THE CONQUEST OF IODINE DEFICIENCY: A SPECIAL CHALLENGE TO AUSTRALIA FROM ASIA

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Summary

There is now evidence that over one billion people living where the soil has been leached of iodine in mountains and flooded valleys, are at risk of iodine deficiency disorders (IDD). Of these, 200 million have goitre and 20 million are suffering from brain damage due to the effects of iodine deficiency in pregnancy and infancy. In the past 30 years there have been notable developments in knowledge and action to which Australians have made a significant contribution. New technology for the correction of severe iodine deficiency in Papua New Guinea by the injection of iodised oil (up to 5 years) and the demonstration of its effects in the prevention of goitre and cretinism, has been the basis for mass injection programmes throughout the world.

The China-Australia Technical Cooperation Programme on the Control of Iodine Deficiency Disorders in China (1985-1990) has led to the training of 20 Chinese professionals in laboratory sciences and epidemiological methods, and the establishment of four monitoring centres for IDD in China.

The establishment in 1986 of the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), a global multidisciplinary expert group with a global secretariat at the CSIRO Division of Human Nutrition, has led, in collaboration with WHO and UNICEF, to new initiatives in Asia, Africa, and Latin America, with excellent progress in the development of national IDD control programmes.

These contributions mainly funded by the Australian International Development Assistance Bureau (AIDAB) have established a significant Australian presence in Asia on which further effort can be mounted directed to the UN objective of elimination of IDD by the year 2000.

I. INTRODUCTION

I am honoured and pleased to accept the invitation of the Nutrition Society of Australia to give the Public Lecture at this 16th Meeting of the Society. I was privileged to give a paper at the initial meeting of the Society in Melbourne in 1976. My title then was "Nutrition and Health: the need for research and action" - It is clear that much has been accomplished in both the areas of research and action since 1976 and I congratulate the members of the Society on this.

My topic today concerns "The Conquest of Iodine Deficiency". Iodine Deficiency is a micronutrient deficiency which has now been shown to be a major international public health problem. Control of iodine deficiency will bring incalculable benefits to many millions of people, particularly in Asia. This is of special significance for Australia because Australia has played a special role in the development of programmes for the control of this problem (Hetzel 1989).P

My personal interest dates from the 1960's when I became involved in the investigation of iodine deficiency in Papua New Guinea (1964-1972); subsequently with the development of animal models at the CSIRO Division of Human Nutrition (1976-85); and involvement in National Programmes in Indonesia and China (1976-). Finally in 1985, I was able to initiate, with overseas

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colleagues, the establishment of the International Council for Control of Iodine Deficiency Disorders which is an international network of scientists, health professionals and technologists committed to the elimination of this problem by the year 2000.

Iodine is an essential trace element that is of particular importance to mammalian development because it is a constituent of the thyroid hormones thyroxine 3.5.3'5'-tetriodothyronine (T_4) and triodothyronine 3.5.3' triodothyronine (T_3).

There is a cycle of iodine in nature. Most iodine resides in the ocean. It was present during the primordial development of the earth, but large amounts were leached from the surface soil by glaciation, snow, and rain, and were carried by wind, rivers, and floods into the sea. Iodine occurs in the deeper layers of the soil and is found in oilwell effluents. Water from deep wells can provide a major source of iodine. In general, the older an exposed soil surface, the more likely it is to be leached of iodine. The most likely areas to be leached are mountainous areas. The most severely deficient are the Himalayas, the Andes, the European Alps, and the vast mountains of China. But iodine deficiency is also likely to occur in flooded river valleys as in the case of the Ganges Valley in India.

Iodine occurs in the soil and in the sea as iodide. Iodide ions are oxidized by sunlight to elemental iodine, which is volatile, so that every year some 400 000 tons of iodine escape from the surface of the sea. The concentration of iodide in sea water is about 50-60 μg/l. In the air it is approximately 0.7 $\mu g/m^3$. The iodine in the atmosphere is returned to the soil by the rain, which has concentrations in the range 1.8-8.5 μg/l. In this way the cycle is completed.

However, the return of the iodine is slow, and in small amounts, compared to the original loss of iodine; and subsequent repeated flooding ensures the continuity of iodine deficiency in the soil. Hence no 'natural correction' can take place, and iodine deficiency persists in the soil indefinitely. All crops grown in these soils will be iodine deficient. As a result, human and animal populations which are totally dependent on food grown in such soil, become iodine deficient. The iodine content of plants grown in iodine deficient soils may be as low as 10 μg/kg compared to 1000 μg/kg dry weight in plants in a non-iodine-deficient soil. This accounts for severe iodine deficiency in vast populations in Asia living within systems of subsistence agriculture.

The story of iodine deficiency begins with the history of goitre and cretinism. These obvious abnormalities of the human body and human behaviour in the form of a lump in the neck and mental deficiency, have aroused comment and speculation over the whole of recorded history.

The first records of goitre and cretinism date back to the ancient civilisations - the Chinese and Hindu cultures, and then to Greece and Rome. In the Middle Ages, goitrous cretins appeared in the pictorial art, often as angels or demons. The first detailed descriptions of these subjects occurred in the Renaissance. The paintings of the Madonnas in Italy so commonly showed goitre that the condition must have been regarded as virtually normal. In the 17th and 18th centuries, scientific studies multiplied, and the first recorded mention of the word 'cretin' appeared in Diderot's Encyclopedie in 1754. The 19th century marked the beginning of serious attempts to control the problem; however, not until the latter half of the 20th century have we come to appreciate the massive nature of the problem.

The relation of iodine deficiency to goitre was defined in the first decade of the 20th century by the studies of Marine on experimental goitre in rats. Marine showed that when the iodine content of the thyroid fell below 0.1%, hyperplasia occurred with enlargement and the production of goitre. Intermittent iodine deficiency produced alternating hyperplasia and involution with the production of the familiar "colloid goitre". The successful prevention of goitre by iodide supplementation was shown by Marine and Kimball in 1921 in a controlled study in school children in Akron, Ohio. Iodized salt was introduced into Switzerland in 1924 and has since been used in many countries (Hetzel 1989).

In the last 30 years the condition of endemic cretinism, well characterised from Alpine Europe in the 19th centuryby the Sardinian Commission of 1848, and described in the North-West frontier region of India by McCarrison (1908), was rediscovered in the remote areas of the world

in the 1960s. The condition had been "forgotten" because of the remoteness of the iodine deficient populations from modern investigative facilities (Pharoah et al. 1980).

As a result of this rediscovery, the effects of iodine deficiency have been studied in many remote, predominantly mountainous areas around the world - including the Himalayas (India, Nepal, Burma) - the Andes (Peru, Ecuador, Bolivia, Chile), and in Indonesia, New Guinea, Africa (Zaire) as well as the less developed parts of Southern Europe (Pharoah et al. 1980). More recently studies from China have been available (Boyages et al. 1989; Ma et al. 1982).

II. IODINE DEFICIENCY AND THE BRAIN

It is now established that endemic cretinism, characterised in its fully developed form by severe mental deficiency, deaf mutism and spastic diplegia, is epidemiologically associated with high rates of goitre and severe iodine deficiency (levels of 25 ug per day or less compared to a normal intake of 80-150 ug per day), while goitre alone is seen at levels below 50 ug per day (Pharoah et al. 1980; Hetzel and Maberly 1986; Hetzel et al. 1990). However, the apparent spontaneous disappearance of endemic cretinism in Southern Europe raised considerable doubts as to the relation of iodine deficiency to the condition (Hetzel 1989).

The development of a new method in the form of the injection of iodised oil for correction of severe iodine deficiency in Papua New Guinea (McCullagh et al. 1963; Buttfield et al. 1965, Buttfield and Hetzel 1967) enabled our group to set up a controlled trial to test this hypothesis for the first time.

The study was carried out with the support and collaboration of the Public Health Department which accepted that the study was ethically justified. Iodised oil or saline injections were given to alternate families in the Jimi River District in the Western Highlands at the time of the first census (1966). Each child born subsequently was examined for evidence of motor retardation, as assessed by the usual milestones of sitting, standing, or walking, and for evidence of deafness. Examination was carried out without knowledge as to whether the mother had received the iodised oil injection or saline (Pharoah et al. 1971).

Infants presenting with a full syndrome of hearing and speech abnormalities, together with abnormalities of motor development with or without squint, were classified as suffering from endemic cretinism. By these criteria, there were seven cretins born to women who had received iodised oil out of a total of 687 children. In six of these seven cases, conception had occurred prior to the iodized oil injections.

In the untreated group, there were 25 endemic cretins out of a total of 688 children born since the trial began. In five of these 25, conception had occurred prior to saline being given.

It was concluded that an injection of iodised oil given prior to pregnancy could prevent the occurrence of the neurological syndrome of endemic cretinism in the infant. The occurrence of the syndrome in thos who were pregnant at the time of oil injection indicated that the damage probably occurred during the first half of pregnancy, possibly in the first trimester.

Subsequent studies have revealed a motor coordination defect in apparently normal children subjected to severe iodine deficiency during pregnancy (Connolly et al. 1979; Pharoah et al. 1981). There is evidence of an associated intellectual defect (Pharoah et al 1984; Fierro-Benitez et al 1986). It is apparent that the effects of severe iodine deficiency in pregnancy are not confined to endemic cretinism but extend to a large segment of individuals submitted to severe iodine deficiency during pregnancy.

The impact of iodised salt in the prevention of goitre and cretinism can be vividly illustrated from Switzerland. The burden of goitre and cretinism was very great throughout the whole country situated as it is in the elevated region of the European Alps. The burden of cretinism was a heavy charge on public funds - In 1923 the Canton of Berne alone, with a population of little more than 700,000 had to hospitalise 700 cretins incapable of any social life. However, following the introduction of iodised salt, goitre rates fell steeply and later deaf and

dumb institutions were closed or diverted for other purposes. Between the years 1925 and 1947 the number of exemptions for military service fell from 31 to less than 1 per thousand.

A recent review after 60 years of iodised salt has confirmed the benefits in the total prevention of all degrees of neurological damage in the Swiss population (Burgi et al. 1990).

The importance of the link between iodine deficiency and brain development has led to studies in animal models to demonstrate the relationship and investigate the mechanisms involved.

III. ANIMAL MODELS

A number of animal models have been investigated in the rat, sheep and marmoset monkey. Of these, the sheep has been most studied in demonstrating the effect of severe iodine deficiency on fetal brain development. A special low iodine diet (5-10 μg per kilo) was developed by our group at the CSIRO Division of Human Nutrition, comprising maize from an iodine deficient area which together with pea pollard and supplementary minerals has provided an adequate nutritional source which has maintained the animals in good condition in spite of severe iodine deficiency (Potter et al 1980).

A significant effect of severe iodine deficiency on fetal brain development as indicated by reduced weight, reduced DNA and protein was first observed at 70 days gestation in the sheep. The effect became more marked at 98 and 140 days (Potter et al 1982) (Table 1).

Histological studies at 140 days revealed delayed cerebellar maturation with less dendritic arborisation of the Purkinje cells. There was also delayed maturation in the hippocampus and motor areas of the cerebral hemispheres.

This pattern in the iodine deficient sheep fetus was associated with absence of wool growth and skeletal retardation indicative of severe hypothyroidism. The condition resembles closely that seen in the hypothyroid form of cretinism in man. So far gross neurological defects such as deafness or spasticity have not been demonstrated in the sheep. Furthermore the condition in the sheep has been substantially reversed by iodine administration in the third trimester. This has also been observed with the human condition in Zaire. However longer term studies are needed in the sheep to observe the effects of severe fetal iodine deficiency on the brain (Mano et al. 1989).

In these studies in the sheep, severe reductions in circulating thyroid hormones in both mother and fetus have been demonstrated following severe iodine deficiency. Stillbirths also increased in the iodine deficient lambs.

The effects of severe iodine deficiency on fetal brain development in the sheep can be reproduced to some extent by fetal thyroidectomy or even better by a combination of maternal and fetal thyroidectomy. The effects of maternal thyroidectomy alone can be demonstrated as early as 70 days gestation while the effects of fetal thyroidectomy (carried out at either 60 days or 98 days gestation) are not significant until term (McIntosh et al. 1983; Hetzel and Potter 1983). These results suggest that the effects of severe iodine deficiency in the sheep occur through reduced maternal and fetal thyroid function.

Table 1 - Effect of severe iodine deficiency on fetal brain development in the sheep*.

		Gestational Age 56 days	70 days	98 days	140 days
Maternal plasma T_4 (nmol/l)	I-defic.	(5) 37[a]	(6) 17[a]	(5) 15[a]	(7) 19[a]
	Control	(3)126	(4)134	(5)141	(3)137[a]
Fetal plasma T_4 (nmol/l)	I-defic.	(5) 3[b]	(6) 4[a]	(5) 4[a]	(7) 6[a]
	Control	(2) 10	(4) 25	(5)125	(3)216
Brain weight (g)	I-defic.	(5)1.79	(7)4.20[c]	(5)19.0	(7)46.4[b]
	Control	(3)1.68	(4)5.01	(5)22.1	(6)53.8
Cell number (mg DNA)	I-defic.	(5)8.86	(7)14.2[c]	(5)27.8[b]	(7)62.6[a]
	Control	(3)8.37	(4)16.2	(5)32.5	(6)74.5
Body weight (g)	I-defic.	(5)31.7	(7)101[c]	(5)662	(7)2930[b]
	Control	(3)32.2	(4)129	(5)753	(6)3820

Number of observations shown in parentheses.
[a]$P < 0.001$ [b]$P < 0.01$ [c]$P < 0.001$ (Two-tailed "t" test)
*Modified from Potter et al. (1982).

Severe iodine deficiency has been produced in the marmoset (Callithrix Jacchus Jacchus) with a mixed diet of maize (60%), peas (15%), torula yeast (10%), and dried iodine deficient mutton (10%) derived from the iodine deficient sheep produced in the study already described (Mano et al. 1985). There was a gross reduction in maternal T_4 levels (Mano et al. 1985) with grossly reduced thyroid iodine. After a year on the diet the animals were allowed to become pregnant and the newborn animals were studied following the first pregnancy and then again following the second pregnancy. The results on brain development were similar to those observed in the sheep and have been fully reported elsewhere (Mano et al 1987). Significant effects were apparent in the first pregnancy with more striking effects apparent in the second pregnancy.

Studies in rats using diets consumed in two endemic areas in China have been carried out. In both instances fetal hypothyroidism with brain retardation has been produced (Zhong 1983; Li et al. 1985).

A new aspect has recently been opened up by the observation that selenium deficiency in the rat is able to block the deiodination of thyroxine (Arthur et al. 1991). This is due to the fact that the Type II deiodinase contains selenium. Severe selenium deficiency is known to occur in parts of China and in Zaire which raises the possibility that selenium deficiency may be an additional factor in the cause of goitre and cretinism in these countries.

IV. THE IODINE DEFICIENCY DISORDERS

Our concept of the effects of iodine deficiency has undergone a rapid evolution since 1970. Originally the problem was designated by the term "goitre" which, while a fascinating phenomenon for many thyroidologists, cannot justify by itself an aggressive prevention

programme in the highly competitive arena of third world health. However, we now know from both human and animal data that iodine deficiency produces a spectrum of effects, particularly on the development of the brain, but with variations at the different stages of life. These various effects are now included in the term 'iodine deficiency disorders' (IDD) which has now been generally adopted (Hetzel 1983; Lancet 1983). These various disorders are listed in Table 2. They all occur in populations subjected to iodine deficiency and can all be prevented by correction of the deficiency.

More general observations following the use of iodized salt and iodized oil indicate community benefits in the form of increased wellbeing and alertness, increased productivity and improved school performance in children. This is vividly illustrated by the report of Li et al. (1987) on the effect of iodized salt on the Chinese Village of Jixian, locally regarded as "the village of the idiots". Between 1978 and 1983, productivity increased by a factor of 5, school performance improved; for the first time recruits were provided for the People's Liberation Army, and girls from neighbouring villages were prepared to marry men from Jixian! Thus iodine deficiency is now seen as a block to human and social development and the achievement of genetic potential for individuals and communities due to the development of a high incidence of hypothyroidism (Hetzel 1989; Hetzel et al. 1990).

One important indicator of IDD is neonatal hypothyroidism. This condition occurs sporadically all over the world due to congenital anomalies of the thyroid including small size or malposition. Routine screening of heel prick samples taken at the 4th day of life reveals about 1 in 4000 neonates with a low level of thyroxine (or high thyrotropic hormone (TSH)). Rapid treatment is provided to prevent any further threat to the rapidly growing infant brain.

In areas of severe iodine deficiency the incidence of neonatal hypothyroidism may be up to 10% (Hetzel and Maberly 1986; Hetzel et al. 1987) which indicates the severity of the threat and the urgency of correction of the iodine deficiency.

The prevention and control of IDD can therefore be regarded as an urgent problem for large populations living in an iodine deficient environment. Some 1 billion people are estimated to be living in an iodine deficient environment - of these 350 million live in China and 200 million in India (World Health Organization Report 1990) (Table 3). These people are at risk of developing one or more of the effects of iodine deficiency on growth and development - other efforts to bring about development will be limited by a passive iodine deficient population due to hypothyroidism, including particularly children. More than 5 million are suffering from mental retardation as gross cretins but in addition three to five times this number suffer from lesser degrees of mental defect due to the effect of iodine deficiency in pregnancy (World Health Organization 1990).

At least 20 million are affected in all of whom mental defect could be prevented. This condition is agreed to be the most common preventable mental defect.

V. THE CONTROL OF IDD

Appropriate mass technology is available in the form of iodized salt and iodized oil. These measures are of proven value in various endemic areas in China, India and Indonesia (Hetzel et al. 1987). Their effective application to the many millions who require iodine is now being achieved (Hetzel 1989; World Health Organization 1990). There are formidable obstacles at the technical, the organizational, and the political level. Injections of iodized oil in Nepal (4 million), Burma (2 million), Zaire (1.5 million) have been carried out as emergency measures in severely iodine deficient countries to meet the problem until an effective salt iodization programme can be introduced. Such a programme has to overcome many obstacles if the production of salt is not under government control, but as in Java, remains with a myriad of small suppliers (70%). In excess of 10 million injections have already been given, but in these circumstances, iodized oil has to be considered as a longer term measure for severe IDD. New technologies need also to be considered and developed (e.g. iodinated water supplies).

Table 2 The spectrum of Iodine Deficiency Disorders (IDD)*

FETUS	Abortions Stillbirths Congenital Anomalies Increase Perinatal mortality Increased Infant mortality Neurological cretinism - (Mental deficiency deaf mutism spastic diplegia squint) Myxedematous cretinism - (dwarfism mental deficiency) Psychomotor defects
NEONATE	Neonatal goitre Neonatal hypothyroidism
CHILD AND ADOLESCENT	Goitre Juvenile hypothyroidism Impaired mental function Retarded physical development
ADULT	Goitre with its complications Hypothyroidism Impaired mental function Iodine induced hyperthyroidism

Table 3 Estimated prevalence of Iodine Deficiency Disorders in developing countries, by region, and numbers of persons at risk (in millions)*

	At risk	Goitre	Overt Cretinism
Africa	227	39	0.5
Latin America	60	30	0.3
South-East Asia	280	100	4.0
Asia (other countries including China)	400	30	0.9
Eastern Mediterranean	33	12	-
Total	1,000	211	5.7

*From World Health Organization Report (1990)

A notable Australian initiative, the China Australia Technical Cooperation Programme for the Control of Iodine Deficiency Disorders in China (1985-1990) has led to the training in Australia at the Westmead Hospital, Sydney, under the supervision of Dr Creswell Eastman and Dr Glen Maberly, of some 20 Chinese professionals in laboratory techniques (immunoassay of T_4 and TSH, and urine iodine) and in modern data processing methods for epidemiological monitoring of iodine deficient populations. This programme funded by the Australian International Development Assistance Bureau (AIDAB) has led to the establishment of four IDD monitoring centres in China. It has also led to a global training programme at Emory University and the Centre for Disease Control (CDC) at Atlanta, Georgia, USA under the leadership of Dr Glen Maberly and Dr F Trowbridge of CDC.

VI. THE INTERNATIONAL COUNCIL FOR CONTROL OF IODINE DEFICIENCY DISORDERS (ICCIDD)

Since 1978, I and other colleagues had been expressing increasing concern about the lag in application of our new knowledge of the iodine deficiency disorders and their prevention (Stanbury and Hetzel 1980; Hetzel 1983). A Symposium at the 4th Asian Congress of Nutrition in Bangkok in 1983 drew the problem to the attention of the international nutrition community (Lancet 1983). This Symposium led to an invitation to me in 1984 to prepare a comnprehensive review of the Prevention and Control of Iodine Deficiency Disorders for the United Nations System. This report was submitted early in 1985 and later published (Hetzel 1988).

During the course of this review I realised that it was essential to create a new body of scientists and other health professionals committed to bridging the wide gap between research and action. In Delhi at a WHO/UNICEF Intercountry Meeting in March 1985, a group of twelve experts agreed to found the International Council for Control of Iodine Deficiency Disorders (ICCIDD). After a necessary period of gestation during 1985 an International Board was established and the ICCIDD was formally inaugurated at Kathmandu, Nepal, in 1986 (Lancet 1986a).

The ICCIDD has welcomed as members, all who have concern and expertise regarding IDD and IDD control (Lancet 1986a). The main role of the ICCIDD is to cooperate and make its expertise available to the international agencies, and the national governments who have responsibility for the control of IDD, and so bridge the great gap between available knowledge and its application. At the inaugural meeting in Kathmandu, Nepal, a global review of the IDD problem took place with an appraisal of current expertise in iodine technology and IDD control programmes. This review led to the first ICCIDD monograph (Lancet 1986b; Hetzel et al. 1987).

The ICCIDD is now a global multidisciplinary group of some 300 members with a quarterly Newsletter and a secretariat in Adelaide, at the CSIRO Division of Human Nutrition, where I as Executive Director have my office. Support is currently being received from UNICEF (New York) and the Australian and Dutch Governments and recently (this year 1991) from Canada.

Since 1987, the ICCIDD has become fully active in facilitating interagency cooperation in the prevention and control of IDD. This has been achieved by a series of interagency meetings, the establishment of regional interagency working groups (particularly involving WHO and UNICEF, but also some of the bilaterals as well as other activities e.g. publications and expert groups).

A global Action Plan has now been endorsed by the UN agencies to take account of these developments. The purpose of the Global Action Plan is to provide global and regional support for the establishment and monitoring of effective national IDD control programmes. It includes activities at the National, Regional and Global levels.

At National level, initial assessments, national seminars, communication packages, intersectoral planning with a National IDD Control Commission, evaluation and monitoring with laboratory services are included. In Indonesia and China, International Working Groups have now been established by ICCIDD in collaboration with WHO and UNICEF.

At Regional level, the development of a series of regional IDD working groups provides for the necessary close working relationship between ICCIDD, WHO and UNICEF. The IDD Task Force for Africa has been particularly successful in developing a coordinated strategy involving both multilateral and bilateral agencies.

At the Global level, the major function of advocacy and public information, and a global monitoring system are covered, together with continuing expert working groups, and research activity.

In view of the progress already achieved and the promising potential of current and planned national prevention and control programmes, the elimination of IDD as a major public health problem by the year 2000 has been recently reaffirmed by the 1990 World Health Assembly (World Health Organization Report 1990). An escalation of funding is now an essential step in the achievement of this goal.

In September 1990, the World Summit for Children held at the United Nations in New York, was attended by 71 Heads of State and 80 other government representatives. The World Summit signed a Declaration and approved a Plan of Action which included the elimination of IDD as a public health problem by the year 2000.

There is now a perceptible tide running towards prevention and control of IDD. It would seem possible that a large measure of control could be achieved in the next decade with incalculable benefits to millions of people now suffering the deadening effects of iodine deficiency on their lives.

In Australia, we have a special opportunity to assist with the conquest of iodine deficiency in Asia. We are already involved in China; additional support is required for Indonesia, the Philippines, Papua New Guinea and in the other countries in SE Asia. It would be a great achievement if we, in the year 2000, could announce the elimination of IDD as a public health problem in Asia.

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