

## Iodine and Neuropsychological Development<sup>1</sup>

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**ABSTRACT** The establishment of the essential link among iodine deficiency, thyroid function and brain development has emerged from a fascinating combination of clinical, epidemiologic and experimental studies. The central human phenomenon that focuses this relationship is the condition of endemic cretinism, described from the Middle Ages and characterized in its fully developed form by severe brain damage, deaf mutism and a spastic state of the hands and feet. The demonstration of the prevention of cretinism in a double-blind controlled trial with injections of iodized oil in Papua New Guinea (1966–1970) established the causal role of iodine deficiency in cretinism by an effect on the developing fetal brain. Cretinism could not be prevented unless the iodized oil was given before pregnancy. Iodine deficiency is now regarded by the WHO as the most common preventable cause of brain damage in the world today, with at least 30 million suffering from this preventable condition. Since 1986 the international NGO, the International Council for Control of Iodine Deficiency Disorders, has worked closely as an expert group with WHO and UNICEF in assisting countries with a program of universal salt iodization for the elimination of iodine deficiency as a cause of brain damage by the year 2000. In 1996, WHO reported that 56% of the population of 83 developing countries now had adequate access to iodized salt. This represents an increase of 750 million since 1990 with protection of 12 million children. *J. Nutr.* 130: 493S–495S, 2000.

**KEY WORDS:** • iodine deficiency • cretinism • goiter • fetus • human brain development

The establishment of the essential link between iodine deficiency, thyroid function and brain development has emerged over the past 20 years from a fascinating combination of clinical, epidemiologic and experimental studies. The central human phenomenon that focuses this relationship is the condition of endemic cretinism, a condition that was well known in Alpine Europe in the Middle Ages; it was mentioned in Diderot's Encyclopedia in 1754 and was of such importance as to warrant a special Commission set up by the King of Sardinia (who was also King of Savoy) in 1848. It was also reported by McCarrison in 1908 from the former N.W. Frontier Region of India, now Pakistan. The condition is characterized in its fully developed form by severe brain damage, deaf mutism and a spastic state of the hands and feet (Hetzel 1989).

### *Iodine deficiency as a cause of fetal brain damage*

The epidemiologic demonstration of the association of cretinism with goiter dates from the Sardinia Commission of 1848. This has been followed by many subsequent studies up to

the present time (Hetzel 1989). In general, cretinism is associated with higher rates of goiter (~30%) in a population (Pharoah et al. 1980). A decline in the prevalence of goiter and cretinism was noted by the Sardinia Commission in 1848. A further decline was apparent in the first half of the twentieth century in Switzerland in Cantons in which iodized salt had not been introduced and in Northern Italy. These observations raised doubt as to whether iodine deficiency was a significant causative factor in cretinism.

The demonstration of the prevention of cretinism in a double-blind controlled trial with iodized oil in Papua New Guinea established the causal role of iodine deficiency in cretinism by an effect on the developing fetus (Pharoah et al. 1971). Cretinism could not be prevented unless the iodized oil was given before pregnancy, i.e., an injection during pregnancy was ineffective. The apparent spontaneous disappearance of cretinism in Europe was attributed to an increase in iodine intake (in the absence of iodized salt) arising from dietary diversification with increasing use of iodine supplements as noted in Switzerland in the 1920s (Bürgi et al. 1990).

### *Mechanism of the effect of iodine deficiency on fetal brain development*

In 1971, the following three mechanisms were suggested for the effect of iodine deficiency on fetal brain development: 1) maternal hypothyroidism, 2) fetal hypothyroidism and 3) elemental iodine deficiency acting directly on the brain (Pharoah et al. 1971).

At that time, maternal hypothyroidism seemed an unlikely

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cause because no such syndrome as cretinism had been noted in children born to hypothyroid mothers; infants suffering from congenital hypothyroidism do not show the features of deaf mutism or neuromuscular defect seen in the common form of cretinism. This made elemental iodine deficiency an attractive hypothesis.

To investigate these various possibilities, an animal model was developed in sheep because of the access provided for both maternal and fetal thyroidectomy and previous experience with trace element deficiencies. Subsequently, a similar model was developed in the primate marmoset monkey (*Callithrix jacchus jacchus*) and in rats (Hetzel and Mano 1989).

Significant effects of iodine deficiency in slowing fetal brain development have been shown in all three species. In sheep and marmosets, there was reduction of brain weight and brain DNA, with histologic changes characterized by delayed maturation of the cerebellum and greater neurone density in the cerebral hemispheres (motor and visual areas). The effect was significant in the sheep from 70 d gestation, which suggests an effect on neuroblast multiplication that is known to occur at 40–80 d gestation (Hetzel and Mano 1989). These findings indicated an effect that could be significant in the pathogenesis of cretinism in humans.

Analysis of the mechanism involved in the sheep has shown a significant effect of maternal thyroidectomy (carried out 6 wk before pregnancy) on the brain at midgestation. There was also an effect at the end of gestation after fetal thyroidectomy at both 60 and 98 d, with a more severe effect after the earlier fetal thyroidectomy. The most striking effect has occurred after the double procedure. It was similar, but more severe than that observed in iodine deficiency associated with a greater reduction in maternal and fetal thyroid hormone levels than in iodine deficiency (Hetzel and Mano 1989).

It was concluded that both maternal and fetal thyroid hormones were involved in the effect of iodine deficiency on the fetal brain. This is now supported by evidence of placental transfer of maternal T4 in rats followed more recently by evidence in humans (Hetzel and Mano 1989).

There has been no support for the role of elemental iodine deficiency from the animal models. The effect of iodine deficiency in early gestation now appears to be due to maternal hypothyroidism with reduced T4 transfer across the placental barrier. However, an additional direct effect of iodine itself cannot be excluded from the existing data.

#### ***Quantitative estimates of the effect of iodine deficiency on brain function at the population level***

The term iodine deficiency disorders (IDD) has been generally adopted to denote the spectrum of diverse effects that result from iodine deficiency in a population, effects that are all preventable by correction of the iodine deficiency (Hetzel 1983). At all ages, the most common IDD is goiter, but the most important effect is on neuropsychological development. The adoption of the term IDD effectively reconceptualized the problem of iodine deficiency from goiter to one of impaired brain development and brain damage.

The major features of the IDD at the different stages of life are varying effects on brain function, which are characteristic of the effect of any environmental stimulus on a population. These states of altered brain function arise from fetal damage or hypothyroidism at various stages of life, i.e., fetus, neonate, juvenile and adult (Delange 1994).

There is much anecdotal evidence coming from long-standing observations in Europe supported by recent reports from China

and India, indicating that iodine-deficient village populations suffer from general lethargy, poor work performance and defective school performance in children. These effects are due to hypothyroidism, particularly cerebral hypothyroidism. Beneficial effects of iodization programs on this general lethargy (even the village dogs) have also been described (Hetzel 1989).

More quantitative data that indicate the effect of iodine deficiency on the brain function of a population are required. Various approaches have already been made which could be developed further (Hetzel et al. 1990, Hetzel 1994).

#### ***Cognitive development in iodine-deficient populations***

A recently published meta-analysis of available studies examined a total of 18 studies in which comparisons could be made between iodine-deficient populations and a suitable control population with a similar social and cultural background (Bleichrodt and Born 1994). These studies revealed that the mean scores for the iodine and noniodine deficient groups were 13.5 IQ points apart. These data further indicate the major population dimension of the effect of iodine deficiency on neuropsychological development.

#### ***Bridging the knowledge application gap: development of a global program for the elimination of brain damage due to iodine deficiency***

Iodine deficiency is now regarded by the WHO as the most common preventable cause of brain damage in the world today with at least 30 million suffering from preventable brain damage (WHO 1993). In 1985, a report on the prevention and control of IDD was made at the request of the United Nations system. The occurrence of a broad spectrum of IDD with >400 million people at risk in Asia as well as millions in Africa and South America was noted. Evidence was available from controlled trials and successful iodization programs that these disorders could be prevented successfully. But there was also evidence of a breakdown of the iodization program.

Although the basic requirement for a national iodization program is the availability of suitable technology in the form of iodized salt and iodized oil, it is only one element of an IDD control program. Analysis of the reasons for success and lack of success indicated the need for a multidisciplinary approach including assessment, communication, planning, political support, monitoring and evaluation. The effect of IDD had to be expressed in social terms, i.e., in terms of economic effect, impaired learning of school children and reduced quality of life. A multidisciplinary model for a national program was developed and has been subsequently adopted in many countries (Hetzel 1989).

In 1985, the establishment of an International Consultative Group (NGO) was recommended as a necessary step to provide multidisciplinary expertise for the international agencies and national governments with major IDD problems for the development of a more active IDD control program. The UN Nutrition Group approved this step at the Nairobi meeting in February 1985 and the following month the International Council for Control of Iodine Deficiency Disorders (ICCIDD) was established.

The ICCIDD was formally inaugurated in Kathmandu, Nepal in March 1986 with the support of the Director General of WHO and the Executive Director of UNICEF. The ICCIDD now comprises an international network of 450 multidisciplinary professionals from 82 countries.

Since 1986, the ICCIDD has worked closely with WHO and UNICEF in the establishment of a global program for the

elimination of IDD by the year 2000. An Action Plan was prepared for the ICCIDD and approved by the UN System and WHO in 1990. Subsequently, in 1990, the goal of elimination was accepted by the World Summit for Children at the UN. Since that time, the policy of Universal Salt Iodization (USI) was adopted and has proved remarkably successful throughout all regions of the world.

At the global level, WHO reported in 1996 that 56% of the population of 83 developing countries now has adequate access to iodized salt. This represents an increase of 750 million since 1990 with protection of 12 million children (WHO Fact Sheet 1996).

Achievement of the goal would eliminate an ancient scourge of mankind; the descriptions of goiter date back to 2500 BC in the ancient literature of India and China and cretinism to the Middle Ages (Hetzel and Pandav 1996).

### LITERATURE CITED

- Bleichrodt, N. & Born, M. P. (1994) A metaanalysis of research on iodine and its relationship to cognitive development. In: *The Damaged Brain of Iodine Deficiency* (Stanbury, J. B., ed.), pp. 195–200. Cognizant Communication Corporation, New York, NY.
- Bürgi, H., Supersaxo, Z. & Selz, B. (1990) Iodine deficiency diseases in Switzerland one hundred years after Kocher's survey: a historical review with some new prevalence data. *Acta Endocrinol.* 123: 577–590.
- Delange, F. (1994) The disorders induced by iodine deficiency. *Thyroid* 4: 107–128.
- Hetzel, B. S. (1983) The iodine deficiency disorders (IDD) and their eradication. *Lancet* 2: 1126–1129.
- Hetzel, B. S. (1989) *The Story of Iodine Deficiency: An International Challenge in Nutrition*. Oxford University Press, Oxford, UK.
- Hetzel, B. S. (1994) Historical development of the concepts of brain thyroid relationships. In: *The Damaged Brain of Iodine Deficiency* (Stanbury, J. B., ed.), pp. 1–7. Cognizant Communication Corporation, New York, NY.
- Hetzel, B. S. & Mano, M. (1989) A review of experimental studies of iodine deficiency during fetal development. *J. Nutr.* 119: 145–181.
- Hetzel, B. S. & Pandav C. S., eds (1996) *SOS for a Billion: The Conquest of Iodine Deficiency Disorders*. Oxford University Press, New Delhi, India.
- Hetzel, B. S., Potter, B. J. & Dulberg, E. M. (1990) The iodine deficiency disorders; nature, pathogenesis and epidemiology. *World Rev. Nutr. Diet.* 62: 59–119.
- Pharoah, P.O.D., Butfield, I. H. & Hetzel, B. S. (1971) Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet* 1: 308–310.
- Pharoah, P.O.D., Delange, F., Fierro-Benitez, R. & Stanbury, J. B. (1980) Endemic cretinism. In: *Endemic Goitre and Endemic Cretinism* (Stanbury, J.B. & Hetzel, B.S., eds.), pp. 395–421. Wiley, New York, NY.
- World Health Organization (1990) Report to 43rd World Health Assembly Geneva, Switzerland.
- World Health Organization (1993) Global Prevalence of Iodine Deficiency Disorders. WHO/UNICEF/ICCIDD Micronutrient Deficiency Information System (MDIS Working Paper #1). WHO, Geneva, Switzerland.
- World Health Organization (1996) Iodine Deficiency Disorders. WHO Fact Sheet No. 121. WHO, Geneva, Switzerland.