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THE IODINE DEFICIENCY DISORDERS: Their Nature and Prevention

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INTRODUCTION

The term *iodine deficiency disorders* refers to the spectrum of effects of iodine deficiency on growth and development (29). These effects arise because iodine is an essential nutrient as a constituent of the thyroid hormones thyroxine 3,5,3',5'-tetraiodothyronine (T_4), 3,5,3'-triiodothyronine (T_3). The major role of iodine in nutrition arises from the importance of thyroid hormones in the growth and development of humans and animals.

Iodine deficiency disorders are now recognized as a major international public health problem because of the large populations at risk due to their iodine-deficient environments, which are characterized primarily by iodine-deficient soil (30).

Goiter is the most familiar effect of iodine deficiency; it is a swelling of the thyroid gland that was well known to the ancient world and has continued to incite interest over the centuries (41). There is, however, a wide spectrum of other effects of iodine deficiency that affect all stages of development, especially the fetal period. These effects are reviewed here in light of recent advances in knowledge. After the review of the nature of iodine deficiency disorders, their prevention is considered, followed by a discussion of public health programs and recent international action designed to expedite these programs (33).

Goiter

Extensive reviews of the global geographic prevalence of goiter have been published (39, 70).

Iodine deficiency causes depletion of thyroid iodine stores with reduced daily production of T_4. A fall in the blood level of T_4 triggers the secretion of increased amounts of pituitary thyroid-stimulating hormone, which increases thyroid activity through hyperplasia of the thyroid. The efficiency of the thyroid iodide pump increases with faster turnover of thyroid iodine. This effect can be demonstrated by an increased thyroidal uptake of radioactive isotopes ^{131}I and ^{125}I. These features were first demonstrated in the field in the classic observations of Stanbury et al (68) in the Andes in Argentina.

Iodine deficiency is demonstrated by determination of urine iodine excretion using either 24-hour samples or, more conveniently, casual samples with determination of iodine content per gram of creatinine. Normal iodine intake is 100–150 μg/day, which corresponds to a urinary iodine excretion in this range (70). In general in endemic goiter areas, the intake is well below 100 μg/day and goiter is usually seen when the level is below 50 μg/day (70). The rate increases as the iodine excretion falls so that goiter may be almost universal at levels below 10 μg/day.

Goiter arises from causes other than iodine deficiency through a variety of agents known as goitrogens. These goitrogens, however, are of secondary importance to iodine deficiency as etiologic factors in endemic goiter.

Recent research (16) has shown that staple foods from the Third World such as cassava, maize, bamboo shoots, sweet potatoes, lima beans, and millets contain cyanogenic glucosides, which are capable of liberating large quantities of cyanide by hydrolysis. Not only is the cyanide toxic but the metabolite in the body is predominantly thiocyanate, which is a goitrogen. With the exception of cassava, these glycosides are located in the inedible portions of the plants, or if in the edible portion, in quantities so small that they do not cause a major problem. Cassava, on the other hand, is cultivated extensively in developing countries and represents an essential source of calories for more than 200 million people living in the tropics (16). The role of cassava with iodine deficiency in the etiology of endemic goiter and endemic cretinism has now been demonstrated by Delange et al (16) from their studies in nonmountainous Zaire. These observations have also been confirmed by Maberly et al (47) in Sarawak, Malaysia.

Endemic Cretinism

A major effect of fetal iodine deficiency is endemic cretinism, which is distinct from sporadic cretinism (61). Endemic cretinism, which occurs with an iodine intake below 25 μg per day in contrast to a normal intake of 80–150 μg per day, is still widely prevalent and affects, for example, up to 10% of the populations living in severely iodine-deficient areas in India (61), Indonesia (61), and China (45). In its most common form, it is characterized by mental deficiency, deaf mutism, and spastic diplegia; this type is referred to as the *nervous,* or *neurologic,* type in contrast to the less common *myxedematous* type characterized by hypothyroidism and dwarfism.

These two types of endemic cretinism were first described in modern medical literature by McCarrison (48), and the condition still exists in the same areas of the Karakoram mountains and in the Himalayas (61). Neurologic, myxedematous, and mixed types still occur in the Hetian district of Sinkiang, China, some 300 km east of Gilgit, where McCarrison made his original observations (45). In both China and India, the condition occurs most frequently in areas below mountain slopes in fertile silt plains that have been leached of iodine by snow waters and glaciation.

Apart from its prevalence in Asia and Oceania (Papua New Guinea), cretinism also occurs in Africa (Zaire) and in South America in the Andean region (Ecuador, Peru, Bolivia, and Argentina) (61). In all these areas, with the exception of Zaire, neurologic features are predominant (6). In Zaire the myxedematous form is more common, probably because of the high intake of cassava (16). The clinical manifestations of neurologic cretinism vary considerably, however, and include varying degrees of isolated deaf mutism and mental defect. In China the term *cretinoid* is used to describe these individuals.

The common form of endemic cretinism is not usually associated with severe clinical hypothyroidism as in so-called sporadic cretinism, although mixed forms with both the neurologic and myxedematous features do occur. The neurologic features are not reversed by the administration of thyroid hormones, however, unlike the hypothyroidism (28).

The apparent spontaneous disappearance of endemic cretinism in southern Europe raised considerable doubts as to the relation of iodine deficiency to the condition. Such a spontaneous disappearance without iodization was noted by Costa et al (12) in northern Italy and by Konig & Veraguth (40) in Switzerland.

A controlled trial in the Western Highlands of Papua New Guinea revealed that endemic cretinism could be prevented by correction of iodine deficiency with iodized oil before pregnancy (58, 59).

The value of iodized oil injection in the prevention of endemic cretinism has been confirmed in Zaire (73) and in South America (63). Mass injection programs have been carried out in New Guinea in 1971–1972 and in Zaire, Indonesia, and China. Recent evaluations of these mass programs in Indonesia and China indicate that endemic cretinism has been prevented where correction of iodine deficiency has been achieved (18, 45).

The apparent spontaneous disappearance of the condition is now attributed to an increase in iodine intake due to dietary diversification as a result of social and economic development that reached the more remote rural areas.

Fetal Development

Iodine deficiency of the fetus results from iodine deficiency in the mother. The condition is associated with a higher incidence of stillbirths, spontaneous abortions, and congenital abnormalities, which can be reduced by public health iodization programs. The effects are similar to those observed in maternal hypothyroidism, which can be reduced by thyroid hormone replacement therapy (49).

Controlled trials with iodized oil have revealed a significant reduction in recorded fetal and neonatal deaths in the treated group, which is consistent with animal evidence indicating the effect of iodine deficiency on fetal survival (35, 61, 73).

Further data from Papua New Guinea indicate a relationship between the level of maternal thyroxine with the outcome of current and recent past pregnancies including mortality and the occurrence of cretinism. The rate of perinatal deaths was twice as high among mothers with very low serum concentrations (<25 ng per ml) of the total thyroxine (TT_4) (36.0%) as the rate of deaths in women with higher levels of TT_4 (16.4%); the same relationship was true for free thyroxine (FT_4) levels (62).

These data indicate the importance of maternal thyroid function to fetal survival and development and are complemented by extensive animal data (35).

The Neonate

An increased perinatal mortality due to iodine deficiency has been shown in Zaire from the results of a controlled trial of iodized oil injections given in the latter half of pregnancy alternately with a control injection (73). There is a substantial fall in perinatal and infant mortality with improved birth weight. Low birth weight (whatever the cause) is generally associated with a higher rate of congenital anomalies and higher health risk through childhood.

Apart from the question of mortality, the importance of the state of thyroid function in the neonate relates to the fact that at birth the human brain has reached only about one third of its full size and continues to grow rapidly until the end of the second year (17). The thyroid hormone, which depends on an adequate supply of iodine, is essential for normal brain development, as confirmed by animal studies (32, 34).

Recent data have been published on iodine nutrition and neonatal thyroid function in Europe. They confirm that the continuing presence of severe iodine deficiency affects neonatal thyroid function and hence poses a threat to early brain development (15).

Similar evidence comes from observations in Zaire, where 10% of the neonatal population has been found to have chemical hypothyroidism (25). In Zaire this hypothyroidism persists into infancy and childhood if the deficiency is not corrected, with resultant retardation of physical and mental development (26).

These observations indicate a much higher risk of mental defect in severely iodine-deficient populations than is indicated by the presence of classic cretinism.

Child Development

Iodine deficiency in children is characteristically associated with goiter. The classification of goiter, which has been standardized by the World Health Organization, is discussed elsewhere (23). The goiter rate increases with age and reaches a maximum at adolescence. Girls have a higher prevalence than boys. Observations of goiter rates in school children of ages 8–14 provide a convenient indication of the presence of iodine deficiency in a community.

Recent studies of school children living in iodine-deficient areas of several countries indicate impaired school performance and intelligence quotients in comparison with those of matched groups from non-iodine-deficient areas.

These studies are difficult to set up because of the problem of the control group. There are many possible causes for impaired performance in school and on intelligence quotient tests, which makes interpretation of observed differences difficult. The iodine-deficient area is likely to be more remote and to suffer from more social deprivation, including a disadvantage in school facilities, a lower socioeconomic status, and poorer general nutrition. All such factors have to be taken into account, apart from the problem of adapting tests that originated in developed countries for use in developing countries.

Initially, studies of psychomotor development, as indicated by tests of motor coordination, revealed differences that could be regarded, to a large extent, as independent of educational status.

In Papua New Guinea, children from the controlled trial in the Western Highlands have been tested periodically. Their differences in bimanual dexterity were revealed by having them thread beads and put pegs into a pegboard; these differences were then compared with the iodine-deficiency status of the mother. These dexterity differences were found to be significantly related to the level of maternal thyroxine (but not triiodothyronine) at the time of the mother's pregnancy and to persist up to the age of 10–12 years (9, 59, 60).

Differences in motor coordination have also been observed in Indonesia. More recent critical studies by Bleichrodt et al (2) in Indonesia and in an iodine-deficient area in Spain, however, have used a wide range of psychological tests and showed that the mental development of children from iodine-deficient areas lags behind that of children from non-iodine-deficient areas. The differences in psychomotor development became apparent from the age of two and one half years.

A study from Chile (54) found that children with goiter demonstrated poorer performance on intelligence quotient tests than did children without goiter from the same area. Similar data are now becoming available from China but have not yet been published (W. Dong, unpublished results).

The next question is whether these differences can be affected by correction of the iodine deficiency. In a pioneering study initiated in Ecuador in 1966, Fierro-Benitez et al (27) reported the long-term effects of iodized oil injections by comparing groups of children from two Highland villages, one (Tocachi) being treated, the other (La Esperanza) acting as a control group. Particular attention was paid to 128 children aged 8–15 whose mothers had received iodized oil prior to the second trimester of pregnancy and a matched control group of 293 of similar age. All children were periodically examined from birth at key stages in their development. Women in Tocachi were reinjected or injected in 1970, 1974, and 1978. According to the authors, assessments in 1973, 1978, and 1981 revealed the following:

> Scholastic achievement was better in the children of treated mothers when measured in terms of school year reached, for age, school dropout rate, failure rate, years repeated and school marks. There was no difference between the two groups by certain tests (Terman-Merrill, Wechsler or Goodenough). However, both groups were impaired in school performance—in reading, writing and mathematics, but more notably the children of untreated mothers.

The results indicate the significant role of iodine deficiency, but other factors were also considered important in the school performance of these Ecuadorean children, such as social deprivation and other nutritional factors (27).

A controlled trial carried out with oral iodized oil in a small Bolivian village (Tiquipaya) 2645 meters above sea level revealed significant benefits to school children's mental performance in association with reduction of goiter (1).

Iodization programs have been shown to increase the level of circulating thyroid hormones in children in India (66) and China (45). These changes occur whether or not the child is goitrous and indicate a mild degree of hypothyroidism without any apparent symptoms.

The major determinant of brain (and pituitary) triiodothyronine (T_3) is serum thyroxine (T_4) and not T_3 (as is true of the liver, kidney, and muscle) (13). Low levels of brain T_3 have been demonstrated in the iodine-deficient rat in association with reduced levels of serum T_4, and these levels have been restored to normal with correction of iodine deficiency (55).

These findings provide a rationale for suboptimal brain function in subjects with endemic goiter and lowered serum T_4 levels and their improvement following correction of iodine deficiency.

Iodine-Induced Hyperthyroidism

A mild increase in the incidence of hyperthyroidism has now been described following iodized salt programs in Europe and South America and following the introduction of iodized bread in Holland and Tasmania (10, 71). A few cases have been noted following iodized oil administration in South America. No cases have yet been described in New Guinea, India, or Zaire. This lack of cases is probably due to the scattered nature of the population in small villages and limited opportunities for observation (42). The condition is largely confined to those over 40 years of age—who make up a smaller proportion of the population in developing countries than in developed countries. Detailed observations are available for the island of Tasmania (71, 76).

The condition is readily controlled with antithyroid drugs or radioiodine. Spontaneous remission frequently occurs. In general, iodization should be avoided in those over the age of 40 because of the risk of hyperthyroidism (69).

The correction of iodine deficiency prevents the formation of an autonomous thyroid and so prevents the condition of iodine-induced hyperthyroidism (76). Hence, this condition is included among the iodine deficiency disorders.

Demography and Epidemiology

Large populations are at risk of developing iodine deficiency disorders because they live in iodine-deficient environments (30). As mentioned, this iodine-deficient environment is characterized by soil from which iodine has been leached by glaciation, high rainfall, or flooding. This leaching occurs most often in mountainous areas as in the Himalayan region, the Andean region, and the vast mountain ranges of China. Low-lying areas subject to flooding, as in the Ganges Valley in India and Bangladesh, however, are also severely iodine deficient. As a result, all the food grown in such soil is iodine deficient; thus, iodine deficiency will persist in the local populations until there is dietary diversification, as occurred in Europe late in the nineteenth century and in the early decades of this century, or until some form of iodine supplement is given.

There is consensus that 800 million people are at risk of developing iodine deficiency disorders; of these 190 million have goiter, more than 3 million are overt cretins, and millions more have some intellectual or motor deficit (30, 75).

In northern India, a high degree of apathy has been noted in populations living in iodine-deficient areas. This apathy may even affect domestic animals such as dogs! Reduced mental function is widely prevalent in iodine-deficient communities and affects the inhabitants' capacity for initiative and decision making. Thus, iodine deficiency is a major block to the human and social development of communities in iodine-deficient environments. Correction of the iodine deficiency represents a major contribution to development, as is more fully discussed elsewhere (30, 35).

An instructive and broad example of the possibilities is provided by observations of the effect of an iodized salt program dating only from 1978 in the northern Chinese village of Jixian in Heilongjiang Province (43). The average income increased from 43 yuan per capita in 1981 to 223 yuan in 1982 and 414 yuan in 1984, which was higher than the average per capita income in the district. In 1983, cereals were exported for the first time. Before iodization, no family had a radio, but by 1984 55 families had televisions. Since 1978, 44 young women had come from other villages to marry young men in Jixian. Seven men had joined the People's Liberation Army, whereas before they had been rejected for goiter. These effects can be largely attributed to the correction of communitywide hypothyroidism by iodized salt.

THE CORRECTION OF IODINE DEFICIENCY

In principle, iodine deficiency is easy to correct. People in deficient areas can receive iodine as an additive to food or water or by direct administration. Additive programs are more practical on a large scale, particularly if the vehicle is one that can readily be controlled, such as salt or water. Establishing such a program, however, frequently involves major changes in marketing and distribution patterns and requires years to achieve. Even then, some target groups may not be reached. Direct administration of iodine is usually in the form of iodized oil, but potassium iodide or iodine in Lugol's solution can also be given. In this section, we describe the major techniques for iodine administration—salt, oil, water, and potassium iodide—and discuss their place in overall iodine deficiency disorders control programs.

Iodinated Salt

Salt is universally desired. In many rural self-sufficient communities, it may be the only commodity that requires importation. These factors make salt an excellent vehicle for supplementation programs.

Salt is produced either from solar evaporation of seawater or brine or from rock deposits (5, 50). Production of crude granular salt may be as simple as collecting it from the salar, letting it dry in the sun, and packaging it. The crude salt is refined by recrystalization or hydromilling. Iodine can be added by dry mixing of the iodine compound with the salt, by addition of a liquid solution of iodine by drip or spray to salt on a conveyor belt, or by submersion. The degree of technical sophistication in these methods varies extensively. For example, dry mixing can consist merely of adding dry potassium iodide to the salt and mixing by hand or on a conveyor belt. The machinery for drip feeding or spray mixing is quite simple and inexpensive. Crushing, grinding, and sieving are uncomplicated if the salt is of sufficient purity, and the entire iodination operation can be successfully adapted to most production sites in developing countries. Of the several methods described, the drip-feed system is the simplest and cheapest, but the spray-mix method achieves more uniform distribution of iodine with very fine salt.

Potassium iodide and iodate are the most common additives. Iodide is cheaper but iodate is more stable, particularly in warm, humid climates or where there are significant impurities in the salt (66). Iodine is usually added at a ratio to salt between 1:10,000 and 1:50,000. The level can be adjusted for the estimated daily consumption of salt, which varies from less than 3 g a day to 15 g per day. The minimum daily requirement of iodine is about 50 μg, and the recommended intake is 100–150 μg.

Salt has several advantages as a vehicle for fortification with iodine. There is a universal requirement for salt, yet its sources are restricted, which usually makes control at the production site simple. Iodination of salt does not require direct contact with each individual, which makes it suitable for mass prophylaxis programs. The technology is straightforward and easily adapted to developing countries, and the overall cost of iodination is low. The major disadvantage of iodinated salt is that it may require years of patient negotiation to alter existing patterns of salt trade sufficiently to incorporate iodination. Obviously these constraints vary widely. In countries where refined table salt is already produced, the addition of an iodination step is simple. In other countries where anyone can collect salt from salars, however, introduction of iodination requires a massive shift in production and distribution strategy.

Iodized Oil

Iodine in covalent linkage with vegetable oils is introduced into the body either by intramuscular injection or orally (19, 22, 36). The injected material is slowly released from the muscle depot, deiodinated either in the muscle or circulation, and presented to the thyroid as iodide. With oral administration, the iodinated fatty acids are absorbed from the gut and deiodinated, either in the gut, circulation, or both, and the iodide is then concentrated from the circulation by the thyroid. Additionally, some iodinated fatty acids appear to be stored in body fat depots, from which they are slowly deiodinated and released. A single dose of injected iodized oil provides adequate iodine for at least 3 years. The most experience has been with iodinated poppyseed oil (Lipiodol), which was developed as a radiocontrast medium and contains 38% iodine by weight. Iodinated walnut and soybean oils, which contain approximately 25% iodine, are also available.

Administration of iodized oil requires direct contact with each target subject, in contrast to iodinated salt. Iodized oil has usually been administered either by mobile teams or via the primary health care system. The most extensive experience is with intramuscular injections. In Zaire the teams consisted of five health service personnel who could inject an average of 500 subjects per day, and allowing for travel, 100,000 doses per year (36). In Nepal, districts are programmed for injection and local vaccinators are recruited, taught, and then sent in teams of two systematically through the area, each team giving at least 50 injections per day or 11,000 per year (1).

The experience with oral iodized oil is more limited than that with the injected form (1, 19, 22, 24, 25, 44). Oral iodized oil is clearly less effective in duration, as would be expected in the absence of an intramuscular depot. A single oral administration appears effective for at least a year and more often at least two. Factors influencing its effective duration include the severity of the initial iodine depletion, the completeness of intestinal absorption, and probably the extent of fat stores. In some studies, oral administration was as effective as intramuscular injection (19, 44). Research studies have provided most of the data on oral iodized oil, since large-scale interventions are lacking, although several are planned. Oral iodized oil is particularly adaptable to areas with a strong primary health care system, because the actual administration requires little more than delivering the oil to a responsible person (a teacher or other village leader), and no special equipment such as syringes is required. A large program designed to administer 1.5 million doses orally is currently underway in Bolivia (1988–1989); the iodized oil is distributed solely through the primary health care system.

Iodized oil provides adequate iodine for several years after its initial administration. Since it is a direct intervention, it requires direct personal contact with the target but avoids the massive logistic problems often associated with iodized salt programs. Thus, an effective intervention with iodized oil can begin almost immediately. Its effects on goiter reduction are often dramatic and can be valuable in demonstrating the beneficial effects of iodine, thus paving the way for the later introduction of iodinated salt.

The need to establish direct contact with each subject sharply limits the number of individuals who can receive iodized oil. In addition, injection programs must be concerned with proper disposal of syringes and with the risk of improper technique resulting in transmission of viruses such as those that cause AIDS and hepatitis. Iodine administered as a bolus once every 3 years is clearly less physiologically desirable than a daily ration such as with iodinated salt. Iodine-induced thyrotoxicosis occasionally occurs as described above, although it is usually mild and self-limited and occurs with any iodine intervention, including iodized salt. Iodized oil is usually somewhat more expensive than iodized salt, although occasionally the cost of transporting iodinated salt may reverse this difference.

From the above considerations, the effective use of iodized oil in prophylaxis has become better defined. Its optimum application is in moderate to severe iodine deficiency in areas that will not be reached by better means of prophylaxis (usually iodinated salt) within a reasonable time, perhaps one or two years. Iodized oil is usually introduced as an emergency stopgap measure to control iodine deficiency in severely affected areas while the introduction of an effective program for iodinated salt is planned. In many areas, unfortunately, the problems in iodinating salt are so complex that many years will elapse before iodine deficiency is corrected by this means.

Other Technologies

Iodine prophylaxis is occasionally achieved by adding iodine to drinking water. In its more sophisticated form, this technique uses a cannister of iodine crystals through which some water is diverted and then returned to the main stream. Regulation of the flow diverted through the iodine bed controls the amount of iodine added. Such a program proved successful in correcting iodine deficiency in villages of Malaysia (46) and in Troina, Sicily (67).

Programs designed to use less skilled persons to monitor the repetitive administration of iodized oil or some other agent have significant advantages in implementation. Such programs have been done through school teachers and community groups in Tanzania using oral iodized oil capsules. In a small program in Bolivia, A. Pardo (personal communication) decreased goiter by providing Lugol's solution to village health workers, school teachers, and family heads with instructions to administer an appropriate dose, such as a drop a day of a properly diluted solution, to school children and others. Such a program, while requiring a responsible administrator, has the advantages of providing a fairly physiologic dose rather than the boluses of iodized oil, and the materials are available in most hospital pharmacies, even in developing countries. This experience recalls the original trial of Marine & Kimball in Akron, Ohio (52); goiter was successfully controlled in school children by administration of 2 g of sodium iodide in 0.2 g doses over a 2-week period twice each year.

Iodine has been added to a number of other vehicles, including bread, candy, and vitamin tablets (21), but since distribution of these items in a population is difficult to predict or control, such programs are rarely serious alternatives to the methods described above.

PUBLIC HEALTH PROGRAMS FOR PREVENTION AND CONTROL

Iodine deficiency disorders control programs can be conveniently divided into the following components: assessment, communication, planning, political decision, implementation, and monitoring and evaluation (30).

Assessment

Assessment comprises establishing the presence of these disorders and assessing their degree. The two major technical tools are estimates of goiter prevalence and urinary iodine determinations. The Pan American Health Organization/World Health Organization has standardized a definition of goiter and a classification for its size (14).

The most useful laboratory marker is the determination of urinary iodine, because most iodine is excreted in the urine and because urine is easy to obtain (3, 4, 37). The best measure, a 24-hour sample, is very difficult to obtain under field conditions, so the value is usually expressed either as a concentration (μg iodine/dl) or in relation to creatinine (μg iodine/g creatinine). The latter measurement correlated reasonably well with 24-hour urine determinations in Spanish schoolchildren (37), but many such samples related poorly to total urinary iodines in many other cultures. Bourdoux (3) makes a persuasive case for relying on the concentration of iodine in casual samples of urine, since, given a large enough sample size (e.g. 40 or 50), differences in urinary dilution among individuals should be overcome. He and others have conducted field studies that support this position. Some investigators have advocated using a timed 2-hour collection.

While thyroid palpation and the urinary iodines are by far the most practical measures for assessing iodine deficiency, other tests of thyroid function can be very valuable if obtainable (4). Thus, in subjects with iodine deficiency, the serum thyroid-stimulating hormone level is typically elevated, the serum thyroxine level low, the ratio of serum thyroxine to serum triiodothyronine levels low, and the radioiodine uptake quite high. These tests can define the severity of the endemia more precisely than goiter surveys and urinary iodine determinations, but blood is frequently difficult to obtain and process under field conditions, isotope measurements are now less acceptable, and these added measures increase the cost of assessment considerably.

The best group for survey is usually school children (14, 33). They are conveniently congregated so that an individual examiner can assess several hundred in several hours. Children represent the current situation of iodine deficiency better than do older people, who may have preexisting, irreversible nodules that remain after iodine deficiency has been corrected for many years. School children also provide a valuable baseline for gauging the effects of any subsequent intervention.

Communication

Communication is another essential component of an iodine deficiency disorders control program (7, 51, 72). All interested parties must be made aware of the presence of these disorders, their consequences, and the importance of their correction. Target groups for these educational efforts include government officials, principally those in the Ministry of Health, the medical community, teachers, civic groups such as mothers' clubs, and the affected population itself. The message should emphasize that the consequences of iodine deficiency are much more severe than goiter alone. It should also stress the irreversible effects of iodine deficiency on mental and physical development of children and the relative ease of its prophylaxis. Many previous efforts at correction have failed to achieve lasting results because the involved parties did not properly understand the control program or its importance. Successful programs have employed a wide variety of communication techniques, ranging from fairly sophisticated medical pamphlets for physicians to simple slide shows and teaching aids designed like comic books for the less educated. Radio, television, and video films are also popular and effective.

Iodine deficiency disorders booths are set up at local fairs to give information and occasionally to administer iodized oil or to distribute iodinated salt.

Planning

Planning will almost always be the responsibility of the government, usually the Ministry of Health and its division of nutrition (37, 57, 64, 74). A National Control Commission for Iodine Deficiency Disorders should be formed and include representatives from major interest groups: various ministries of the government such as Commerce, Transportation, and Mining, academic institutions, the medical profession, the media, citizen representatives, and appropriate others.

The planners must consider the severity and distribution of the disorders and on that basis recommend the most appropriate response. They also need to analyze existing patterns of salt production and distribution and decide how quickly and easily salt iodination can be achieved. If the extent of iodine deficiency disorders is severe and if effective iodination of salt will be delayed, plans for an interim program with another modality, probably iodized oil, should be developed.

Political Decision

Once the plan is developed, the government must decide to back its implementation (30, 64). In most instances, this process requires passage of a law mandating iodination of all salt for human and animal consumption. It also requires a commitment of national resources to execute the program. The most important element is a clear determination by the government to carry out a successful program. The law usually requires iodination of salt but leaves details of implementation, such as the level of iodine in the salt, to subsequent regulation by the Ministry of Health. The government must provide enough funding to permit the program to become successful. An unimplemented law is of little value. For example, almost every Latin American country has a law for salt iodination, but in only a few is the law applied seriously (20).

Implementation

The next step is implementation of the plan for correction of iodine deficiency. Leadership in implementation will usually come from the Ministry of Health but should be in close cooperation with other ministries and interest groups, preferably through a National Control Commission for Iodine Deficiency Disorders. The program organization should include sufficient personnel to carry out all its various components, many of which extend beyond the Ministry of Health.

Monitoring and Evaluation

To be successful the program must also provide for monitoring and evaluation of its effectiveness (53). The assessment techniques described above are the most useful ones for monitoring and evaluation, specifically goiter surveys and determinations of urinary iodine levels. The program must also monitor the levels of iodine in salt, both at the site of production and of consumption. Monitoring and evaluation are perhaps the least "glamorous" components of the program but are vitally important to its long-term success. A suitable budget must be provided and continue many years after initiation of the program. Many initially successful programs have foundered for lack of effective follow-up control. For example, school children in Guatemala had a goiter prevalence of 38% in 1952, which an effective salt-iodination program reduced to 7% by 1964. Failure to monitor salt iodination ensued, however, with the goiter prevalence rising to 11% in 1979 (65) and 21% in 1987 (A. Noguera, personal communication). Columbia provides a similar example (11).

Further details of the experiences of different countries with national iodine deficiency disorders control programs are reviewed elsewhere (8, 23, 30).

INTERNATIONAL ACTION

The wide gap between new knowledge of the iodine deficiency disorders and the application of this knowledge through national control programs in developing countries has led to the formation of the International Council for the Control of Iodine Deficiency Disorders (ICCIDD). The inaugural meeting of this multidisciplinary group of epidemiologists, nutritionists, endocrinologists, chemists, planners, and economists was held in Kathmandu, Nepal, in March 1986. A series of papers presented in Kathmandu on all aspects of iodine deficiency disorder control programs was published (33). The ICCIDD has now established a global multidisciplinary network of some 300 people with expertise relevant to these disorders and programs to control them. It works closely with the World Health Organization, the United Nations International Children's Emergency Fund (UNICEF), and national governments within the United Nations system in the development of national programs (31).

The feasibility of substantial progress in the prevention and control of iodine deficiency disorders in the next 5–10 years was endorsed in a World Health Assembly Resolution in 1986 (77). A global strategy for a ten-year program has now been adopted by the United Nations agencies (31, 75). These various developments encourage the hope that significant progress can be made in the prevention and control of iodine deficiency disorders within the next decade with great benefits to the quality of life of the many millions affected.

Literature Cited

1. Bautista, A., Barker, P. A., Dunn, J. T., Sanchez, M., Kaiser, D. L. 1982. The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school-age children from an area of endemic goiter. *Am. J. Clin. Nutr.* 35:127–34
2. Bleichrodt, N., Garcia, I., Rubio, C., Morreale de Escobar, G., Escobar Del Rey, F. 1987. Developmental disorders associated with severe iodine deficiency. See Ref. 34, pp. 65–84
3. Bourdoux, P. P. 1988. Measurement of iodine in the assessment of iodine deficiency. *Iodine Defic. Disord. Newsl.* 4:8–12
4. Bourdoux, P., Thilly, C., Delange, F., Ermans, A. M. 1986. A new look at old concepts in laboratory evaluation of endemic goiter. See Ref. 23, pp. 115–29
5. Burgi, H., Rutishauser, R. 1986. Iodization of salt and its surveillance. See Ref. 23, pp. 155–63
6. Buttfield, I. H., Hetzel, B. S. 1969. Endemic cretinism in Eastern New Guinea. *Australas. Ann. Med.* 18:217–21
7. Chawla, N. 1987. Reaching the hundredth monkey: Problems and opportunities in communication for IDD control. See Ref. 33, pp. 177–80
8. Clugston, G. A., Dulberg, E. M., Pandav, C. S., Tilden, R. L. 1987. Iodine deficiency disorders in South East Asia. See Ref. 33, pp. 273–308
9. Connolly, K. J., Pharoah, P. O. D., Hetzel, B. S. 1979. Fetal iodine deficiency and motor performance during childhood. *Lancet* 2:1149–51
10. Connolly, R. J., Vidor, G. I., Stewart, J. C. 1970. Increase in thyrotoxicosis in endemic goiter area after iodation of bread. *Lancet* 1:500-2
11. Cordoba, C. A., Carrillo, J. C., Marin, C. A. 1986. Current status of endemic goiter and salt iodization in Colombia. See Ref. 23, pp. 266–70
12. Costa, A., Cottino, F., Mortara, M., Vogliazzo, U. 1964. Endemic cretinism in Piedmont. *Panminerva Med.* 6:250–59
13. Crantz, F. R., Larsen, P. R. 1980. Rapid thryoxine to 3,5,3'-triiodothyronine conversion binding in rat cerebral cortex and cerebellum. *J. Clin. Invest.* 65:935–38
14. Delange, F., Bastani, S., Benmiloud, M., DeMaeyer, E., Isayama, M. G., et al. 1986. Definitions of endemic goiter and cretinism, classification of goiter size and severity of endemias, and survey techniques. See Ref. 23, pp. 373–76
15. Delange, F., Heidemann, P., Bourdoux, P., Larsson, A., Vigneri, R., et al. 1986. Regional variations of iodine nutrition and thyroid function during the neonatal period in Europe. *Biol. Neonate* 49:322–30
16. Delange, F., Iteke, F. B., Ermans, A. M. 1982. *Nutritional Factors Involved in the Goitrogenic Action of Cassava.* Ottawa: Canada 1, Int. Dev. Res. Cent.
17. Dobbing, J. 1974. The later development of the brain and its vulnerability. In *Scientific Foundations of Paediatrics,* ed. J. Davis, J. Dobbing, pp. 565–77. London: Heinemann Medical
18. Dulberg, E. M., Widjaja, K., Djokomoeljanto, R., Hetzel, B. S., Belmont, L. 1983. Evaluation of the iodization program in Central Java with reference to the prevention of endemic cretinism and motor coordination defects. In *Current Problems in Thyroid Research,* ed. N. Ui, K. Torizuka, S. Nagataki, K. Miyai, pp. 19–22. Amsterdam: Excerpta Medica
19. Dunn, J. T. 1986. Oral iodized oil for the control of IDD. *Iodine Defic. Disord. Newsl.* 2:2
20. Dunn, J. T. 1986. Prophylaxis of iodine deficiency disorders with iodized salt in Latin America. In *Iodine Deficiency Disorders and Congenital Hypothyroidism,* ed. G. Medeiros-Neto, R. M. B. Maciel, A. Halpern, pp. 133–38. Sao Paulo:Ache
21. Dunn, J. T. 1987. Alternatives to salt and oil for iodine supplementation. See Ref. 33, pp. 135–38
22. Dunn, J. T. 1987. Iodized oil in the treatment and prophylaxis of IDD. See Ref. 33, pp. 127–34
23. Dunn, J. T., Pretell, E. A., Daza, C. H., Viteri, F. E., eds. 1986. *Towards the Eradication of Endemic Goiter, Cretinism, and Iodine Deficiency.* Washington, DC: Pan Am. Health Organ. 403 pp.
24. Duran Garcia, S., Duarte Ortiz, B., Alvarez Benitez, J. C., Hurtado Ayusa, J. E., Picamilla Vela, M. T., et al. 1987. Effectos de la administracion oral de aceite yodado sobre la prevalencia de bocio, elminacion urinaria de yodo y niveles de tiroxina en areas de endemia bociosa de Andalucia occidental. *Endocrinologia* 34:23–28
25. Ermans, A. M., Bourdoux, P., Lagasse, R., Delange, F., Thilly, C. 1980. Congenital hypothyroidism in developing countries. In *Neonatal Thyroid Screening,* ed. G. N. Burrow, pp. 61–73. New York: Raven

26. Ermans, A. M., Mbulamoko, M., Delange, F., Ahluwalia, eds. 1980. *Role of Cassava in the Etiology of Endemic Goiter and Cretinism*. Ottawa: Int. Dev. Res. Cent.
27. Fierro-Benitez, R., Cazar, R., Stanbury, J. B., Rodriguez, P., Garces, F., et al. 1986. Long-term effect of correction of iodine deficiency on psychomotor and intellectual development. See Ref. 23, pp. 182–200
28. Fierro-Benitez, R., Stanbury, J. B., Querido, A., De Groot, L., Alban, R., Endova, J. 1970. Endemic cretinism in the Andean Region of Ecuador. *J. Clin. Endocrinol. Metab*. 30:228–36
29. Hetzel, B. S. 1983. Iodine Deficiency Disorders (IDD) and their eradication. *Lancet* 2:1126–29
30. Hetzel, B. S. 1987. An overview of the prevention and control of iodine deficiency disorders. See Ref. 33, pp. 7–31
31. Hetzel, B. S. 1987. Progress in the prevention and control of iodine deficiency disorders. *Lancet* 2:266
32. Hetzel, B. S., Chavadej, J., Potter, B. J. 1988. The brain in iodine deficiency. *Neuropathol. Appl. Neurobiol*. 14:93–104
33. Hetzel, B. S., Dunn, J. T., Stanbury, J. B., eds. 1987. *The Prevention and Control of Iodine Deficiency Disorders*. Amsterdam: Elsevier. 335 pp.
34. Hetzel, B. S., Potter, B. J. 1983. Iodine deficiency and the role of thyroid hormones in brain development. In *Neurobiology of the Trace Elements*, ed. I. Dreosti, R. M. Smith, pp. 83–133. New Jersey: Humana
35. Hetzel, B. S., Potter, B. J., Dulberg, E. M. 1989. The iodine deficiency disorders: Nature, pathogenesis and epidemiology. *World Rev. Nutr. Diet*. In press
36. Hetzel, B. S., Thilly, C. H., Fierro-Benitez, R., Pretell, E. A., Buttfield, I. H., Stanbury, J. B. 1980. Iodized oil in the prevention of endemic goiter and cretinism. See Ref. 70, pp. 513–32
37. Jolin, T., Excobar Del Rey, R. 1965. Evaluation of iodine creatinine ratios of casual samples as indices of daily urinary output during field studies. *J. Clin. Endocrinol. Metab*. 25:540–42
38. Karmarkar, M. G., Deo, M. G., Kochupillai, N., Ramalingaswami, V. 1974. Pathophysiology of Himalayan endemic goiter. *Am. J. Clin. Nutr*. 27:96–103
39. Kelly, F. C., Snedden, W. A. 1960. Prevalence and geographical distribution of endemic goiter. In *Endemic Goiter*, pp. 27–333. Geneva: WHO
40. Konig, M. P., Veraguth, P. 1961. Studies of thyroid function in endemic cretins. In *Advances in Thyroid Research*, ed. R. Pitt-Rivers, pp. 294–98. London: Pergamon
41. Langer, P. 1960. History of goiter. In *Endemic Goiter*, pp. 9–25. Geneva: WHO
42. Larsen, P. R., Silva, J. E., Hetzel, B. S., McMichael, A. J. 1980. Monitoring prophylactic programs: General consideration. See Ref. 70, pp. 551–66
43. Li, J. Q., Wang, X. 1987. Jixian: A success story in IDD control. *Iodine Defic. Disord. Newsl*. 3:4–5
44. Lu, T. A., Ma, T. 1986. Clinical investigation in China on the use of oral versus intramuscular iodized oil in the treatment of endemic goiter. See Ref. 20, pp. 103–9
45. Ma, T., Lu, T., Tan, U., Chen, B., Zhu, H. I. 1982. The present status of endemic goiter and endemic cretinism in China. *Food Nutr. Bull*. 4:13–19
46. Maberly, G. F., Eastman, C. J., Corcoran, J. M. 1981. Effect of iodination of a village supply on goiter size and function. *Lancet* 2:1270–72
47. Maberly, G. F., Eastman, C., Waite, K. V., Corcoran, J., Rashford, V. 1983. The role of Cassava. See Ref. 18, pp. 341–44
48. McCarrison, R. 1980. Observations on endemic cretinism in the Chitral and Gilgit valleys. *Lancet* 2:1275–80
49. McMichael, A. J., Potter, J. D., Hetzel, B. S. 1980. Iodine deficiency, thyroid function, and reproductive failure. See Ref. 70, pp. 445–60
50. Mannar, M. G. V. 1987. Control of iodine deficiency disorders by iodination of salt: Strategy for developing countries. See Ref. 33, pp. 111–25
51. Manoff, R. K. 1987. Social marketing: New tool to combat iodine deficiency disorders. See Ref. 33, pp. 165–75
52. Marine, D., Kimball, O. P. 1921. The prevention of simple goiter in man. *J. Am. Med. Assoc*. 77:1068–72
53. Medeiros-Neto, G., Djokomoeljanto, R., Benmiloud, M., Deblanco, M. C., Irie, M., et al. 1987. The monitoring and evaluation of IDD control programs: Report of an ICCIDD committee. See Ref. 33, pp. 157–63
54. Muzzo, S., Leiva, L., Carrasco, D. 1986. Influence of a moderate iodine deficiency upon intellectual coefficient of school age children. See Ref. 20, pp. 40–45
55. Obregon, M. J., Santisteban, P., Rodriguez-Pena, A., Pascual, A., Cartagena, P., et al. 1984. Cerebral hypothyroidism in rats wth adult-onset iodine deficiency. *Endocrinology* 115:614–24
56. Olesen, R. 1927. Iodization of public water supplies for prevention of endemic

goiter. *Public Health Rep.* 42:1355–65
57. Pandav, C. S., Carriere, R. C., Kochupillai, N., Ma, T., Nath, L. M. 1987. The planning and management of IDD control programs: Report of an ICCIDD committee. See Ref. 33, pp. 149–56
58. Pharoah, P. O. D., Buttfield, I. H., Hetzel, B. S. 1971. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet* 1:308–10
59. Pharoah, P. O. D., Connolly, K. J. 1987. A controlled trial of iodinated oil for the prevention of endemic cretinism: A long term follow up. *Int. J. Epidemiol.* 16:68–73
60. Pharoah, P. O. D., Connolly, K. J., Hetzel, B. S., Ekins, R. P. 1981. Maternal thyroid function and motor competence in the child. *Dev. Med. Child Neurol.* 23:76–82
61. Pharoah, P. O. D., Delange, F., Fierro-Benitez, R., Stanbury, J. B. 1980. Endcmic cretinism. Scc Ref. 70, pp. 395–421
62. Pharoah, P. O. D., Ellis, S. M. N., Ekins, R. P., Williams, E. S. 1976. Maternal thyroid function, iodine deficiency and fetal development. *Clin. Endocrinol.* 5:159–65
63. Pretell, E. A., Torres, T., Zenten, V., Comejo, M. 1972. Prophylaxis of endemic goiter with iodized oil in rural Peru. In *Human Development and the Thyroid Gland: Relation to Endemic Cretinism*, ed. J. B. Stanbury, R. Korc. *Adv. Exp. Med. Biol.* 30:249–65. New York: Plenum
64. Rivadeneira, M., Acevedo, A., Concha, D., Ferraro, O., Garmendia, F., et al. 1986. Recommendations on the functions of the government and international institutions in prophylactic programs. See Ref. 23, pp. 393–96
65. Sigui, A. A. 1986. Endemic goiter in Guatemala. See Ref. 23, pp. 300–2
66. Sooch, S. S., Deo, M. G., Karmarkar, M. G., Kochupillai, N., Ramachandran, K., Ramalingaswami, V. 1973. Prevention of endemic goiter with iodized salt. *WHO Bull.* 49:307–12
67. Squatrito, S., Vigneri, R., Runello, F., Ermans, A. M., Polley, R. D., Ingbar, S. H. 1986. Prevention and treatment of endemic iodine deficiency goiter by iodination of a municipal water supply. *J. Clin. Endocrinol. Metab.* 63:368–75
68. Stanbury, J. B., Brownell, G. L., Riggs, D. S., Perinetti, H., Itoiz, J., Del Castillo, E. B. 1954. *The Adaptation of Man to Iodine Deficiency*, pp. 11–209. Cambridge: Harvard Univ. Press
69. Stanbury, J. B., Ermans, A. M., Hetzel, B. S., Pretell, E. A., Querido, A. 1974. Endemic goiter and cretinism: Public health significance and prevention. *WHO Chron.* 28:220–28
70. Stanbury, J. B., Hetzel, B. S., eds. 1980. *Endemic Goiter and Endemic Cretinism: Iodine Nutrition in Health and Disease*. New York: Wiley & Sons 606 pp.
71. Stewart, J. C., Vidor, G. I., Buttfield, I. H., Hetzel, B. S. 1971. Epidemic thyrotoxicosis in Northern Tasmania: Studies of clinical features and iodine nutrition. *Aust. N. Z. J. Med.* 1:203–11
72. The IDD Messagc: Gctting it to the consumer. 1987. *Iodine Defic. Disord. Newsl.* 3:3–7
73. Thilly, C. H. 1981. Goitre et cretinisme endemiques: Role etiologique de la consommation de manioc et strategie d'eradication. *Bull. Belg. Acad. Med.* 136:389–412
74. Thilly, C H., Calderoli, V. G., Castillo, V. O., Daza, C. H., Feican, M. I. T., et al. 1986. Recommendations for planning, surveillance, and technical conduct of prophylactic programs. See Ref. 23, pp. 387–92
75. United Nations Adm. Coord. Comm. Subcomm. Nutr. 1987. A global strategy for the prevention and control of iodine deficiency disorders: Proposal for a ten-year program of support to countries. Rome: United Nations Adm. Coord. Comm.
76. Vidor, G. I., Stewart, J. C., Wall, J. R., Wangel, A., Hetzel, B. S. 1973. Pathogenesis of iodine-induced thyrotoxicosis. Studies in Northern Tasmania. *J. Clin. Endocrinol. Metab.* 37:901–9
77. World Health Assembly. 1986. 39th World Health Assem., Resolution 29. Geneva: WHO