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IODINE DEFICIENCY, IODINE EXCESS AND THE USE OF IODINE FOR PROTECTION AGAINST RADIOACTIVE IODINE

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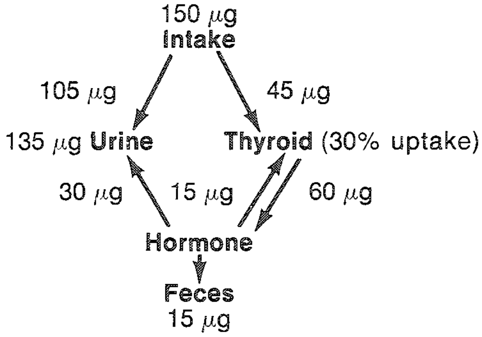
Iodine deficiency goiter, the most common form of endemic goiter, is still a major public health problem in many parts of the world. In the United States, however, as in a number of other formerly affected countries this disease has totally disappeared. In part, this is a result of a program of iodine supplementation. But even more, at least in some areas, it stems from changes in food production and availability so that the iodine content of certain foods is high and few regions are isolated from iodine in their food supply. In fact, the change in iodine intake in the United States has been so profound in the past 20 years or so, that it now exceeds the normal requirement by a considerable amount.

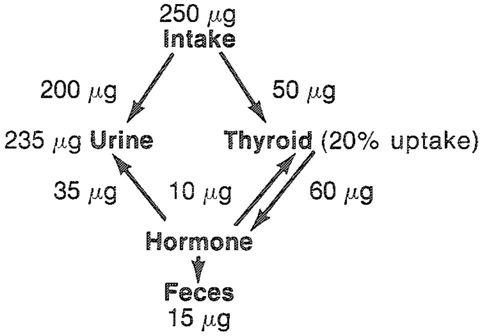
The normal adult thyroid gland secretes about 60 μg of iodine per day in the form of thyroid hormone, mainly thyroxine, when dietary iodine is adequate.[1] About 15 μg of this iodine is excreted in the feces, leaving 45 μg to be distributed between the thyroid and the urine after the hormone is deiodinated. Figure 1 depicts the overall iodine balance in the USA before 1960 ("usual" daily intake=150 μg) and after 1960 ("usual" intake=250 μg, "upper normal" intake=600 μg). Before 1960, balance was achieved when the thyroid uptake was 30% of the total intake. After 1960, the "usual" thyroid uptake is near 20% and may be as low as 8 to 9%. A borderline sufficient intake of 60 μg is seen in parts of Europe. There the thyroid uptake is 50% and the urine excretion about 45 μg.[2] As the intake becomes lower, however, the thyroid becomes more efficient by secreting T3 in preference to T4; thus, the body's needs are met by a smaller amount of iodine in the gland's secretion.

Figure 1.
Daily Iodine Balance in the U.S.A.

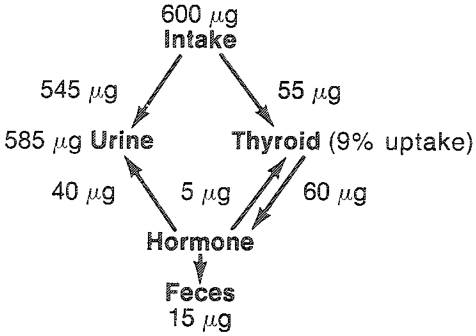
Before 1960, "usual" intake



After 1960, "usual" intake



After 1960, "upper normal" intake



The simplified scheme shown in Figure 1 also does not take into account the intrathyroid turnover and reutilization of iodine derived from deiodination of mono- and diiodotyrosine. Furthermore, under some conditions (e.g., excess iodine intake over a prolonged period of time), this non-hormonal iodine leaves the gland as the so-called "iodide leak" and reenters the extrathyroid iodide pool.

Table 1 gives the "optimal" and "safe" levels of iodine intake defined by the Food and Nutrition Board, National Research Council[2] and compares these with the levels prevalent in the United States and in regions of iodine deficiency. It is evident that the thyroid can adapt to extreme variations in iodine intake. An adjustment, mainly in fractional thyroid uptake, occurs very slowly so that "absolute" iodine uptake remains relatively fixed (Fig.1). Although there typically are large swings in iodine intake from day to day,[3] this causes no change in the fractional thyroid uptake, so as a result iodine balance on a particular day may be either positive or negative.

Table 1.
Daily Iodine Intake Ranges[1,2]

	μg/day
"Optimal" intake	150-300
"Safe" intake	50-1000
USA: "usual" intake pre 1960	150
"usual" intake post 1960	200-300
"upper level" intake post 1960	600-700
Mild deficiency (no goiter but increased thyroid uptake)	60-80
Mild endemic goiter	50-80
Severe endemic goiter	10-20

The iodine which is ingested comes from a number of food sources, the major ones being seafood, dairy products and eggs. When iodized salt is used (1 part KI in 10,000 in the USA), an intake of 10 g NaCl carries with it 760 μg of iodine.[4] In other countries, the KI level in salt is 10 times lower. Thus, salt can be an important source of iodine in the American diet.

An extensive search for goitrogenic substances—compounds which inhibit hormonogenesis—has failed to implicate them as a cause of endemic goiter, except in a few instances. Ironically, one of the best documented is "coastal goiter" in Hokkaido, Japan, caused by iodide *excess* (see below). Another is the recent partial elucidation of a goitrogen in water in Colombia, South America.[5] It is generally believed, however, that mild goitrogens may synergize with mild iodine deficiency to cause hormone production to fall into a clinically significant range. The resulting increase in TSH secretion from the pituitary produces a diffuse goiter which in time becomes grossly nodular. When the gland reaches the limit of its ability to compensate by increasing the rates of iodine accumulation, organification and secretion, and by converting from T4 to T3 production, a state of hypothyroidism ensues.

In areas of severe iodine deficiency, cretinism occurs among the children, often associated with deafness and neuromuscular disorders. After considerable efforts to identify additional etiologic factors for this devastating disorder, it is now generally accepted that its only cause is severe thyroid hormone deprivation during the early development of the nervous system.[6] Adequate iodine replacement in women and children completely eliminates endemic cretinism from the population.

The method of iodine replacement must take into account the socioeconomic status of the community. In more highly developed areas, iodination of salt or bread is the most common approach. In primitive or isolated societies, however, the recent introduction of intermittent treatment wih iodized oil (40% iodine) has had a dramatic effect.[1,2] Administered either by mouth or, more commonly, by depot injection in the muscle, a dose of 100 to 1000 mg iodine given once every 3 to 5 years can totally eradicate the occurrence of goiter, hypothyroidism and cretinism.

Effect of Mild Iodine Excess (2 mg or less per day)

None of these considerations apply to health in the United States. Instead, it has gradually been recognized that we must address the question of whether the unusually high iodine content of our diet might produce disorders of iodine excess. Although there are a few indications that this could happen, it is probably correct to state that the chronic ingestion of up to 2 mg iodine per day is safe. A large scale investigation of the ingestion of 2 to 4 mg iodine, at least half of which was derived from the use of iodine to purify drinking water, failed to reveal any detrimental effects in 750 individuals studied over a period of 9 months.[7]

One effect which probably does occur is the exacerbation of hyperthyroidism in individuals affected by Graves' disease or autonomously functioning nodular goiter. This has been seen in regions of endemic goiter when iodine supplementation is instituted,[1,2] indicating that hyperthyroidism can sometimes be averted by limiting the intake of iodine and thus the ability to make thyroid hormone. Introduction of a few hundred micrograms of iodine apparently can transform a euthyroid Graves' disease to active hyperthyroidism; whether increasing iodine intake further can convert mild hyperthyroidism to more severe thyrotoxicosis is not well documented. It is said, however, that the cases encountered during prophylaxis of endemic goiter, including those given large amounts of iodized oil, are generally mild and easily treated.[8] The possibility of inducing or exacerbating hyperthyroidism when iodine is added to foods or water is a significant question for epidemiologists. At present, however, we have no guidelines on which to base a firm conclusion about the risk-benefit relationship. The present concensus is that these levels of mild iodine excess are not of sufficient risk to require any modification.

Effects of Large Iodine Excess

The ingestion of a large iodine excess is usually the result of taking a medication which contains iodine, the simplest of which is sodium or potassium iodide. The amount usually given to control hyperthyroidism is 150 to 300 mg iodine per day. Larger amounts of iodide, 500 to 1000 mg per day, are often used as expectorants in chronic lung disease. Many other drugs used for non-thyroid purposes also contain iodine. These include the x-ray contrast "dyes" used for venography and arteriography, pyelography, cholecystography, myelography and other radiographic procedures. A large spectrum of agents is used, differing mainly in their rate of excretion. All are iodine-substituted organic chemicals, and the usual dose contains from 5 to 40 g of iodine. Enough iodine is liberated during their metabolism to affect thyroid iodine metabolism.

When such a large quantity of iodine is ingested, there is a possibility that thyroid iodine metabolism will be adversely affected.[9,10] In most normal individuals, there is only a transient and clinically unimportant interference with hormone synthesis[11]—the so-called Wolff-Chaikoff effect. A small proportion of the American population, however, has a genetic inability to escape from this inhibition, so if high iodine intake with blood iodide above 20 μg/dl continues over a prolonged period, usually a few months to years, hypothyroidism and goiter (so-called "iodide goiter") ensues. This is the etiology of "coastal goiter" in Japan, where about 10% of the population is affected.[12] In these people, ingestion of 10 to 200 mg of iodine per day, mostly in the form of seaweed, causes this very unusual type of endemic goiter. Hypothyroidism, however, is rare. A particularly dangerous but rare form of iodide goiter occurs in susceptible infants when exposed to excess iodide during fetal life. Whereas iodide goiter and the resulting hypothyroidism is completely reversible in adults, the newborn child may have irreversible brain damage and seriously compromised respiration caused by the large goiter. Also, as in endemic iodine deficiency, a co-goitrogen in a medication (for example, lithium or sulfadiazine or aminopyrine) may intensify the block of hormonogenesis induced by the high iodide level.

In the United States, a much more common event which enhances the effect of iodine excess is the presence of a second, unrelated thyroid disorder. As a result, the ingested iodine can produce either hypothyroidism or hyperthyroidism, depending on the particular thyroid abnormality. Hypothyroidism may be induced when 150 to 200 mg iodine per day is given to subjects with lymphocytic thyroiditis or with a thyroid gland partially destroyed by therapeutic radioiodine or thyroidectomy.[13,14] In these cases, the damaged thyroid is unable to escape from the Wolff-Chaikoff effect. In cystic fibrosis, although there is no known thyroid disease, prolonged use of high doses of KI may cause goiter in a high proportion of patients.[10,15] Hyperthyroidism may occur when a similarly large amount of iodine is given to individuals with nodular goiter.[16] In this instance, if there is autonomous iodine metabolism in the goiter, the excess substrate is converted into excess hormone.

Despite the fact that thyroiditis and nodular goiter are relatively common in the American population, we can conclude that a large iodine excess can be safely given to a large segment of the population. This comes from the observation that probably more than 10^8 doses of 300 mg of iodide are administered annually with apparently very few untoward reactions attributable to the iodine.[17]

The same can be said for the extrathyroidal effects of iodine excess. Large doses of iodine are capable of producing, in susceptible persons, acute inflammation of the salivary glands, a pustular skin eruption, and a variety of symptoms including fever, joint pains and other allergic manifestations.[17,18,19] These, also, must be rare occurrences, and the effects are reversible. Altogether, when one considers the enormous number of people exposed to large amounts of iodine, these effects appear to represent a trivial public health hazard. This is especially so when considering the brief duration of thyroid blockade to be discussed below. On the other hand, thought should be given to the possibility of developing guidelines to identify persons who would be especially sensitive to iodide side reactions.

Protection of the Thyroid Gland Against Damage by Radioiodine

Much thought has been given to the use of iodine to protect the thyroid gland in the event of unwanted exposure to radioactive iodine isotopes. Potential sources of exposure are widespread and are increasing; they include medical uses of radioiodine, nuclear explosives and, especially, nuclear power reactors. The subject has recently been dramatized by the Three Mile Island reactor accident in Pennsylvania, and considerable controversy has arisen over the risk-benefit considerations. Inasmuch as no clear guidelines have been issued on the subject, it is even more important that physicians should have enough information to act or provide advice in an emergency.

A recent report on the subject by the National Council on Radiation Protection[17] and a related article[20] thoroughly discuss the background of the problem, including the nature and risks of reactor accidents, alternative methods for protecting the thyroid gland, and the problems and methods in using iodine. Certainly the thyroid gland is not the only, or even the most important, organ at risk; but radioiodine isotopes are prominent contaminants in reactor accidents, and protection against their effects is both possible and feasible, and therefore, a reasonable goal.

Radioiodines with mass numbers 131 to 135 have sufficiently long half-lives to be important as potential hazards, and an operating reactor core accumulates large quantities of these isotopes in a few weeks (Table 2). A power reactor which, at one-third efficiency produces 700 megawatts (electrical) from 2100 megawatts (thermal), will contain 6.1×10^7 curies of ^{131}I alone. A loss-of-coolant accident which releases to the surroundings only 1% of the radioiodine from such a reactor has been estimated, under the most unfavorable weather conditions, to give almost 500 rads from ^{131}I to a child's thyroid at 75 Km and to an adult's thyroid at 30 Km (from Ilin, et al., quoted in reference 20). Thus, even a small leak may not be trivial.

In the event of radioiodine fall-out on cow pastures, the isotopes are concentrated in milk, which may then be ingested. The best protection, obviously, is to avoid intake of fresh milk products. Radioiodine can also be accumulated by inhalation. For this, the alternatives are evacuation to a safe distance or blockade of thyroid iodine uptake. To block uptake, a number of drugs can be considered, but iodide is known to be effective and is the least toxic. A dose of 100 mg (130 mg KI) given simultaneously with radioiodine will reduce the uptake to 0.5 to 1%, at least in the U.S.A.,[21] and this dose given once daily will maintain the blockade indefinitely. A dose of iodide considerably smaller than 100 mg is effective when administered chronically,[22] and a single large dose of iodized oil, as used to control endemic goiter, also gives a prolonged blockade. Such long term prophylaxis, however, is unlikely to be needed. The exact mechanism of the blocking effect of iodide is still obscure but is not simply a dilution effect and probably involves some metabolic product of the iodine produced in the thyroid gland and affecting iodide transport.[20]

Table 2.
Iodine isotopes which are potential hazards[17,20]

Mass Number	Half-life	Yield* (%)	Saturation Inventory† Ci/Megawatt (thermal)	Contribution to Total Thyroid Dose in First Few Days** (%)
131	8.05d	2.9	2.5×10^4	60
132	2.3h	4.6	3.8×10^4	
133	20.8h	7.2	5.6×10^4	30
134	0.88h	10.0	6.6×10^4	
135	6.7h	8.4	5.1×10^4	

*Sum of direct and decay yields.

†Curies of isotope present in the reactor at equilibrium per megawatt energy produced.

**^{132}I, ^{134}I, ^{135}I contribute the remaining 10%. After a few days, almost all of the dose is from ^{131}I.

Since most of a given dose of radioiodine is taken up by the thyroid within a few hours, early administration of the blocking dose has an obvious advantage. In a reactor accident, however, exposure to radioiodine is likely to continue over some period of time, and blockade during any part of it can be useful. The dosage form of iodide can be as a liquid (saturated KI solution which contains 1 gm KI/ml), but tablets are much more advantageous because they are easy to store and administer. The Food and Drug Administration has approved a tablet containing 130 mg KI (100 mg I^-) for this purpose. If properly stored, for example, in sealed individual light-proof wrappers, the chemical should be stable for long periods and this could be easily monitored.

Since stockpiling of KI tablets and the provision of means for rapid distribution in an emergency are not only expensive but also formidable logistic problems, one must ask whether a situation could ever arise in which its use would be indicated. This question is still under debate. That the thyroid gland is at risk when exposed to radiation is not arguable, but the radiation effects—hypothyroidism, and thyroid tumors which have a relatively benign clinical behavior—are perhaps tolerable. In a cost-benefit analysis, however, one must consider not only the threat to life and well-being but also the economic and emotional cost associated with the requirement for diagnosis and surgical treatment of thyroid nodules. To me, the question is not whether KI prophylaxis will *ever* be needed, but rather at what level of exposure will it be required. It does seem that the dose tentatively proposed by the NCRP (10 to 30 rad) may be unnecessarily low.

Extensive data are available on the risk to the thyroid of exposure to x-rays.[23] Although even a dose as low as 6 rads to a child's thyroid can produce a detectable increase in thyroid cancer, it requires about 100 rads to give an incidence of additional thyroid nodules of about 0.1% per year, about one-third of which are malignant. The risk of thyroid cancer and total nodules after radiation in childhood are about 4 and 12 cases per million per rad per year, respectively.

Similar information for exposure to radioiodine is meager, but it appears that ^{131}I is 10 to 50 times less damaging on a rad for rad basis.[17,23] A few data suggest that diagnostic doses of ^{131}I, giving an estimated mean exposure to the thyroid of 159 rads in young subjects (<20 years), have had no deleterious effect,[24] whereas treatment of hyperthyroidism with 2 to 10 mCi of ^{131}I (3000 to 17,000 rads) produces hypothyroidism in about 20 to 50% of the cases, usually many years after treatment.[23] Larger doses of ^{131}I (>20,000 rads) can produce radiation thyroiditis and early hypothyroidism. Marshallese children, who probably received about 1000 rads, had a high incidence of thyroid nodules and cancer developed in one of 23 who were exposed.[25] In this accident, radiation came from short-half-life iodine isotopes as well, and it is believed that these are more damaging than ^{131}I.

From these considerations, it can be proposed that 500 rads from radioiodine isotopes might be a reasonable exposure for which iodide blockade on a large scale should be considered. This dose is produced by about 400 μCi ^{131}I in adults. In a child's thyroid, which develops a higher radioiodine concentration because of its smaller size, 500 rads is produced by about 150 μCi at age 10 years, by 50 μCi at 1 year, and by 15 μCi in a newborn infant.[26] Although any guidelines such as these are quite arbitrary, we need to establish reasonable criteria for administering iodide blockade to a large population. Assuming that ^{131}I would cause one nodule per million per rad per year, a dose of 500 rads in a child can be estimated to increase the incidence of thyroid nodules from about 0.1% per year (the rate in the general population) to 0.15% per year. If the death rate from thyroid cancer were to increase proportionately, and since this rate was 1150 in the U.S. population in 1976, we would expect about 2.5 additional deaths per million persons per year. In adults, the risk would be much smaller. These exposures are tentatively chosen as being of a high enough potential risk for producing thyroid disease to warrant large scale iodide administration, which itself might be associated with some morbidity and even mortality. They are obviously subject to change as more information on risk/benefit is developed.

There seems to be little argument against making KI available to reactor personnel, since these individuals would be at high risk and the logistics of providing KI are simple. Distribution to a large population in the reactor's vicinity, however, would be a formidable task, especially when emergency workers are overwhelmed with other tasks. Perhaps the most favored idea is to stockpile KI tablets in community centers such as fire houses, police stations, clinics, etc., from which 10-day supplies of the tablets would be provided. Another possibility is to distribute KI to all households within an appropriate range of each reactor facility. A compromise would be to distribute one dose of KI for each person in a household, together with explanatory material about taking the medication and information on how to obtain the continuing supply. This could decrease the delay in instituting the blockade if the need should come with little warning. It seems that this amount of KI in the community is unlikely to lead to serious abuse, and the brief exposure to KI which is anticipated (probably no more than 10 days) is unlikely to give serious side reactions.

Special consideration must be given to the use of iodide in pregnant or lactating women and young children. The most important point is that the fetus and the young child are more vulnerable to radiation effects and, therefore, more in need of either evacuation or iodide blockade. Despite the serious effects of iodide goiter in the fetus, it is extremely unlikely that the amount and duration of iodide therapy recommended for protection would have this result. In lactation, one should note that iodide is secreted in the milk, but the amount in a woman receiving iodide should not be relied upon to protect the infant. Thus, pregnant women and young children should be given KI when the risk of significant exposure is high. The blocking dose in infants could be reduced to one-half (65 mg KI), but there is no reason to believe that the full adult dose is less safe.[17]

The above discussion applies to giving KI to a large population; other considerations are needed in dealing with exposures of one or a few persons. Iodide, usually 500 mg, is routinely given to persons who work with volatile forms of radioiodine 10 to 30 minutes preceding the potential exposure, or to patients receiving certain ^{131}I-containing diagnostic agents. A more complicated situation arises after radioiodine has already accumulated in the thyroid gland. If the exposure criteria discussed earlier are met, release of the isotope from the gland can be induced by injecting bovine TSH (10 U, i.m. each day). The accumulated radioiodine can be monitored to determine the need for the procedure, and the expected prompt effect of the TSH can also be monitored. About 15% of thyroid ^{131}I is released after 1 day, and about 50% after 5 days, if thyroid uptake is blocked.[27] To block further uptake of radioiodine, an antithyroid drug (e.g., 20 mg of methimazole or 150 mg of propylthiouracil, q6h) has a theoretical advantage since iodide might reduce the discharge rate of the isotope already in the thyroid. On the other hand, this effect of KI on the secretion rate from a normal gland appears to be small. Obviously, this type of treatment would not be feasible on a large scale, and the potential toxicity of TSH and antithyroid drugs, as well as the possible enhancement of thyroid carcinogenesis by TSH and the added radiation to the body from the discharged organic iodine, need to be considered. At the present time, it is not clear that any therapy other than iodide blockade of uptake, if begun early enough to be effective, is warranted.

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