integrity* development of their offspring, both in 'replete-area' and in 'replete-area'. Babies with 'transient-neuromotor-impairment' will undergo neuropsychological defects later in their life. In the meantime cohort of neonates born with TSH above 5 uU/ml resulted in transient impairment of neurological integrity development '. (Bambang Hartono 2001). This is in agreement with observation by Reuss et al.(1996) who showed the relationship between transient hypothyroxinemia of preterm infants to neurologic development at two years of age.

Table 5. UEI, TGR, TSH of pregnant mothers in Cetral Java (1996)

	TGR - % Children	TGR - % Mothers	UEI < 100 ug/l % mothers	UEI < 50 ug/l % mothers	TSH > 5 uU/ml % mothers
Tegal muncipal	0.0	1.1	16.6	6.3	22.8
Tegal regency	5.0	9.7	37.7	13.5	10.9
Kebumen reg.	5.6	10	30.5	13.3	19.5
Kendal reg.	5.6	6.6	26.5	8.9	16.2
Boyolali reg.	3.6	10.5	30.6	13.2	15.8
Bolra regency	0.1	0.7	24.0	6.8	11.9

Djokomoeljanto 1997

The IP-GAKY Evaluation (Departemen Kesehatan 2005) which was done in 2003 was reported in 2005 showed the following data:

1. TGR among schoolchildren was 11.0% compared to 9.8% in earlier survey. The change of TGR was noted in higher endemia. TGR in moderate provinces dropped by 55%. Maluku province belongs to severe endemia while East Java and Nusa Tenggara Timur to moderate endemia.
2. Median national UEI is 229 µg/L from 147 in the earlier survey. More than 35% with UEI<30 µg/L. This increases risk for IIH (*Iodine induced hyperthyroidism)* and AITD *(autoimmune thyroid disease)*
3. 61.4% of household surveyed consumed adequate (*meaning > 30 ppm iodine)*. There is a shift from lower to higher UEI among population, despite *higher TGR* and *below target* iodized salt *consumption in housholds.*

From those observation we can conclude that :

a. Evaluation of the Iodine status of a population cannot be based on TGR and / or UEI of schoolchildren only since *normal TGR/UEI* in this segment does not reflect necessarily reflect that of pregnant women

b. Mothers from mild and *replete-areas* are still bearing consequences for the neuropsychological development impairment of their offspring

c. TSH increase of *mothers* in *mild and replete* areas is an indicator of the risk for abnormal development of their children, while transient TSH increase in the *neonates* is a risk only in *mild* iodine deficient area. Many authors had shown earlier that neonatal TSH profile may be used as a tool of index for severity of iodine deficiency and surveillance of prophylactic program (Sullivan 1997, Rajatanavin 1997, Delange 1998, Delange 1999). Haddow showed that pregnant mothers with high TSH during the second trimester of gestation have neurodevelopmental impairment of their progeny at 10 months after delivery. Therefore *screening of pregnant* mothers for clinical and subclinical hypo-thyroidism which is based on *second trimester elevated* maternal TSH has been proposed (Moreale de Escobar, G 2000)

d. There most recent report indicates that iodine nutrition is shifting to higher level despite 'cosntant' TGR and 'the WHO criteria of 90% household iodized salt consumption still un-met'

e. Level of iodine fortification in salt (e.g. 30 ppm) should be reevaluated.

Strength and weaknesses of Indonesian IDD Control Program

The Strength. The existence of political commitment to continue the IDD-CP, the existing regional goiter map which is updated, the existing Presidential Decree and Inter-Ministerial Decree

and Commitments on iodized salt regulation and the good collaboration between Dept of Health and researchers – universities.

In order to have a referral center for IDD and IDD control program especially in Indonesia, IDD Center (Pusat GAKY) was established in 2001. The site of the center is in Semarang, in the same site of internationally acknowledged IDD Laboratory. The mission of the center is to develop expertise and support facilities of all IDD related issues, to support national IDD control in Indonesia, and collaborate with all stakeholders in Indonesia and other countries in virtually eliminating IDD. The board of the center consists of all experts and interest scientists in IDD from all universities and research centers in Indonesia. A scientific journal on IDD and other information and communication system are developed to meet the mission, annual IDD seminar is organized. In the latest Final Evaluation of IIDC Project (Intensified Iodine Deficiency Project), the Center together with IDD laboratory take significant task.

The RAN-KPP-GAKY (2005) as an intersectoral guideline for programmer, policy makers, implementors, iodized salt producers has been published recently.

The Weaknesses. Geographical condition of an archipelago like Indonesia, the diverse cultural pattern that dictates various preferences of type of food and salt, public awareness on IDD is not adequate, there are many locally produced salt of different quality that involve poor farmers with their specific socioeconomic problems, and the early stage of decentralization which make difficult to develop and disseminate standardized strategy for IDD elimination.

The decentralisation system adopted requires more cooperation and coordination at the kabupaten – provincial and national level.

RECOMMENDATION

USI should be given priority especially in prominent salt producing provinces. Intensive enforcement and control should be given for guarantee only iodized salt is distributed in non-producing provinces, especially those which still keep IDD endemic pocket. Imported or inter-island salt for consumption should be iodized at the focal pouint before distribution, or it should be iodized earlier. Program and human impact must be monitored regularly. Since in our study urinary iodine excretion is the most appropriate outcome indicator for iodine deficiency at field conditions at district level (Pardede 1998), IDD Center with its IDD lab may support this program.

Appropriate iodized salt production technology should be available to the *poor* farmers or to groups (cooperative) to enable them to produce better salt to be iodized and lengthen the retrievement period to improve the selling price. In this case the Ministry of Industry and Commerce has tremendous heavy task to cope with the problem to attain the goal in 2010. Law enforcement must be endorsed.. Social enforcement should be taken into account.

It seems that iodinated oil still have some functions in the IDD control program to cover pregnant and nursing women as well as child bearing age women. In the meantime people's awareness through all kinds of media must be enhanced

Since iodine deficiency is equal to intellectual capacity loss, and since treatment is relatively *easy*, and iodine leached soil will not be replaced within centuries, the prevention program is a lifelong effort and iodine nutrition monitoring is mandatory.

ACKNOWLEDGMENT

We would like to thanks Professors Dr Andries Querido (passed away Jan 2001), Basil S Hetzel, F Delange, John Dunn (passed away 2004) and many others who showed their interest and support in stimulating the work of IDD eradication program in Indonesia. Thanks are also due to the former and present officials of the Dept of Health Republic of Indonesia who were responsible for the IDD prevention project. Friends members of the Indonesian IDD Group and IDD Workgroup Diponegoro Medical Faculty , Iodine Reference Lab Diponegoro University and some NGO's who had worked hard do far.

REFERENCES

References are available on request (directed to the Organizing Committee)

Statement Regarding Iodine Deficiency:

We note the progress toward eliminating iodine deficiency disorders (IDD) in all parts of the world in reports from the World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and the International Council for Control of Iodine Deficiency Disorders (ICCID.D);

REFERENCES

1. *Ares S, Escobar-Moreale HF Quero J et al.* Neonatal hypothyroxinemia:effects of iodine intake and prema ture birth. J Clin Endcinol Metab 82 ; 1704-12, 1997
2. *Bambang - Hartono.* Minimal Brain Damage (MBD) dan Gangguan Akibat Kurang Iodium (GAKI). (Minimal brain damage and IDD). Editors Djokomoeljanto, Darmono, Tony Suhartono : III National Thyroid Meeting, Semarang 1996, page 37.
3. *Bambang – Hartono.* The influence of iodine deficiency during pregnancy on neurodevelopment from birth to two years. Academisch proefschrift. Sept 5, 2001, Free University , Amsterdam.
4. *Benny Kodyat, Djokomoeljanto, Darwin Karyadi, Tarwotjo, Muhilal, Husaini andAsmira Sukaton* Micronutrient Malnutrition. Intervention program. An Indonesian experience. Min of Health, Dir Gen Community Health, Directorate of Community Nutrition 1991.page 26
5. *Bleichrodt N, Garcia I, Rubio C et al.* Developmental disorders associated with severe iodine deficiency. The prevention and control of Iodine Deficiency Disorders. Ed:BS Hetzel, JT Dunn and JB Stanbury. Elsevier 1987, page 65
6. *Bleichrodt N, Born M Ph.* A metaanalysis of research on Iodine and Its relationship to cognitive development. The damaged brain of iodine deficiency. Ed JB Stanbury Cognizant Communication Co , New York, Sydney Tokyo , 1994, page 195.

7. *Boyages S.* The damaged brain of Iodine deficiency: evidence for a continuum of effect on the population at risk. 1994, Idem , page 251.
8. *Calvo RM, Juaniaux E, Gulbis B et al. Fetal tissues are exposed to biologically relrvant free thyroxine concentrations during early phases of development. J Clin Eendocrinol Meta 87; 1768-1777, 2002*
9. *Cao XY, Jiang XM, Dou ZH et al.* Timing of vulnerability of the brain to iodine deficiency in endemic cretinism . N Engl J Med 1994 ; 331 : 1739.
10. *Choufoer JC, van Thijn M, Querido A.* Endemic goiter in Western New Guinea : II. Clinical picture , incidence and pathogenesis of endemic cretinism. J Clin Endocrinol Metab 25, 385, 1965.
11. *Cobra C, Muhilal , Rusmi K et* al. Infant survival is improved by oral iodine supplementation. J Nutr 127 ; 574-578, 1997
12. *Contempre B, Many MC, Vanderpas J, Dumont JE.* Interaction between two trace elements: selenium and iodine. Implications of both deficiencies.in :The damaged brain of iodine deficiency. Cognitive, behavioral, neuromotor and educative aspects. Ed JB Stanbury. Cognizant Commuincation Corporation, New York Sydney Tokyo 1994, page 133.
13. *Delange FM.* Relation of thyroid hormones to human brain development. In: Fetal brain disorders- recent approaches to the problem of mental deficiency. Eds. BS Hetzel, RM Smith, CSIRO Adelaide, Elsevier Nort h Holland, 1981, page 285
14. *Delange F.* Anomalies in physical and intellectual development associated with severe endemic goitre. In: JT Dunn et al (editors): Endemic goiter, cretinism and iodine deficiency.PAHO Scientific Publ. No 502, Washington DC, 1986 : page 49-67.
15. *Delange F.* Effect of maternal thyroid function during pregnancy on fetal developmment. In "The Thyroid And Pregnancy" International MERCK – Symposium in Brussels 1991, Eds: C Beckers and D. Reinwein. Schattauer Stuttgart – New York, 1991.
16. *Delange F.* Screening for congenital hypothyroidism used as an indicator of the degree of iodine deficiency and its control. Thyroid, 1998 ; 8 : 1185.
17. *Delange F.* Neonatal thyroid screeing as monitoring tool for the control of iodine deficiency. Acta Paediatr Suppl 432 : 21-24, 1999
18. *Delong RG.* The effect of iodine deficiency on neuromuscular development. IDD Newsletter, August 1990.
19. *Delong GR.* Observation on the neurology of Endemic cretinism. In Iodine and the Brain. Editors: Delong, Robbins and Gondliffe. Plenum Press New York, 1989 page 231.
20. *De Nayer, Dozin B.* Thyroid hormones and the brain. in the Thyroid and Tissues. Merck European Sympsosium Strasbourg 1994, eds: Orgiazzi J, Leclere J, Hostalek U. Scattauer 1994
21. *Dept of Health*, Jakarta 1992. Guidelines for the distribution and dose of yodiol capsules.
22. *Departemen Kesehatan* - Badan Pusat Statistik. Hasil Survei Konsumsi Garam Yodium Rumah Tangga 1998. Badan Pusat Statistik dengan Departemen Kesehatan ,Jakarta Agustus 1998.
23. *Departemen Kesehatan RI.* Laporan Akhir. Bantaun Tehnis untuk Studi Evaluasi Proyek Intensifikasi Penanggulangan Gangguan Akibat Kekurangan Yodium (IP-GAKY). 2005
24. *Dini K Latief.* Program of the Elimination of Iodine Deficiency Disorders. Towards the absence of newbom cretins by the year 2000 in Indonesia. 1st Workshop on Measures Against Iodine Deficiency Disorders, Japan International Corporation of Welfare Services, Tokyo Dec 1997
25. *Dini K Latief MSc.* Program Intensifikasi Penanggulangan Gangguan Akibat kekurangan Yodium di Indonesia, Disajikan pada Konsultasi Managemen GAKY Regional III di Bukitttinggi, Sumatera Barat, 1 Febr, 2000.
26. *Djokomoeljanto R.* The effect of severe iodine deficiency : a study on a population in Central Java Indonesia. Doctoral dissertation, Diponegoro University Semarang Indonesia, 1974.
27. *Djokomoeljanto R.* Goiter mapping and IDD in Central Java. Media Medika Indonesiana (1997) 32: 1.
28. *Djokomoeljanto R,* Setyawan H, Dramaix M, Hadisaputro S, Soehartono T, Delange F. The Thyromobil model for standardized evaluation of Iodine Deficiency Disorder Control in Indonesia. THYROID ; 11 : 365, 2001.
29. *Djumadias A, Latinulu S, Sumarno I, Syafrudin, Sudjono M.* Studi Penilaian terhadap Gangguan Akibat Kekurangan Iodium di propinsi Jawa Barat, 1996.
30. *Escobar GM de , Obregon MJ, Calvo R, Escobar del Rey F.* Effects of iodine deficiency on thyroid hormone metabolism and the brain fetal rats:role of the matemal transfer of thyroxin. Am J Clin Nutr Suppl; 57:280 S, .1993.
31. *Escobar GM de, Obregon MJ, Escobar del Rey.* Is neurophysiological development related to maternal hypothyroidism or to matemal hypothyroxinemia ? J Clin Endocrinol etab 85; 3975, 2000
32. *Escobar GM, Escobar del Rey F.* Consequences of Iodine Deficiency for Brain Development. In: The Thyroid and Brain. Eds. Morreale de Escobar, de Vijlder, S Butz and U Hostalek. Merck European Thyroid Symposium, Seville, May 30, 2002 Scahattauer 2003 page 33..
33. *Glinoer D, Delange F.* The potential Repercussions of Maternal , Fetal and Neonatal Hypothyroxinemia on The progeny. Thyroid 10: 871, 2000

34. *Goslings BM, Djokomoeljanto R, Hoedijono R, Soepardjo H, Querido A.* Studies on hearing loss in a community with endemic cretinism in Central Java, Indonesia. Acta Endocrinol (Copenh) 1975 : 78(4) : 705
35. *Goslings BM,Djokomoeljanto R, van Hardeveldt et al.* Hypothyroidism in an area of endemic goiter and cretinism in Central Java, Indonesia. J Clin Endocrinol Metab,44:481, 1977.
36. *Halpern JP.* The neuromotor deficit in endemic cretinism and its implications for the pathogenesis of the disorder. The Damaged Brain of Iodine Deficiency, Ed JB Stanbury, Cognizant Communication Co. New York Sydney Tokyo 1994 page 15.
37. *Heindel JJ, Zoeller RT.* Thyroid hormone and brain development : translating molecular mechanisms to population risk. Guest Editorial. THYROID, 13 : 1001, 2003
38. *Hetzel BS.* A review of the control program for endemic goitre and endemic cretinism. First National Seminar on Endemic Goiter and Cretinism. Diponegoro Medical School – Dr Kariadi Hospital, Semarang Dec, 1978 page 176.
39. *Hetzel BS and Querido A.* Iodine deficiency, thyroid function and brain development. In: Endemic Goiter and endemic Cretinism. Iodine Nutrition in Health and Disease. Eds JB Stanbury and BS Hetzel. A Wiley Med Public John Wiley & Sons Inc, 1980, page 461
40. *Hetzel BS.* Historical developments of the concepts of brain-thyroid relationship. in: The damaged brain of iodine deficiency.Ed:JBStanbury. Cognizant Communication Corp. New York-Sydney-Tokyo, 1994, page1
41. *Hume R, Simpson J, Delahunty C et al.* Human Fetal and cord serum thyroid hormones: developmental trends and interrelationships. J Clin Endocrinol Metab 89 ; 4097-4103, 2004
42. *Jones SA, Thoemke KR, Anderson GW.* The role of thyroid hormone in fetal and neonatal brain development . Curr Opin Endocrinol Diabetes 12 : 10-16, 2005.
43. *Leonard JL.* Regulation of T3 production in the brain. 4th Thyroid Symposium Brain and Thyroid, Graz-Austria, Acta Medica Austriaca, 1992, Sonderheft1, vol 19: page 5
44. *McMichael AJ, Porter JD, Hetzel BS.Iodine Deficiency,Thyroid Function and Reproductive Failure.* In: Endemic Goiter and Endemic Cretinism, eds. Stanbury and Hetzel. John Wiley and Sons, 1980, p 445.
45. *Meinhold H, Campos-Barros A, Behne D.* Effects of selenium and iodine deficiency on iodothyronine deiodinases in brain, thyroid and peripheral tissue, 4th Thyroid Symposium Brain and Thyroid, Graz-Austria, Acta Medica Austriaca, 1992, Sonderheft1, vol 19: page 8
46. *Muhilal et al.* Final Report. National Survey for Mapping of Iodine Deficiency Disorders (IDD). Collboration between Nutrition Research an d Development Centre and Directorate of Community Nutrition, Ministry of Health. 1998.
47. *Obregon MJ, Calvo RM, Escobar del Rey F et al.* Thyroid hormones and fetal development. In The Thyroid and Age. Merck Symposium , Italy 1998. Schattauer Stuttgart New York 1998 page 49
48. *Oppenheimer JH, Schwatrz.* Molecular basis of thyroid hormone-dependent brain development. Endocrine Reviews, 18 : 462-475, 1997
49. *Pharoah POD. Delange F, Fierro-benitez , Stanbury J, Endemic cretinism.* in Endemic Goiter and Endemic Cretinism.Iodine Nutrition in Health and Disease. ed: JB Stanbury, BS Hetzel. John Wiley and Sons Inc , 1980, page 395.
50. *Porterfield SP, Hendrich CE.* The role of thyroid hormones in prenatal and neonatal neurological development, current perpectives. Endocrine Review 1993 ; 14 : 94-106.
51. *Potter BJ, McMichael AJ, Hetzel BS.*Iodization and thyroid status in relation to stillbirths and congenital anomalies. Int J Epiodemiol 1979; 8 : 137.
52. *Querido A.* History of iodine prophylaxis with regard to cretinism and deaf-mutism. In: Human Development and the Thyroid Gland.Relation to Endemic Cretinism. Ed JB Stanbury and L Kroc. Plenum Press, 1972, page 191
53. *Querido A, Bleichrodt N, Djokomoeljanto R.* Thyroid hormones and Human Mental Development. in Maturation of the Nervous System, Progress in Brain Research, vol 48, edited by MA Corner et al. Elsevier North Holland Biomedical Press, page 337, 1978.
54. *Rachmi-Untoro.* Summary of IDD Program in Indonesia. Regional Consultation to Promote Sustainaable IDD Program in SEAR and EMRO, Chiang Mao, Thailand June 2003.
55. *Rajatanavin R, Kewali Unachak, Pradit Winichakoon et al.* Neonatal Thyrotropin profile as an index for severity of iodine deficiency and surveillance of iodine prophylactic program. Thyroid, 1997; 7: 599.
56. *RAN-KPP-GAKY.* Rencana Aksi Nasional Kesinambungan Program Penanggulangan Gangguan Akibat Kurang Yodium. Tim Penanggulangan GAKY Pusat Jakarta, DirJen Binkesmas, Departemen Kesehatan RI, 2005
57. *Reuss ML, Paneth N, Pinto-Martin JA et al.* The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age. N Engl J Med 1996 ; 334 : 821-7
58. *Sullivan KM, May W, Nordenberg et al.* Use of thyroid stimulating hormone testing in newborns to identify iodine deficiency. J. Nutr. 127 : 55-58, 1997.

59. *Tarwotjo , Maspaitella F, Soekimo H, Spedarjono, Djokomoeljanto.* Goiter prevalence among school age population in endemic areas of Central Java, Indonesia/ 2nd Asia Oceania Thyroid Assosiaction Meeting, Tokyo, 1982.
60. *Thilly C, Lagasse R, Roger G et l.* Impaired fetal and post natal development and high perintal death rate in a severe iodine deficient area, Thyroid Research VIII, Proc 8th International Congress of Thyroid , Sydney 1980, page 20.
61. *Untoro J.* Use of oral iodized oil to control iodine deficiency in Indonesia. PhD dissertation. Agriculture University, Wageningen, Holland, Febr 17, 1999.
62. *Vanderpas JB, Contempre B, Duale NI et al.* Iodine and selenium deficiency associared with cretinism in northern Zaire. Am J Clin Nutr 52: 1087, 1990.
63. *Vermiglio F, Lo Presti VP, Moleti M et al.* Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency : a possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab 89 ; 6054-6060, 2004.
64. *Vulsma T, Gons MH, de Vijlder JJM.* Maternal-fetal transfer of thyroxin in congenital hypothyroidism due to a total organification defect or thyroid agenesis. N Engl J Med 1989 ; 321 : 549-555.
65. *WHO/NHD/01.1* Assessment of Iodine Deficiency Disorders and Monitoring thir Elimination. A guide for programme managers. 2nd edition. ICCIDD, Unicef, WHO, 2001.
66. *Wijaya, Kamilah BR, Moh Effendi.* Electroencepahlographic pattems of children in a severe goiter area afterlipiodol injection. First National Seminar on Endemic goiter and cretinism, Semarang 1978, p.164.
67. *Yasin F.* Evaluation f an iodization programs inpregnant women and their babies in Dukun district, Central Java. Thesis submitted to the University of Western Australia for the degree of M.Med.Sc, 1989.
68. *Zimmermann MB, Kohrle J.* The impact of iron and selenium deficiencuies on iodine and thyroid metabolism: biochemistry and relevance to public health. THYROID ; 12 : 867, 2002
69. *Zoeller RT.* Thyroid hormones and brain development: environmental influences. Curr Opin Endocribnol Diabetes 12 : 31-35, 2005.

We recognize and affirm the need for national priority attention in each country to achieve the goal of virtual elimination as recommended by the United Nations Special General Assembly on Children;

We are concerned that Iodine Deficiency remains a serious public health problem in many places as a major threat to preventable brain damage to millions of children, as well as threats of cretinism, miscarriage, stillbirth, and physical impairment;

We strongly support the effort to achieve Universal Salt iodization because regular iodine consumption constitutes one of the most cost-effective public nutrition interventions, contributing to economic and social development;

We recognize that still one-third of the global population remains at risk, mostly in the poorest and economically least developed areas of the world;

We commend the work of the World Health Organization, the United Nations Children's Fund and ICCIDD in the global effort to initiate, improve and support national programs for the virtual elimination of Iodine Deficiency and Kiwanis International for its steadfast financial and other support to those efforts;

We strongly support the World Health Assembly (WHA) Resolution calling for additional political commitment, improved national oversight and monitoring, and improved reporting on iodine nutrition status; and

Further, we request all of the Members of the International Thyroid Association become associated with and support the National Committee formed in each country for oversight, public reporting and monitoring of progress;

Therefore, we call upon all Members, national and international, to seek collaboration with national leaders of iodination programs in order to achieve the goal of virtual elimination of Iodine Deficiency.

Buenos Aires, October 31, 2005

American Thyroid Association President — Paul W. Ladenson

European Thyroid Association President — Wilmar M. Wiersinga

Asia and Oceania Thyroid Association President — Bo Youn Cho

Latin American Thyroid Society President — Doris Rosenthal

REFERENCES

1. *Ares S, Escobar-Moreale HF Quero J et al.* Neonatal hypothyroxinemia:effects of iodine intake and prema ture birth. J Clin Endcinol Metab 82 ; 1704-12, 1997
2. *Bambang - Hartono.* Minimal Brain Damage (MBD) dan Gangguan Akibat Kurang Iodium (GAKI). (Minimal brain damage and IDD). Editors Djokomoeljanto, Darmono, Tony Suhartono : III National Thyroid Meeting, Semarang 1996, page 37.
3. *Bambang – Hartono.* The influence of iodine deficiency during pregnancy on neurodevelopment from birth to two years. Academisch proefschrift. Sept 5, 2001, Free University , Amsterdam.
4. *Benny Kodyat, Djokomoeljanto, Darwin Karyadi, Tarwotjo, Muhilal, Husaini andAsmira Sukaton* Micronutrient Malnutrition. Intervention program. An Indonesian experience. Min of Health, Dir Gen Community Health, Directorate of Community Nutrition 1991.page 26
5. *Bleichrodt N, Garcia I, Rubio C et al.* Developmental disorders associated with severe iodine deficiency. The prevention and control of Iodine Deficiency Disorders. Ed:BS Hetzel, JT Dunn and JB Stanbury. Elsevier 1987, page 65
6. *Bleichrodt N, Born M Ph.* A metaanalysis of research on Iodine and Its relationship to cognitive development. The damaged brain of iodine deficiency. Ed JB Stanbury Cognizant Communication Co , New York, Sydney Tokyo , 1994, page 195.

IODINE DEFICIENCY IN INDONESIA

PAST, PRESENT AND FUTURE

R. Djokomoeljanto

Dept of Medicine, Diponegoro University/Dr Kariadi Hospital
IDD Center Semarang Indonesia

1. The clinical impact of IDD
2. Previous efforts and intervention
   3.1. Salt iodization and legislation
   3.2. Iodinated oil injection and capsules
   3.3. Other measures
4. Evaluation and monitoring
5. Condition in 2006
6. What next ?

THE CLINICAL IMPACT OF IODINE DEFICIENCY

Iodine Deficiency Disorders are spectrum of disorders that disappear with correction of iodine deficiency.

Spectrum of Iodine Deficiency Disorders

Fetus	Abortions, Stillbirths, Congenital abnormalities, Increased perinatal mortality, Increased infant mortality, *Neurological cretinism*:mental def, deaf mutism, spastic diplegia, squint *Myxedematous cretinism*: dwarfism , mental deficiency, hypothyroidism Psychomotor defects
Neonate	Neonatal goiter, Neonatal hypothyroidism increased susceptibility to nuclear radiation
Child and adolescent	Goiter , Juvenile hypothyroidism Impaired mental function, Retarded physical development, Increased susceptibility to nuclear radiation *
Adult	Goiter with its complications, Hypothyroidism , Impaired mental function, Iodine induced hyperthyroidism, Increased susceptibility to nuclear radiation *

* Due to increased uptake of radioactive iodine.

ENDEMIC CRETINISM

1. Epidemiological aspect ~ *iodine deficiency*
2. Clinical aspects ~ *neurological and myxedematous*
3. Pathologic aspects ~ *intrauterine and irreversible*

Endemic cretinism

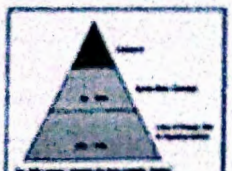
a. Neurological endemic cretinism
Mental retardation, deaf-mutism
Hearing loss bilateral perceptive
spastic diplegia, squint etc

b. Myxedematous endemic cretinism
Dwarfism, mental retardation,
hypothyroidism

Hypothyroidism

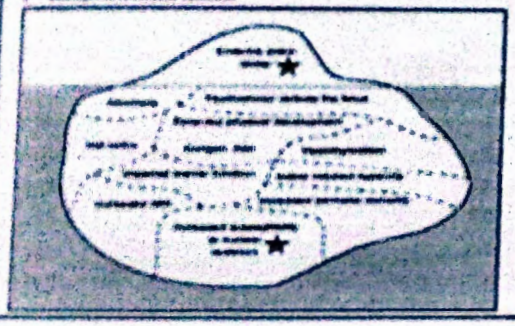
Clinical hypothyroidism
- 20% in cretins
- 17% in non cretin population

Biochemical hypothyroidism
- 21% in cretins
- 57% in non cretin population



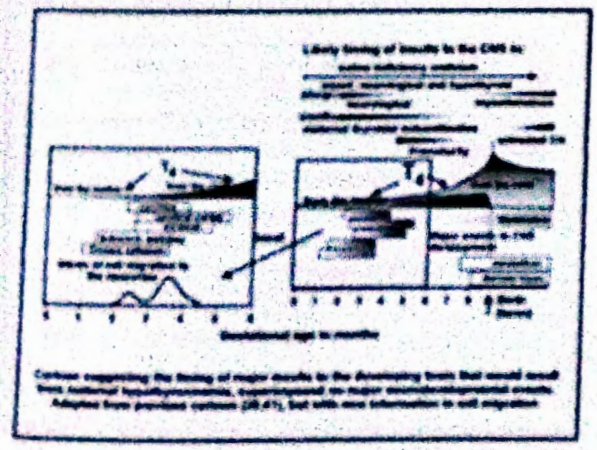
Spectrum of IDD:

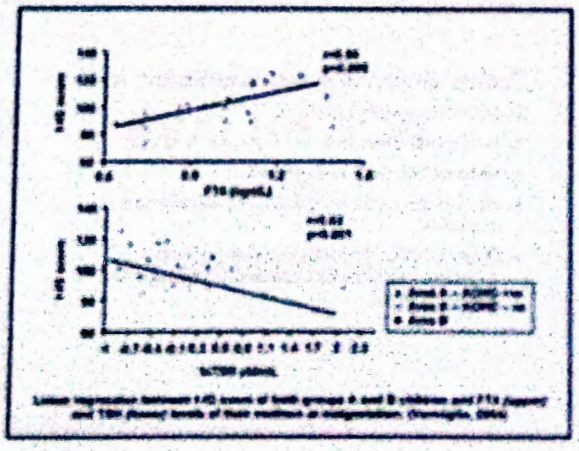
- Endemic goiter and cretinism
- Goiter phenomenon
- Susceptible to nuclear radiation

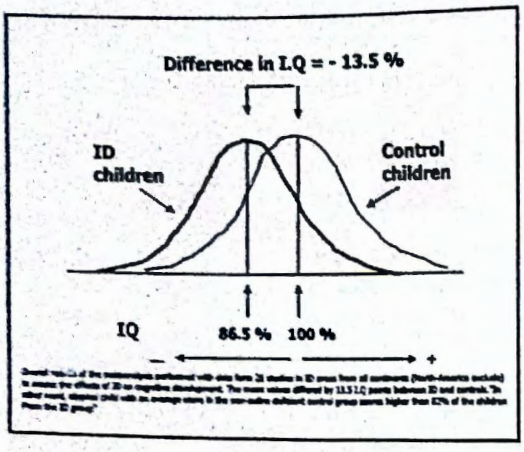


Critical periods

1. *Critical period phase late* in gestation extending through 1-2 yr of age
2. Deficiencies of thyroid hormones during this time → serious structural development / organizational damage
3. Replacement therapy begun subsequent to this time *can never entirely* correct the damage
4. *Hypothyroxinemia* : of pregnant women is the level of T4 that below the normal range of women in the same trimester of pregnancy, whether or not 'clinical hypothyroidism' was evident

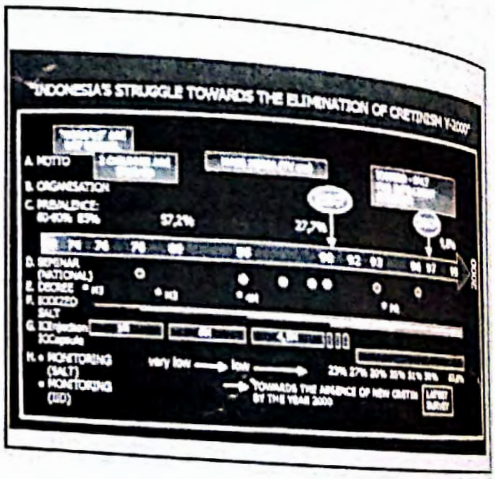






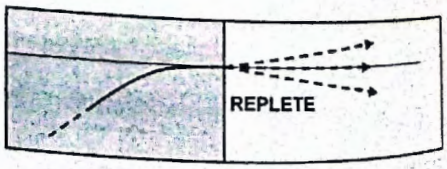
PREVIOUS EFFORTS AND INTERVENTION PROGRAMS

Prevention programs:
Social process involved in a national IDD control programme



Iodine deficiency may corrected with :

a. Life style modification
b. Nutritional change
c. Intervention with iodized salt
d. Intervention with iodinated oil (injection or capsule)
e. Other routes (fish soya, Iodine with other vehicles, iodated well, iodated drinking water or tap water etc)



CRITERIA :
Total Goiter Rate ?
Urinary Excretion of Iodine ?
Thyroglobulin concentration ?
TSH ?
Thyroid volume ?

Which criteria are used ?

- the disappearance of IDD ? iceberg phenomenon

- non endemia ?
  - classification WHO 1994 / WHO 2001
  - TGR ? (classical - clinical – palpation – USG / thyroid volume)
  - UEI ? (median value and proportion)
  - Neonatal TSH ?
  - Serum Tg and UEI ?
  - Combination

Indicator for the severity of IDD as a public health problem

Indicator	Severity of public health problem: Non endemia	Mild	Moderate	Severe
Goiter – palpation > 0	< 5%	5.0 – 19.9%	20.0 – 29.9%	>30%
USG > 97th percentile	< 5%	5.0 – 19.9%	20.0 – 29.9%	>30%
Median UEI (µg/L)	> 100	50-99	20 – 49	< 20
TSH > 5 µU/ml whole blood	< 3%	3.0– 19.9%	20.0 – 30.9%	>40.0%
Median Tg (ng/ml)	< 10	10.0-19.9	20.0 – 39.9	> 40

Criteria to monitor progress towards eliminating IDD as a public health problem

Indicator	Goal (WHO 1994) significant as a public health problem	Goal (WHO 2001) sustainable elimination of problem
Salt indication proportion household consuming effective iodized salt	> 90 %	> 90 %
Urinary iodine Proportion < 100 µg/L Proportion < 50 µg/L	< 50 % < 20 %	< 50 % < 20 %
Thyroid size in school – children age 6-12 years	< 5 %	–
Neonatal TSH proportion with TSH > 5 µU/ml	< 3 %	–
Programmatic indicators attainment	–	at least 8 out of 10 indicators

Proportion of UEI - Filter - IE consumption - sustainability

INTERVENTION EFFORTS

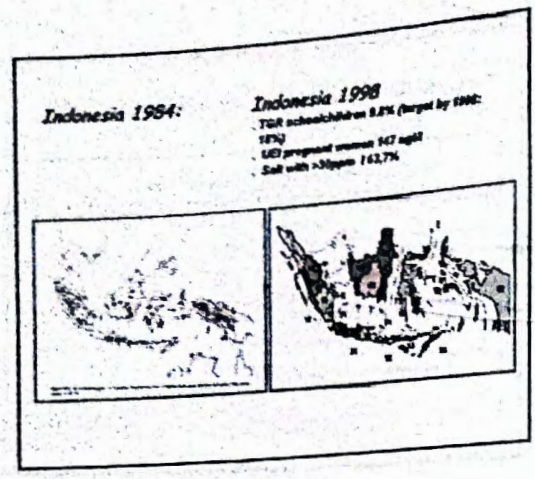
- IODIZED SALT
- IODINATED OIL , ORAL OR INJECTION
- OTHER METHODS

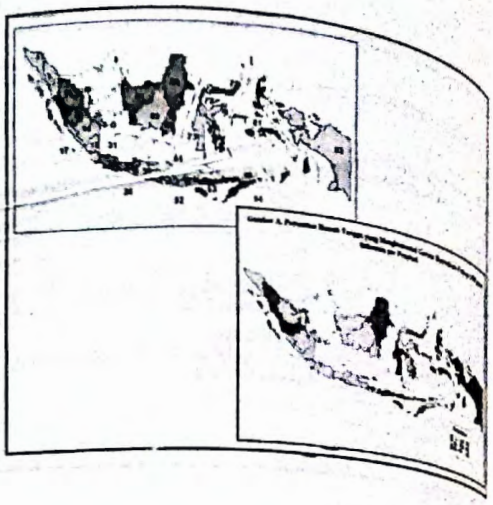
- AWARENESS, INVENTING NEEDS, ORGANIZATION, STUDIES, MONITORING AND EVALUATION

For Indonesia it is huge efforts, due to

a. number of population
b. geographical distribution
c. archipelago with > 10000 islands
d. many possible entries for non iodized salt
e. lack of awareness
f. many simultaneous national problems
g. does *not kill* people
h. etc

EVALUATION AND MONITORING





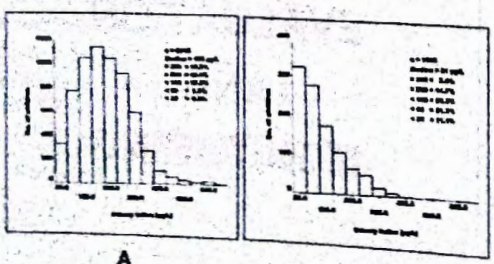
Results of National IDD Mapping Survey 1998 (Dept of Health)

TGR schoolchildren	9.8 %
TGR pregnant women	16.0 %
Median UEI pregnant women	147.0 ug/l
50 – 99 ug/l	13.0 %
≥ 100 ug/l	72.0 %
Median TSH pregnant women	4.0 uU/ml
≥ 5 uU/ml	30.0 %
Iodine in salt > 30 ppm	64.0 %
No iodine in salt	11.0 %
Intelligence damage (IQ points loss)	130.793.313

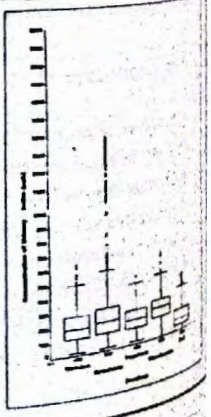
ThyroMobil project Indonesia

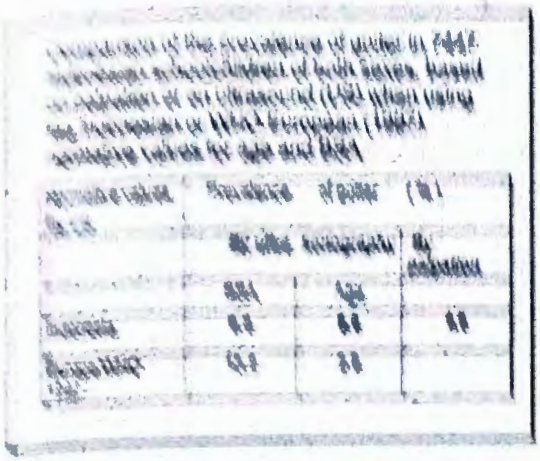
The distribution of UEI in Java and Sumatra (A) and in Bali (B)

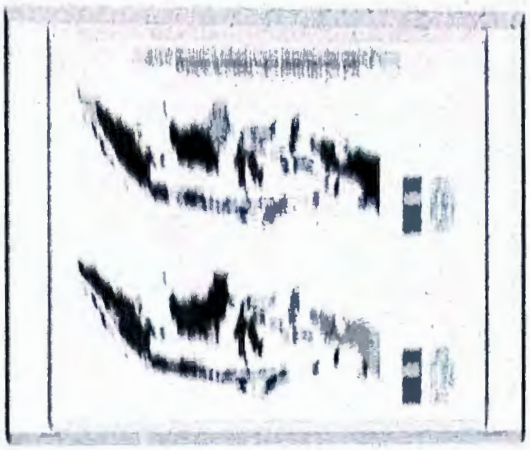
Mind the proportion of excessive UEI !

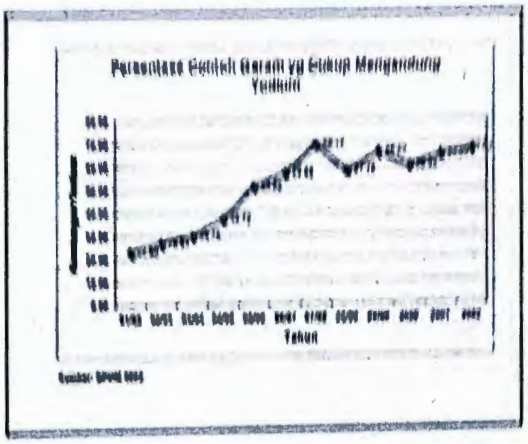


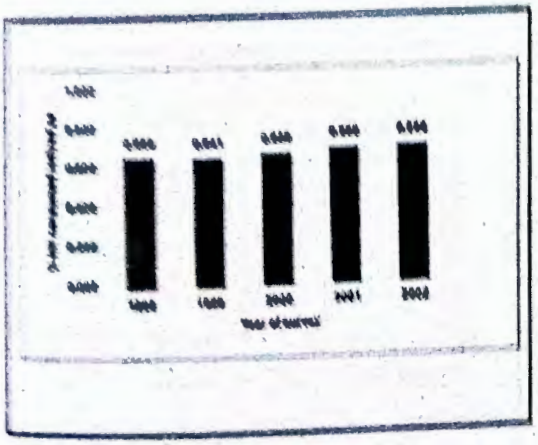
Box plot showing UEI in 5 provinces. Note individual values falling outside the range (P75) + 1.5 IQR *(interquatile range)* from Central Java (more precise : Sukohardjo)











Iodinated oil

Number of iodinated injection (lipiodol) given and its coverage

Plan (years)	Target	Total injections	% coverage
II (1974-1979)	1 036 000	1 036 000	100%
III (1979-1984)	6 484 000	5 930 010	91.5 %
IV (1984 - 1989)	5 672 000	4 466 000	78.8 %
Total	13 193 000	11 432 100	86.66 %

Benny Kosiyet et al. 1991

COVERAGE OF IODINATED OIL CAPSULES (Yodiol®) IN THE YEAR 2000

Item	WCBA	Pregnant W	Nursing W	Primary SC
Target	7.177.819	870.273	814.740	678.861
Distributed	4.385.609	756.683	660.720	668.444
Coverage %	60.8 %	86.9 %	81.3 %	83.9 %

Source : Directorate of Nutrition , MoH, Nov, 2001

IDD CONDITION IN 2005

Minimal Brain Damage in *newly replete* schoolchildren

Item	Sengi (n=30)	Tirtosari (n=30)	
UEI (ug/l) TSH (uU/ml) Body weight (kg) Height (cm) Dysarthria	188 (29-191) 2.8 (0.8-7.0) 24.8 138.3 23.3 %	184 (84-196) 1.3 (0.8-2.8) 26.1 128.7 0 %	P<0.05
IQ full scale IQ performance IQ verbal	76.8 79.9 77.2	87.6 87.8 86.8	P<0.05 P<0.05 P<0.05
MBD positive No MBD	73.3 % 26.7 %	23.3 % 76.7 %	P<0.05

...if control works

In replete areas:

Item	NIDA	RIA	IDA
UEI (median) ugUl(ch)	190	128-135	47-66
Goiter rate (ch)	0.1 %	4.3%	16-76%
Birth weight (neonates)	3740g	3690g	3040g
Neonates > 5uU/ml	-----	45 %	53%
Retarded reflex	3,2 %	17.2 %	29.2%

- Despite normal thyroid status , IQ differs significantly
- Despite normal thyroid status, MBD is still prevalent

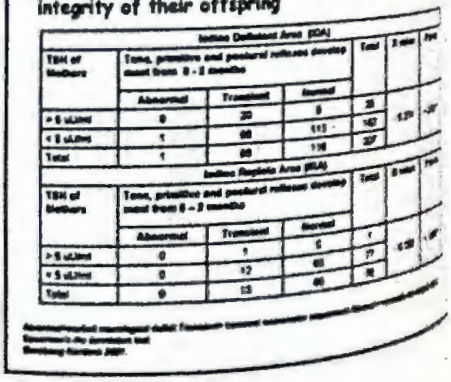
(Bandung Hariana 1999)

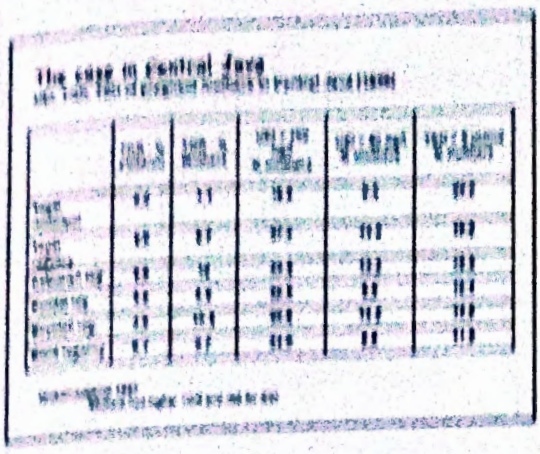
Iodine deficiency and pregnancy risks

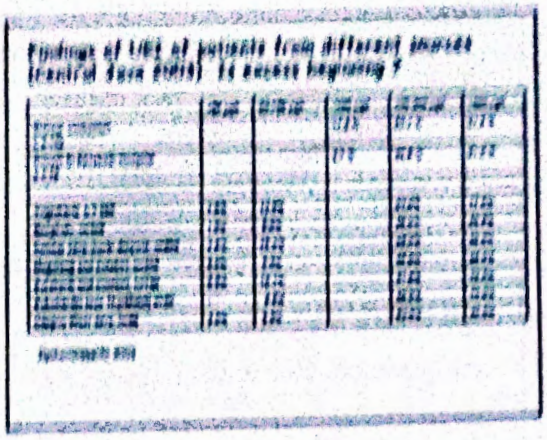
Pregnant women	IDA (n=249)	IRA (n=99)	p level
Iodine status , median UEI ug/dl TSH uU/ml (>5uU) TGR % T4 (>82 nmol/L)	44 1.88 (10.2%) 86.3 116 (12.6%)	78 1.15 (1.2%) 11.1 124 (2.5%)	< 0.01 ns (p < 0.01) < 0.01 ns (p < 0.01)
Spontaneous abortion Premature birth Stillbirth	14.7 % 7.8 % 2.6 %	6.1 % 1.0 % 1.0 %	< 0.05 < 0.05 ns
Oral iodinated capsules	26.5 %	53.8 %	< 0.01

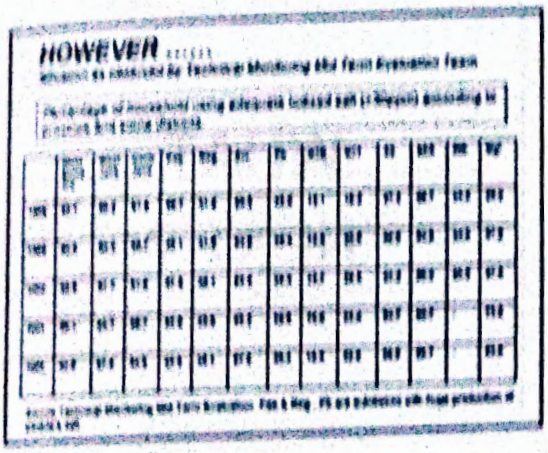
Bandung Hariana 2001

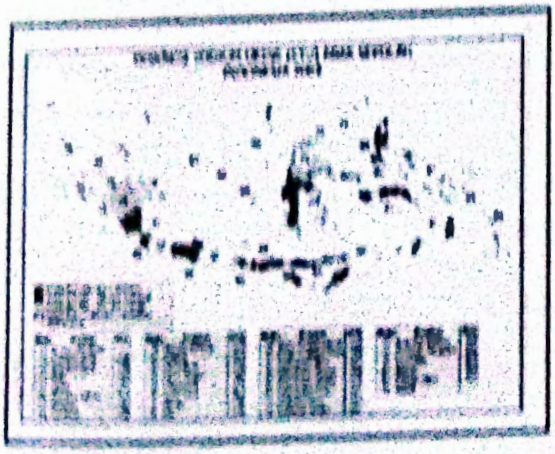
TSH of mothers and development of neurological integrity of their offspring

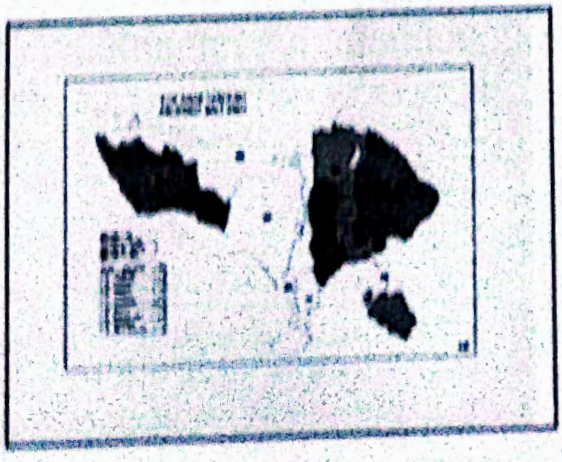












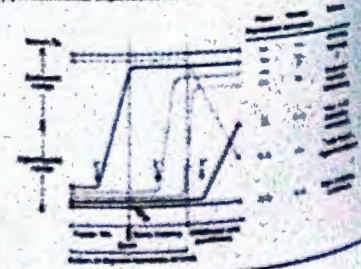
Contoh	Kadar Yodium		
	< 20 ppm	20 – 30 ppm	≥ 30 ppm
Rumah tangga n = 260	57,5 %	17,5 %	25,0 %
Ibu hamil n = 20	53,0 %	23,1 %	23,9 %

Results of National IDD Mapping Survey 1998 and 2003 (Dept of Health)

	1998	2003
TGR schoolchildren	8.3 %	11.0 %
TGR pregnant women	16.0 %	
Median UEI of children		229.6 ug/l
UEI < 100 ug/l		16.3 %
UEI > 300 ug/l		38.4 %
Median UEI pregnant women	147.6 ug/l	
50 – 99 ug/l	13.0 %	
> 100 ug/l	72.0 %	
Median TSH pregnant women	4.8 uU/ml	
≥ 5 uU/ml	36.0 %	
Iodine in salt > 30 ppm	64.0 %	91.4 %
No iodine in salt	11.0 %	
Intelligence damage (130.793.513 IQ points loss)		

WHAT NEXT ?

The fate of fetus as a function of iodine supply



Child Bearing Age Women ('WUS')
(Iodine Nutritional Status)

↓

Maternal Iodine Nutritional Status

↓

Fetal Iodine Nutritional Status

↓

Fetal Development
(Psycho – neuro – intellectual - physical)

Recommendations (1)

a. Priority for IDD prevention is not due to goitre but on its impact on physical – psycho – neurological - mental and intellectual impairment.
b. Iodinated capsule are still needed for special reasons and cases
c. Appropriate iodized salt technology for salt farmers
d. Law enforcement should be implemented
e. Special attention should be given to pregnant, nursing and child bearing age women
f. Evaluation and monitoring system based on UEI should periodically be organized , hence more IDD lab should be established
g. It is timely to reconsider the recommended iodine content of iodized salt

Recommendations (2)

h. Coast goiter in the Maluku and NTT must get special attention, including further studies on its pathophysiology and etiology
i. IDD team at the provincial and district level should be revived and stimulated
j. RAN-KKP-GAKY of 2005 may be used as guideline for organizing IDD control at the provincial and district level
k. Stress must be given that iodine deficiency is a long -lasting affair and efforts should be sustained.

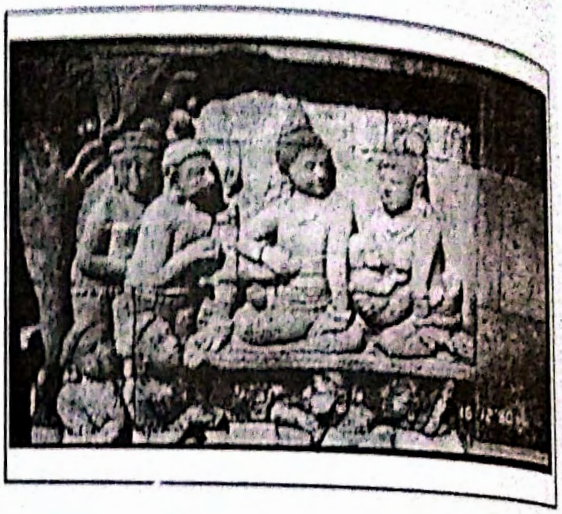
.....for the children.....

Every child has the right to an adequate supply of iodine to ensure his (or her) normal developments....

.....for the unborn child.....

Every mother has the right to an adequate iodine nutrition to ensure her unborn child experiences normal mental development

Declaration from
Convention on the Rights of the Child, UN Assembly, New York 1989, World Summit for Children, UN New York 1990, The Survival, Protection and Development of Children , World Conference on Micronutrients Eliminating the Hidden Hunger, Montreal 1991 (United, FAO,WHO, ICCIDD), World Conference on Nutrition, Rome 1992 WHO, FAO



Acknowledgement:

The late Prof Andries Querido and Prof John T Dunn
Prof Basil S Hetzel Adelaide, Prof F Delange Belgium

Officials Dept of Health : Dr Tarwotjo PhD, Prof Muhilal PhD, Dr Benny A Kodyat, Dr Dini Latief MSc, Dr Rachmi Untoro MSc, National and Provincal IDD Teams.

ICCIDD, Unicef and World Bank. Members of IDD Center and reference – IDD -- Lab Semarang.