

R & R REGISTRATIONS

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October 19, 2000

Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

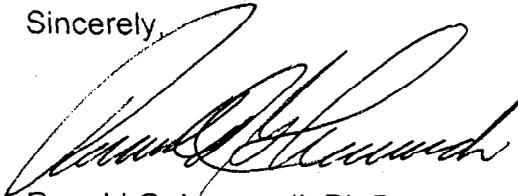
**RE: "POTASSIUM IODIDE RECIP" 65 MG TABLETS
Citizens Petition**

Dear Sir/Madame:

The enclosed submission is in reference to Section 505 of the Federal Food, Drug and Cosmetic Act (21 USC §355), and is a "Citizens Petition" requesting the Food & Drug Administration to allow the filing of an Abbreviated New Drug Application (ANDA) for Potassium Iodide 65 mg tablets.

Please do not hesitate to contact me at 858 586-0751 if there are any questions or you require additional information.

Sincerely,



Ronald G. Leonardi, Ph.D.
for Recip AB

Enclosure

CC: K. Schullstrom, Recip AB

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CITIZENS PETITION

The undersigned submits this Petition under Section 505 of the Federal Food, Drug and Cosmetic Act (21 USC §355), which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR §5.10. Petitioner requests the Commissioner of Food and Drugs to declare that the drug product, hereinafter described, is suitable for consideration in an abbreviated new drug application.

A. ACTION REQUIRED

By this petition, the undersigned requests permission of the Commissioner of Food and Drugs to file an abbreviated new drug application for a Potassium Iodide tablet dosage form containing 65 mg of Potassium Iodide.

B. STATEMENT OF GROUNDS

The Federal Food, Drug and Cosmetic Act as amended in 1984 provides under Section 505(j)(2)(C) that a petition may be filed with the Secretary seeking permission to file an abbreviated application for a new drug which has an active ingredient which differs from the listed drug in dosage form or strength. Such a petition must be granted unless the Secretary finds that investigations must be conducted to show the safety and effectiveness of the drug.

The petitioner requests permission to file an abbreviated new drug application for Potassium Iodide, 65 mg tablets. The listed drug is available as a tablet containing 130 mg of Potassium Iodide presently manufactured by ANBEX, Inc. and Carter-Wallace, Inc., the companies that have received FDA new drug application (NDA) approval for their non-prescription "radiation emergency potassium iodide" drugs.

It should be noted that the Federal Register (Volume 47, No. 125) dated June 29, 1982, states "FDA recommends that potassium iodide in doses of 130 milligrams (mg) per day for adults and children above 1 year and 65 mg per day for children below 1 year of age be considered for thyroid blocking in radiation emergencies..." It would be convenient

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to have this potency available so that adults could take two tablets for 130 mg dosage requirement and children one tablet for the prescribed 65 mg/day.

The Agency also states (Federal Register, Vol. 50, No. 142, p. 30258, July 24, 1985) that risks of side effects, such as allergic reactions, from the short-term use of relatively low doses of potassium iodide for thyroid blocking in a radiation emergency, are outweighed by the risks of radioiodine induced thyroid nodules or cancer, if the projected dose to the

thyroid gland is 25 rems or greater. Because FDA has authorized the non-prescription sale of "radiation emergency potassium iodide," it is legally available to organizations or individuals who, based on their own corporate or personal analysis, choose to have the drug immediately available.

Additionally, it states "This recommendation is made in full recognition of the potential positive effects of the drug, action by the FDA permitting KI over-the-counter sales, and the authority of State and local health officials to elect to distribute and use the drug based on the specific needs of individual sites.

Since the proposed product, containing 65 mg Potassium Iodide would be identical in active ingredient, and route of administration to currently marketed product, the safety and effectiveness of the proposed drug product is not expected to be different from that of the listed drug. Two tablets of the proposed potassium iodide tablet will be therapeutically equivalent to the 130 mg tablet IosatTM marketed by Anbex. This is based on the well known solubility, dissolution and absorption of potassium iodide resulting in an appropriate bioavailability profile for the 65 mg tablet of Potassium Iodide. The solubility¹ of potassium iodide is 1.43g per mL. The dissolution² profile of the 65 mg tablet is >85% in 30 minutes. The absorption³ of potassium iodide is well documented and noted to be rapid and high.

To the best of our knowledge, the proposed dosage form will not be violating any patents relating to the composition of the product or the method of manufacture.

We submit that the criteria of Section 505(j)(2)(C) are met and that the requested permission to file an abbreviated new drug application for the dosage form described above should be granted.

C. ENVIRONMENTAL IMPACT

The subject matter of this petition is covered in 21 CFR §25.23(c).

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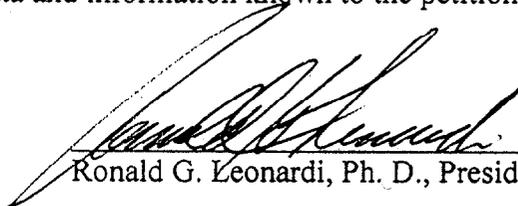
D. ECONOMIC IMPACT

The petition will provide this information upon request.

E. CERTIFICATION

The undersigned certifies, that, to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Signature:



Ronald G. Leonardi, Ph. D., President, R & R Registrations

Name of petitioner: Recip AB, c/o R & R Registrations

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References

1. Solubility – The Merck Index Twelfth edition, p. 1316
2. Dissolution – Recip's Specification for Potassium Iodide Tablets
3. Absorption –
 - 3.1 Matovinovic J. Iodine. Present knowledge in nutrition. 5 ed. Washington DC, The Nutrition Foundation, Inc. 1984:587-606
 - 3.2 Zanzonico PB, Becker DV. Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by ¹³¹I from radioactive fallout. Health Phys 2000;78(6):660-7.

✓
 THERAP CAT: Topical antiseptic (mucous membrane).
 THERAP CAT (VET): In feeds as a source of iodine.

7809. Potassium Iodide. Iodid; Thyroblock; Thyro-jod. KI ; mol wt 166.00. I 76.45%, K 23.55%. KI . Potassium iodide of commerce contains about 98.5% KI . Prep'd from HI and $KHCO_3$. Purification by melting in dry hydrogen: Lingane, Kolthoff, *Inorg. Syn.* 1, 163 (1939). Continuous electrolytic process for large scale industrial prep: Morylott, Elkins, U.S. pat. 2,989,450 (1961 to Dow). Toxicity data: Mikisbanczi, *Arch. Exp. Pathol. Pharmacol.* 96, 292 (1923). Use in the treatment of radiation poisoning resulting from a nuclear accident: W. K. Waterfall, *Brit. Med. J.* 281, 988 (1980); *Bull. N.Y. Acad. Med.* 57, 395 (1981).

Colorless or white, cubical crystals, white granules, or powder. Slightly deliquescent in moist air; on long exposure to air becomes yellow due to liberation of iodine, and small quantities of iodate may be formed; light and moisture accelerate the decomps. Aq solns also become yellow in time due to oxidation, but a small amount of alkali prevents it. d 3.12. mp 680° (volatilizes at higher temp). One gram dissolves in 0.7 ml water, 0.3 ml boiling water, 22 ml alcohol, 8 ml boiling alcohol, 51 ml abs alcohol, 8 ml methanol, 75 ml acetone, 2 ml glycerol, about 2.5 ml glycol. Potassium iodide solns readily dissolve elemental iodine. The aq soln is neutral or, usually, slightly alkaline. pH: 7-9. 30 g KI with 21 ml water gives 30 ml of a saturated soln at 25°. Approx LD₅₀ i.v. in rats: 285 mg/kg (Hildebrandt).

Incompat: Alkaloidal salts, chloral hydrate, tartaric acid and other acids, calomel, potassium chlorate, metallic salts.

USE: Manual photographic emulsions; in animal and poultry feeds to the extent of 10-30 parts per million; in table salt as a source of iodine and in some drinking water; also in anal. chemistry.

THERAP CAT: Antifungal; expectorant; iodine supplement. **THERAP CAT (VET):** In actinobacillosis, actinomycosis. For simple goiter. As expectorant. In iodine deficiency and in chronic poisoning with lead or mercury. Orally only, not by injection. Externally for treatment of bursal enlargements.

7810. Potassium Manganate(VI). K_2MnO_4 ; mol wt 197.13. K 39.67%, Mn 27.87%, O 32.46%. Preps: Scholder, *Waterstradt. Z. Anorg. Allgem. Chem.* 277, 172 (1954).

Dark green crystals; dec at 190°. Sol in water. Sol and stable in KOH solns. It is an oxidizing agent. With HCl it gives free chlorine.

7811. Potassium Metabisulfite. *Potassium pyrosulfite.* $K_2O_2S_2$; mol wt 222.33. K 35.17%, O 35.98%, S 28.85%. $K_2S_2O_5$. The article of commerce contains ~95% $K_2S_2O_5$.

White crystals or crys powder; sulfur dioxide odor; cold reaction; liberates SO_2 with acids; oxidizes in air to sulfate, more readily in presence of moisture. It may catch fire if much heat develops in powdering it. Freely sol in water; insol in alcohol. *Keep dry and well closed.*

USE: As antifermentative in breweries and wineries; bleaching straw; preservative for fruits and vegetables.

7812. Potassium Metaphosphate. *Potassium Kopp's salt; potassium polymetaphosphate; potassium polyphosphate.* $(KPO_3)_n$. High mol wt polymer; degree of polymerization dependent upon preparative conditions. Prep'd by dehydration of KH_2PO_4 : *Plantsch. Ber. J. Am. Chem. Soc.* 74, 6059 (1952). Structural studies: *Jost, Acta Cryst.* 16, 623 (1963); *Jost, Schulze, ibid.* 25B, 1110 (1969); *idem, ibid.* 27B, 1345 (1971). *Reviews of metaphosphates:* J. R. Van Wazer, *Phosphorus and its Compounds* vol 1 (Interscience, New York, 1958) pp 601-678; *Tilla, Advan. Inorg. Chem. Radiochem.* 4, 1-75 (1962).

White, monoclinic crystals. d 2.45. Insol in pure water. Sol in aq solns of alkali metal (except potassium) salts.

7813. Potassium Methyl Sulfate. CH_3KO_2S ; mol wt 150.20. C 8.00%, H 2.01%, K 26.03%, O 42.61%, S 21.35%. KCH_3SO_4 .

Hexahydrate, white crystals. Sol in water, alcohol. **USE:** In organic syntheses.

7814. Potassium Molybdate(VI). K_2MoO_4 ; mol wt 238.13. K 32.84%, Mo 40.29%, O 26.87%.

Pentahydrate, white, deliquescent, crys powder. Sol in 0.6 part water; insol in alc. *Keep dry.*

7815. Potassium Nitrate. Saltpeter; salm. wt 101.10. K 38.67%, N 13.85%, O 47.48%. ~99.5% KNO_3 .

Colorless transparent prisms, white gran powder; cooling, saline, pungent taste. d 2.11. at 400° with evolution of O_2 . One gram dissolves in 0.5 ml boiling water, 620 ml alc. Insol in abs alc. Dissolves in water with a temp. pH ~7. LD₅₀ orally in rabbits: 1.0 Doilehite, Rowe, *Southwest Vet.* 27, 346 (1974).

Caution: Ingestion of large quantities may cause gastroenteritis. Prolonged exposure to small amounts causes anemia, methemoglobinemia, nephritis.

USE: In fireworks, flares, pickling meats, matches, gunpowder, blasting powder, brass impregnating candle wicks; treating tobacco to evenly; tempering steel.

THERAP CAT: Diuretic.

7816. Potassium Nitrite. KNO_2 ; mol wt 45.94%. N 16.46%, O 37.60%. The article usually contains ~85% KNO_2 , the remainder chiefly of nitrate.

White or slightly yellow, deliquescent granules even by weak acids with evolution of brown nitrous anhydride. d 1.913; mp 441° (decolor 350°). Sol in 0.35 part water, slightly in abs alcohol. LD₅₀ orally in rats: 1.0 g/kg. Doilehite, Rowe, *Southwest Vet.* 27, 346 (1974).

USE: In analytical chemistry.

THERAP CAT: Vasodilator; antidote (cyanide).

7817. Potassium Nitroprusside. *Diphenyl (cyanonitrosyl)ferrous(2-)-K potassium nitroprusside(II).* $C_{10}FeK_2N_7O_{10}$; mol wt 294.14. N 18.99%, K 26.59%, Fe 28.57%, O 5.44%. $K_2Fe(CN)_5NO$. Dihydrate, garnet-red, hygroscopic crystals. Sol in alcohol. *Keep well closed.*

7818. Potassium Oleate. *Oleic acid potassium salt.* $C_{18}H_{33}KO_2$. Yellowish or brownish, soft mass. Sol in water; aq soln is alkaline to phenolphthalein. **USE:** Detergent.

7819. Potassium Oxamate(VI). $K_2O_2N_2$; mol wt 114.12. K 23.52%, O 19.25%, N 57.23%. $K_2C_2O_4$. Dihydrate, violet, hygroscopic crystals. Sol in water; insol in alcohol, ether. Slowly dec in formation of the ferruxide. *Keep well closed.*

7820. Potassium Oxalate. $C_2K_2O_4$; mol wt 144.14. K 47.03%, O 38.50%. $K_2C_2O_4$. Monohydrate, colorless, odorless crystals; warm dry air. *Poisonous!* d 2.13. Loses its water when ignited; is converted into carbonate with a little charring. Sol in 3 parts water.

USE: Cleaning and bleaching straw, microphotography; in vitro blood anticoagulant; anal. chemistry.

7821. Potassium Percarbonate. $K_2C_2O_8$; mol wt 198.22. C 12.12%, K 39.45%, O 48.43%. $K_2C_2O_8$. Practically anhydrous comp'd; Partington, *Patent Soc.* 1908, 1934.

Monohydrate, white, granular mass. Sol with evolution of oxygen. One part potassium percarbonate dissolves in 15 parts of cold water; dec in boiling water dissolve 6.5 parts potassium percarbonate at 100° temp. *Keep dry and protected from light.*

Caution: Strong irritant. Causes vomiting. Large quantities can be fatal.

USE: Has been used in microscopy for delimiting stained with fuchsin in smears; in photography the same *Anti-fog*, to remove last traces of sulfide; also as oxidizing agent in chem. anal.

stick may be inserted into a section of rubber tubing, or wrapped several times with tin foil, to avoid cauterizing the fingers of the operator. In industry it is used in the manufacture of soft soap, in electroplating, in paint and varnish removers, and in many other processes.

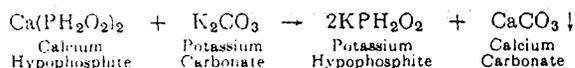
POTASSIUM HYPOPHOSPHITE N. F.

[Potassii Hypophosphis; Sp. Hipofosfito Potásico]

Potassium Hypophosphite, dried at 105° for 1 hour, contains not less than 98 per cent of KPH_2O_2 (104.09).

Caution should be observed in compounding Potassium Hypophosphite with other substances, as an explosion may occur if it is triturated or heated with nitrates, chlorates, or other oxidizing agents.

Preparation—When solutions of calcium hypophosphite and potassium carbonate are mixed, potassium-hypophosphite and calcium carbonate are produced by double decomposition, thus:



The calcium carbonate is removed by filtration, and the clear solution is evaporated until a pellicle forms, after which it is constantly stirred, with continuance of the heat, until the salt granulates. The heat employed in the evaporation should be kept considerably below 100° for fear of explosion.

Description—White, opaque hexagonal plates, crystalline masses, or a granular powder, and is very deliquescent. It is odorless and has a pungent, saline taste. Its aqueous solution (1 in 20) is neutral or alkaline to litmus. The N. F. provides tests for *Identification*.

Solubility—One Gm. is soluble in about 0.6 ml. of water and in about 9 ml. of alcohol at 25°; it is somewhat more soluble in boiling water or boiling alcohol.

Tests for Purity—The N. F. provides tests and limits for *Loss on drying* (5 per cent), *Alkalinity*, *Phosphate*, *Arsenic*, *Calcium*, and *Heavy metals* (20 p. p. m.).

Assay—The salt is assayed by oxidation with excess standard bromine solution. The surplus bromine is caused to liberate an equivalent quantity of iodine which is titrated with standard sodium thiosulfate, using starch as the indicator. See page 1251.

Storage—Preserve in tight containers.

Incompatibilities—Sodium citrate promotes the solubility of the less soluble hypophosphites. Most *oxidizing agents* convert them to phosphates with simultaneous reduction of the agent. Trituration of the dry chemical with a *strong oxidizing agent* may produce an explosion. When rubbed with *calomel* the latter substance is darkened due to its reduction to metallic mercury. *Ferric salts* precipitate from solution as ferric hypophosphite. *Bismuth subnitrate* is darkened due to the production of metallic bismuth.

Uses—See *Compound Hypophosphites Syrup* below.

Dose—Usual, 500 mg.

Compound Hypophosphites Syrup N. F.

[Syrupus Hypophosphitum Compositus; Sp. Jarabe de Hipofosfitos Compuesto]

Calcium Hypophosphite	35 Gm.
Potassium Hypophosphite	17.5 Gm.
Sodium Hypophosphite	17.5 Gm.
Ferric Hypophosphite	2.2 Gm.
Manganese Hypophosphite	2.2 Gm.
Quinine	1.1 Gm.
Strychnine	0.1 Gm.
Sodium Citrate	3.7 Gm.
Hypophosphorous Acid	5 ml.
Dextrose	250 Gm.
Glycerin	300 ml.
Purified Water, a sufficient quantity,	
To make	1000 ml.

Mix the ferric and manganese hypophosphites with the sodium citrate, add 30 ml. of purified water, warm on a water bath, and stir until a clear solution is obtained. Dissolve the calcium, potassium, and sodium hypophosphites in 400 ml. of purified water, to which 2 ml. of hypophosphorous acid has been added; then dissolve the quinine and strychnine in 30 ml. of purified water with the aid of 3 ml. of hypophosphorous acid, and add the glycerin; mix the solutions, and dissolve the dextrose in them by agitation. Add sufficient purified water to make the product measure 1000 ml., and strain.

Storage—Preserve in tight, light-resistant containers and avoid excessive heat.

Uses—The therapeutic value of the hypophosphites has been repeatedly questioned in medical literature. This Syrup has been proposed as an *alterative*, a *tonic*, and a *source of phosphorus*.

Dose—Usual, 8 ml.

POTASSIUM IODIDE U. S. P., B. P., Ph. I.

[Kalii Iodidum Ph. I.; Potassii Iodidum B. P.; Sp. Yoduro Potásico]

Potassium Iodide, dried at 105° for 4 hours, contains not less than 99 per cent of KI (166.01).

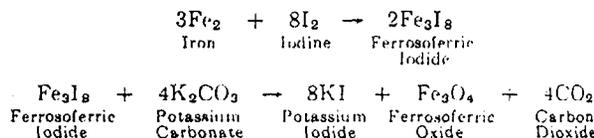
Preparation—A hot aqueous solution of potassium hydroxide is treated with iodine in slight excess. The result is the formation of two salts, potassium iodide and potassium iodate.



The solution is concentrated by heating over a free flame in an iron kettle, then an excess of powdered charcoal is added and well incorporated. The mixture is evaporated to dryness, then ignited. The charcoal (carbon) reduces the iodate to iodide and all of the iodine is thus obtained as Potassium Iodide. The mass is lixiviated with water, filtered, evaporated to a suitable concentration, and set aside to crystallize, or it is granulated from the hot solution.

Potassium Iodide is also prepared by first forming ferrous-ferric iodide through the reaction between iron wire and iodine in the presence of water. A solution of pure potassium carbonate is then added until the solution is faintly alkaline, boiled for a few moments, and filtered; the filtrate is concentrated and set aside to crystallize.

The reactions are expressed separately as follows:



Potassium Iodide is always crystallized from an alkaline solution and to prevent discoloration, due to formation of free iodine, a small amount of free alkali is permitted. See also the equations under *Potassium Bromide*.

Description—Hexahedral crystals, either transparent and colorless or somewhat opaque and white, or a white, granular powder. It is stable in dry air, but slightly hygroscopic in moist air. On prolonged keeping it may become yellowish through the formation of free iodine by oxidation. The aqueous solution is neutral or slightly alkaline to litmus, and gradually becomes yellow because of the formation of free iodine. The addition of small amounts of sodium thiosulfate removes the yellow color. The U. S. P. provides tests for *Identification*.

Solubility—One Gm. dissolves in 0.7 ml. of water, in 22 ml. of alcohol, in 2 ml. of glycerin, in 75 ml. of acetone at 25°, and in 0.5 ml. of boiling water. When dissolved in water heat is absorbed. One hundred ml. of its aqueous solution saturated at 25° contains 100 Gm. of KI.

Tests for Purity—The U. S. P. provides tests and limits for *Alkalinity*; *Loss on drying* (1 per cent); *Iodate*, *nitrite*, *thiosulfate*, and *barium*; *Nitrate*, *nitrite*, and *ammonia*; and *Heavy metals* (10 p. p. m.).

Assay—An acidified solution of the salt is titrated, in the presence of chloroform, with standard potassium iodate solution. See page 1250.

Storage—Preserve in well-closed containers.

Incompatibilities—Iodides are water-soluble except the *lead*, *silver*, *mercury*, and *cuprous salts*. These are soluble in the presence of alkali iodides, the lead and silver iodides least readily.

In the presence of *acid*, iodides are decomposed rapidly with the liberation of iodine. Sugar retards the reaction. *Oxidizing agents* liberate iodine with simultaneous reduction of the agent. Thus, by reaction with *cupric sulfate*, iodine is liberated and cuprous iodide is precipitated; with *ethyl nitrite spirit*, iodine and nitric oxide (which forms brown NO₂ on contact with air) are evolved. Ammonium io-

$$\frac{1}{0.7} = 1.4285 = 1.43 \text{ gm/ml.}$$

TEST METHODS AND LIMITS

- a) **Content of Potassium Iodide**
Quantification was performed by titration with silver nitrate
Limits: 61.8 – 68.3 mg/tablet
Refer to Method: USP XXII
- b) **Content of Iodine**
In-house colorimetric assay using diethyl-p-phenylendiamin and detection at 550 nm
Limits: < 1.3 µg I₂/tablet
- c) **Content of Iodate**
Titrimetric assay using starch
Limits: < 4ppm
Refer to method: USP XX, p. 645
- d) **Hardness**
The strength required to crush a tablet was measured. The mean value of ten determinations was reported.
Limits: 4.0 – 7.0 kp
Refer to Ph. Eur. 2.9.8.
- e) **Disintegration Time**
Six tablets were examined during disintegration with water. The maximum time was noted.
Limits: All tablets disintegrated within 15 minutes
Refer to Ph. Eur. 2.9.2.
- f) **Dissolution**
Dissolution medium, apparatus and sample withdrawal according to USP XXIII, P. 1791-93, Apparatus 2
Quantification of potassium iodide is performed as described above.
Limits: ≥ 80% of labeled content after 15 minutes
- g) **General Appearance**
Approximately 100 tablets were examined by eye regarding color, surface and defects. The tablets are white to off-white, round, bevelled, with a cross line on one side. The diameter is 9 mm.
Limits: Approved
- h) **Microbiological Control**
Limits:
Aerobic bacteria: ≤ 10³/g
Fungi: ≤ 10²/g
E. coli: Absence
Refer to Ph. Eur.
Limits: Approved

46. I.H. Tipton, H.A. Schroeder, H.M. Perry, Jr. and M.J. Cook: Trace Elements in Human Tissues III. Subjects from Africa, the Near and Far East and Europe. *Health Phys* 11: 403-451, 1965
47. K.M. Hambidge in *The Newer Trace Elements in Nutrition* W. Mertz and W.E. Cornatzer, Editors, pp. 169-194. Marcel Dekker, Inc., New York, 1971
48. Y. Murakami, Y. Suzuki, T. Yamagata and N. Yamagata: Chromium and Manganese in Japanese Diets. *Chem. Abstracts* 65: 11033, 1966
49. A. Walker and L. Page: Nutritive Content of College Meals. *J. Am. Diet. Assoc.* 70: 260-266, 1977
50. J.T. Kumpulainen, W.R. Wolf, C. Veillon and W. Mertz: Determination of Chromium in Selected United States Diets. *J. Agric. Food Chem.* 27: 490-494, 1979
51. P. Koivistoinen: Mineral Element Composition of Finnish Foods. *Acta Agr. Scand. Suppl.* 22, 1980
52. D.H.P. Streefen, M.M. Gerstein, G.M. Marmor and R.J. Doisy: Reduced Glucose Tolerance in Elderly Human Subjects. *Diabetes* 14: 579-583, 1965
53. H.A. Schroeder: Chromium Deficiency in Rats. A Syndrome Simulating Diabetes Mellitus with Retarded Growth. *J. Nutr.* 88: 439-445, 1966
54. W.R. Wolf, W. Mertz and R. Masironi: Determination of Chromium in Refined and Unrefined Sugars by Oxygen Plasma Ashing Flameless Atomic Absorption. *J. Agric. Food Chem.* 22: 1037-1042, 1974
55. E.G. Offenbacher and F.X. Pi-Sunyer: Temperature and pH Effects on the Release of Chromium from Stainless Steel into Water and Fruit Juices. *J. Agric. Food Chem.* 31: 89-92, 1983
56. W.R. Wolf: Nutrient Trace Element Composition of Foods: Analytical Needs and Problems. *Anal. Chem.* 50: 190A-194A, 1978
57. R.A. Anderson, J.H. Brantner and M.M. Polansky: An Improved Assay for Biologically Active Chromium. *J. Agric. Food Chem.* 26: 1219-1221, 1978
58. D. Behne and F. Diehl in *Activation Techniques in the Life Sciences*, pp. 407-414. International Nuclear Atomic Energy Agency, Vienna, 1972
59. I.W.F. Davidson and R.L. Burt: Physiologic Changes in Plasma Chromium of Normal and Pregnant Women: Effect of Glucose Load. *Am. J. Ob. Gyn.* 116: 601-608, 1973
60. J. Versieck and R. Cornelis: Normal Levels of Trace Elements in Human Blood, Plasma or Serum. *Anal. Chim. Acta* 116: 217-254, 1980
61. F.J. Kayne, G. Komar, H. Laboda and R.E. Vanderlinde: Atomic Absorption Spectrophotometry of Chromium in Serum and Urine with a Modified Perkin-Elmer 603 Atomic Absorption Spectrophotometer. *Clin. Chem.* 24: 2151-2154, 1978
62. J. Versieck, J. Hoste, F. Barbier, H. Steyaert, J. DeRudder and H. Michels: Determination of Chromium and Cobalt in Human Serum by Neutron Activation Analysis. *Clin. Chem.* 24: 303-308, 1978
63. R.A. Anderson, M.M. Polansky, N.A. Bryden, E.E. Roginski, W.H. Glinesmann, K.Y. Patterson and C. Veillon: Urinary Chromium Excretion of Human Subjects: Effect of Chromium Supplementation and Glucose Loading. *Am. J. Clin. Nutr.* 36: 1184-1193, 1982
64. R.A. Anderson, M.M. Polansky, N.A. Bryden, E.E. Roginski, K.Y. Patterson and J. Reamer: Effect of Exercise (Running) on Serum Glucose, Insulin, Glucagon and Chromium Excretion. *Diabetes* 31: 212-216, 1982

Iodine

The multiple, often cybernetic relationships between disorders in iodine nutriture and thyroid disease are evidence of the complexity of humans and their environment. Our present knowledge about iodine stems from many observations, empirical experiments and scientific investigations. The nemesis of both understanding and controlling nutritional disorders of iodine metabolism, however, has been in mistaking the complex for the simple, and the beginning for the end. This has been true both before and after it became obvious that an environment either deficient or excessive in iodine is an important source of ill health. Because of unpredictable and perplexing man-made changes in life and environment, simple prevention programs of these two abnormalities are not sufficient. A national and international policy on iodine nutriture is mandatory as an integral part of a world-wide improvement of nutrition in general.

An artificial division of the environment into inorganic, organic and human worlds may be helpful in the discussion of the relationship of iodine and the thyroid gland in health and disease. This topic will be discussed from these three viewpoints after a brief look at the history of iodine.

History

The sense of taste for iodine, in contrast to that for chloride, does not regulate the intake of this nutrient. But, long before history came to be written, the peoples of the Pacific coasts of China and

South America empirically learned to eat iodine-rich seaweed for the cure of goiter.¹ The Greeks and probably other ancient maritime peoples had the same experience. Finally, in the twelfth century, Ruggiero Frugardi (Roger of Salerno) from the great Hippocratic School of Medicine at Salerno, Italy, recommended an electuarium of ashes of sea sponges for the treatment of goiter, and this remedy has remained in use for centuries.²

Ironically, iodine was born as a stepchild of potassium nitrate, a basic ingredient of gunpowder. Continuous wars and the English blockade of Europe forced Napoleon's chemists to intensify the production of salpeter from seaweed (Normanic, varec; Scottish, kelp) deposited by the sea on the coasts of Bretagne and Normandie.

As part of this major undertaking, Bernard Courtois (1777-1838), the son of a salpeter producer and formerly a pharmacist who isolated morphine from opium, was forced by circumstances to take over his father's business in Paris. Late in 1811, while crystallizing potassium nitrate, he probably added too much sulfuric acid to the concentrated cooling mother liquid of the varec ashes. Thus beautiful violet fumes were formed and a brownish violet crystalline substance was deposited on the wall of the vat. Impressed by its color, he named the substance "iode," the Greek word for violet-colored.³

In 1816, Prout in England was the first to use iodine in the treatment of goiter.⁴ Francois Coindet (1774-1848) was the individual who most promoted iodine as goiter therapy. In 1820, he demonstrated to the Swiss Society of Natural Sciences the results of such goiter treatment. He was the first to observe iodine-hyperthyroidism in goitrous patients given large doses of iodine. He warned, "I cannot sufficiently emphasize the well-known axiom of Boerhaave: At prudenter a prudente medico, si methodum nescis, abstine..."⁵

Iodine and the Inorganic World

Iodine, like chlorine, silica and bromine, was present in the primordial waters of the earth. In the inorganic world of small particles and large energies, the uneven distribution of iodine in water, soil and air has been determined by the second law of thermodynamics.

The atomic number of iodine is 53, and its atomic weight is 126.91. It is poorly soluble in water, but molecular iodine (I_2) com-

bins with iodide to form polyiodides, which accounts for the high solubility of iodine in water.

During the last glaciation period, 18,000 to 8000 years ago, mature iodine-rich soil was swept away by glaciers and was replaced with new crystalline soil, which, lacking humus, could not retain iodine. According to the medical geographic map, most of Canada and the northern regions of the United States are in the goiter belt of the northern hemisphere, as are the Pyrenees, the Alps and the Himalayan region. In addition, the mountain ranges of Canada, the United States and Mexico were also depleted of iodine by weathering of the soil during eons of time.

The intensity of iodine deficiency reflects the cycle of simultaneous depletion and repletion of soil iodine (from parental rocks to the sea and back again via wind, rain, snow and flora and fauna). Some variants are also caused by geological and climatic factors as noted in the Andes as well as in the tropical areas of South America, Africa and Asia.⁶ Thus the condition of iodine distribution in the inorganic world is responsible for a world-wide low iodine content of the soil in many countries which are inhabited by about one billion people.⁷

Iodine is a trace element. Its concentration in the inorganic world varies considerably. Approximate values of iodine in the air, soil, terrestrial water and sea water are 0.7 μg per cubic meter, 300 μg per kilogram, 5 μg per liter and 50 μg per liter, respectively (Figure 1).

Combustion of coal and gasoline enriches the air with iodine. Iodine is returned to the earth in the rain in concentrations of 1.8 to 8.5 μg per liter (Figure 1). The given value for terrestrial waters represents an average with very wide variations. Sea water contains the largest total amount of iodine, mostly in the form of iodates. Solar light with the wavelength of 560 μm can oxidize iodide to iodine, and about 400,000 tons of iodine escape each year from the ocean into the air. The highest concentration of this halogen (about 0.5 to 2.0 g per kilogram) is found in the deposits of Chilean nitrate, where it was brought by the Antarctic anticyclonic air flow from the Pacific Ocean. The brine of rock salt and especially fossil oil are important industrial sources of iodine.⁸

Iodine and the Organic World

In the organic world of macromolecules, iodine became a permanent part of diverse structures in most living organisms. The iodine

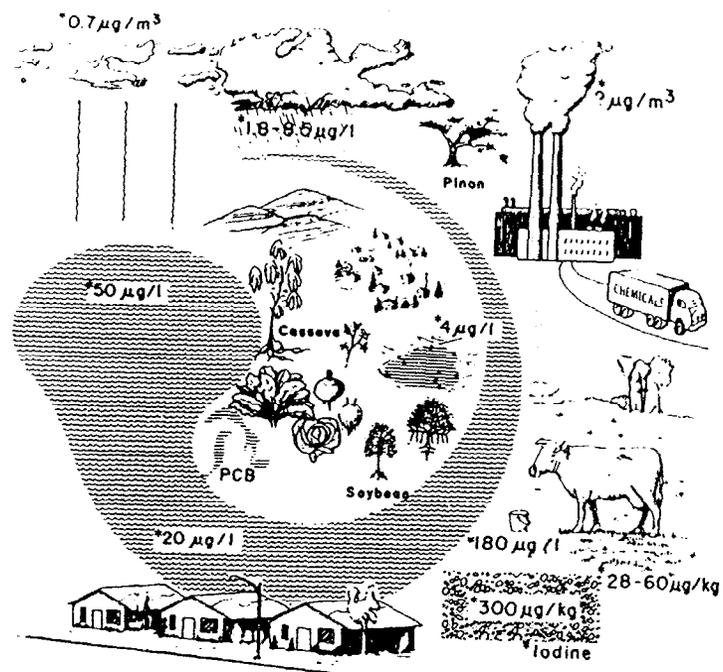


Figure 1. Simple Model of Iodine Turnover *Iodine in air, rain, river, sea, soil, grass and milk. Goitrogens: Disulfide of hydrocarbons in sedimentary rock, bacteria in high table water cassava, goitrogenic cabbage, soybean and PCBs.

(Reproduced by permission from R.L. Voight in *Trace Substances in Environmental Health*—V D.C. Hemphill, Editor, p. 303 University of Missouri Press, Columbia, 1972)

concentration in plants varies directly with the environment. Most plant iodine is in inorganic form. Terrestrial plants are usually iodine-poor, and their average iodine content is 1 mg per kilogram of dry weight. The iodine content is higher in marine plants. Brown seaweed is very rich in inorganic iodine (0.7 to 4.5 g per kilogram dry weight) and is important for production of iodine in Japan.

In marine animals, such as sponges, and in the skeleton of the corals, iodine is in the form of diiodotyrosine.⁸ Only vertebrates developed the thyroid gland, which is mainly concerned with iodine metabolism. The cause of this revolutionary event is consid-

ered to be the origin of vertebrates in sweet, often iodine-deficient water. Accordingly, the thyroid has been engaged in accumulation of iodine and in synthesis and storage of iodotyrosine and iodothyronines. Iodotyrosine represents the reserves of iodine in the thyroid. The iodothyronine hormones are secreted in the bloodstream as messengers with different functions (regulators of metamorphosis and homeothermy, stimulators of protein synthesis and of sexual development) in various groups of organisms.

Surprisingly, marine fish do not undergo metamorphosis, and are poikilothermal, but have retained the thyroid gland. The same is true for poikilotherm frogs and lizards. They need the thyroid hormone only for larval metamorphosis; in the adult organism, the thyroid has no evident endocrine function.

These observations, and especially the exceptional persistence of the thyroid without adaptative value to some organisms, prompted Etkin⁹ to suggest that: 1) iodine is a micronutrient per se, independently from being a constituent of thyroid hormone, and 2) the thyroid gland is also the storage organ for iodine (in the form of iodotyrosines) in support of its special metabolic and/or structural function in various tissues of the body.

The most important phenomenon of the "iodine:organic world" relation is the development of goiter. A goiter represents a compensatory enlargement of the thyroid gland caused by difficulties in secretion and/or utilization of thyroid hormone. Arbitrarily, the prevalence of sporadic and endemic goiter in the whole population is 5 percent and above 5 to 10 percent, respectively. Endemic goiter in humans and animals is the same disease and occurs in the same areas.

Iodine Deficiency. Absolute iodine deficiency is the most common world-wide cause of endemic goiter and cretinism. In 1960, about 200 million people from all continents, races and cultures were afflicted by endemic iodine-deficient goiter.¹⁰ Since that time, reduction of goiter prevalence has been accomplished in many areas, and especially in more developed countries. Because of a great increase in population in less developed countries, however, at present more than 200 million people have goiter.

Natural Goitrogens. Natural goitrogens, usually in combination with iodine deficiency, are the cause of endemic goiter. The most important natural goitrogens are cassava, cabbage, disulfides of saturated and unsaturated hydrocarbons from geological organic

sediments in drinking water, bacterial products of *Escherichia coli* in drinking water, soybean and iodine excess in seaweed and brown and green kelp.

Iodine and the Human World

During the last 60 years, progress in the prevention of endemic goiter has not been successful everywhere. In less developed countries, the protagonists of goiter prophylaxis were confronted by the phantom of Jod-Basedow and many were exhausted by the powerful obstacles of ignorance, economic difficulties, civil disorders and war.

In contrast, the problems of iodine nutriture in some more industrialized countries are now of a different nature. Most of these societies introduced successful iodine prophylaxis about 30 to 55 years ago. In addition, after World War II, many industrialized countries have developed economic and efficient technologies of food production paralleled by a large growth of complex chemical industries. Thereafter, during the last 20 years, an upward trend towards high to excessive nutritional iodine intake was noted, and in the last five to ten years several warnings on animal feed and human food contamination with synthetic goitrogens were published.¹¹⁻¹⁸ The most important cause of these complex changes in iodine nutriture of animals and humans comes from use of iodine-rich compounds and various goitrogenic chemicals.

Iodine-rich compounds are used in dairy farming and industry (ethylenediamine dihydroiodide for therapy and prevention of lumpy-jaw, actinomycosis, foot rot necrobacillosis and iodophor-antiseptics for udder and teats as well as cleansing agents for dairy equipment and containers) and in the baking industry (iodates as dough-conditioners in "continuous-vacuum/mix process" and as cleansing agents for equipment).¹² Milk and dairy products as well as bread and bakery products are the largest source of iodine in human food.¹²

Pollution is another source of iodine-rich compounds. A potential pollution of iodine is possibly in the large industrial and pharmaceutical production of iodinated chemical compounds (1,500,000 kg iodine is used per year by industry in the United States alone), which either directly, or via sewage turned fertilizer, find their way into the drinking water and food.^{12,13}

The goitrogenic pharmaceuticals and industrial chemicals have great applications in agriculture (organochlorine insecticides and fungicides releasing ethylthiourea) and animal husbandry (bacteriostatic sulfonamides and antibiotics of the tetracycline group). The total effect of the goitrogens used in agriculture and animal husbandry is not yet known.

For the last fifty years, the chemical industry has produced plasticizers of the polychlorinated biphenyls (PCBs). Since 1978 the production of these compounds has been banned, but 375,000 tons still in use of the total 750,000 tons produced in the United States will eventually end up in the rivers, lakes and seas.¹⁴ Most contaminated are the Great Lakes and their tributaries. Since 1972 it has been documented that PCBs cause severe endemic goiter in predator fish of the Great Lakes waters.¹² In 1972, the PCB content in 45 percent of the U.S. population was 1 µg per gram of body fat.¹⁵

Fire retardants of the polybrominated biphenyls (PBBs) act like PCBs. In 1973, a limited, accidental contamination of animal feed with PBBs occurred in Michigan. Biochemical evidence of disordered thyroid function was detected in some individuals who had consumed contaminated meat and milk,¹⁷ but was not confirmed in another study.¹⁸

Iodine in Food

In areas completely dependent on local food supplies, the iodine content of water is a reliable indicator of its content in the soil and nutrients. Drinking water, except for some "mineral waters," is rarely an important source of iodine. Vegetables and fruits supply little iodine. Meat contains more iodine and its content depends on the feed and food of domestic and wild animals, respectively. Iodine is concentrated in milk and eggs, which are second only to seafood as the richest sources of iodine. Marine salt contains little iodine. After crystallization of sodium chloride, the mother liquid, containing all the iodine, is separated to prevent the precipitation of the bitter magnesium chloride. With only a few exceptions, crude rock salt contains little iodine, which has escaped during the eons of slow evaporation of sea water.

Data on the iodine content of food from goiter free Washington, D.C. and Athens, Greece, as well as from the "Greek Endemic

Areas" (401 μg , 202 μg , and 41 μ , respectively) illustrate the difference in nutritional iodine supply of a country with modern food technology versus that of a predominantly agricultural, less developed country.⁸ In the industrialized countries, milk and dairy products, and bread and bakery products are the most important nutritional sources of iodine (as discussed later in this chapter).

Iodine Requirements

As an essential constituent of thyroid hormone, iodine is an indispensable ingredient of human and animal nutrition. The nutritional need of iodine is influenced by growth, body weight, sex, age, nutrition, climate and disease. The iodine requirement was determined by several methods, and estimates differ considerably. In many individuals living in a goiter-free area, the average urinary excretion of iodine was about 150 μg per day.¹⁹ The mean thyroidal uptake of stable iodine was 72 ± 48 μg per 24 hours as determined by neutron activation analysis.²⁰

The daily requirement in adults is placed at about 1 to 2 μg per kilogram of body weight. An iodine intake between "a minimum of 50 μg and a maximum of 1000 μg " is considered to be safe.²¹ The 1980 U.S. recommended daily allowance (RDA) for iodine is in the range of 40 to 120 μg for children up to age ten, and 150 μg for older children and adults. An additional 25 μg and 50 μg are recommended during pregnancy and lactation, respectively.²²

The Thyroid Gland: Structure and Function

The normal human thyroid weighs about 0.3 g per kilogram of body weight, or 20 to 25 g in adults. The thyroid, a storage gland, has an iodine content of about 8.0 to 10.0 mg per 20 g gland. Approximately 95 percent of thyroid iodine is bound to thyroglobulin. About 45 percent of thyroidal iodine is in the form of thyroxine, and 3 percent is in the form of triiodothyronine; approximately 42 percent is in iodotyrosines.

The thyroid structure and function are regulated by two interrelated systems. The phylogenetically older regulator is iodine itself. Its purposes are the homeostasis of thyroid hormone secretion and the preservation of optimal iodine reserves in the form of iodotyro-

sines in thyroglobulin. The pivotal factor in this regulatory mechanism is the quantity of iodine. At a critically low iodine supply, all functions of the thyroid gland are accelerated. Inversely, at a fixed excessive iodine intake, all processes in the thyroid are slowed down or chronically modified, depending on the duration of abnormally high iodine intake.

The younger control system is geared to maintaining a normal concentration of free thyroid hormones in the bloodstream. The function of the thyroid is similar to that of a thermostat, for it interrelates the concentration of free thyroid hormone in the serum with a secretion of the pituitary thyroid stimulator (thyrotropin, TSH) and the thyrotropin-releasing hormone of the hypothalamus (TRH).

Both control systems, the iodine and the TSH, probably regulate the intermediate metabolism of the thyroid cell mostly via the adenylyl-cyclase-cyclic adenosine monophosphate (AMP) system. Their effects are complementary under physiological conditions.²³

Absorption of Iodine from Food. After ingestion, iodine is reduced to iodide, and within an hour it is quantitatively absorbed from the small bowel. Iodotyrosines, iodothyronines, some short-chain iodopeptides and radiographic iodinated compounds are absorbed without deiodination. Iodine in all inorganic compounds and many organic compounds is bioavailable.

Utilization of Iodine by the Thyroid. The utilization of iodine for secretion of thyroid hormone proceeds by three steps. First, from the plasma across the cell membrane is an active process against electrical and mass gradients. The normal concentration of iodide in the thyroid cell is 30 to 40 times higher than that in the serum. Second, at the interface of the cell and the colloid, a peroxidase is instrumental in oxidizing iodide into an "iodine-intermediate." The enzyme also facilitates the formation of monoiodotyrosines and diiodotyrosines by incorporating iodine into the tyrosyl residues of thyroglobulin. The subsequent oxidative coupling of iodotyrosines into the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), is also carried out by the same peroxidase, possibly in cooperation with another enzyme. Finally, thyroglobulin is engulfed by the cytoplasm of the thyroid cells. The digestion of thyroglobulin is accomplished by proteolysis. The secretory phase ends by diffusion of the hormones into the capillaries via extracellular space.²⁴

Thyroid Hormones

About 80 to 90 μg of T_4 and 10 to 20 μg of T_3 are secreted daily into the bloodstream. The simultaneously liberated iodotyrosines are de-iodinated in the thyroid, and iodine is returned to the thyroidal pool for reutilization.

Most T_4 in the serum is bound to thyroxine-binding globulin. The normal serum levels of T_4 and T_3 are $8.6 \pm 0.5 \mu\text{g}$ and $128 \pm 6.7 \text{ ng}$ for 100 ml, respectively. During the passage in blood through the liver, about 50 percent of T_4 is deiodinated to T_3 , and a very small amount is deiodinated to physiologically inactive reverse T_3 (rT_3). Significant amounts of T_4 and T_3 are also enzymatically bound to glucuronate and sulfate, respectively, and thus are excreted in the bile. The T_4 glucuronate and T_3 sulfate are hydrolyzed in the intestine, and most of the T_4 is reabsorbed into the blood. After metabolic degradations of thyroid hormones, a large fraction of iodine is reutilized by the thyroid.

The primary function of the thyroid hormone is to stimulate heat production (by increased oxygen utilization) for the preservation of a constant body temperature. In addition, the hormone influences the synthesis of protein; during embryonal life and childhood, it promotes physical and mental growth and development.

Normal Iodine Metabolism

The complex multicompartamental system of iodine metabolism was conveniently simplified and divided into three compartments by Riggs.¹⁹

Inorganic Iodine Compartment (I^-). After absorption, iodide is distributed in the I^- compartment, which represents about 35 percent of body weight (25.5 liters per 70 kg) and consists of plasma, extracellular space, alimentary tract secretions, red cells and the thyroid gland. The concentration of plasma iodide is considered representative of this compartment (mean, 0.18 μg per deciliter; range, from 0.04 to 0.57 μg per deciliter). Therefore, the inorganic iodine pool is approximately 98 to 120 μg . Very little iodide is excreted in expired air, perspiration and feces. A little more, 4.5 to 9 μg per deciliter, is excreted in milk. The renal clearance of iodide (40 ml per minute) is constant over a wide range of plasma iodide concentration. In contrast, thyroidal iodide clearance varies with thyroid activity, and

especially with iodine intake; the average is about 30 ml per minute. Therefore, in adults, the daily thyroidal uptake is about 70 μg and the urinary clearance is 144 μg . Finally, about 55 μg I^- per 24 hours enters into this compartment after degradation of thyroid hormone in the tissue. Thus, the I^- input and output of this compartment are well-balanced.

Thyroidal Organic Iodine (T). The iodine concentration is about 400 μg per gram wet thyroid tissue; a 20-g thyroid contains about 8 mg iodine. A small fraction of iodide (1 to 2 percent) is not accounted for. The thyroidal fractional uptake from the inorganic iodide pool is measured with ^{131}I and varies with the pool size of inorganic iodide and thyroid activity. In this model, it represents 32.7 percent of the iodide pool. The absolute iodine uptake (AIU) can be calculated from the urinary iodide specific activity and the plasma radioactivity: $\text{AIU} = \text{UE}/(1 - \text{U})$, where U is thyroidal ^{131}I uptake per 24 hours as a fraction, and E is urinary iodide (^{127}I) excretion per 24 hours. In this model, $\text{AIU} = 70 \mu\text{g}$ per 24 hours or 2.9 μg per hour. The thyroid secretes about 70 μg iodine in the form of thyroid hormone per 24 hours.

Extrathyroidal Organic Iodine (B). All thyroid hormones in the blood, tissues and enterohepatic circulation belong in this compartment. The average serum thyroxine iodine is accepted as the concentration of iodine in this compartment. Because its volume is about 9.41 liters in adults, the organic iodine pool is about 470 μg .²⁵ Approximately 55 μg of organic iodine (in the form of thyroid hormones) is utilized by the tissue and thereafter is released as iodide into the inorganic iodide pool. About 3.1 percent (15 μg) of the extrathyroidal iodine is excreted per day via bile in the feces.

Endemic and Sporadic Goiter

Classification of Thyroid Enlargement. The Pan American Health Organization classification is retained for estimation of thyroid size. It is a slight modification of the system of Perez et al.²⁶ and is delineated as follows:

- Stage O-A: Normal thyroid.
- Stage O-B: Goiter detectable only by palpation and not visible, even when the neck is fully extended.

- Stage I: Goiter palpable and visible only when the neck is fully extended. This stage also includes nodular glands, even if not enlarged (see below).
- Stage II: Goiter visible with neck in normal position; palpation is not needed for diagnosis.
- Stage III: Very large goiter which can be recognized at a considerable distance.

In case of doubt between any two stages, the lower one should be recorded.

The diffuse or nodular structure of the thyroid should be recorded, because nodules develop in areas of chronic severe iodine deficiency. This estimation is independent of the thyroid size, except when nodules are found in a gland of normal size. Then it is recorded as Stage I, because nodules imply a significant change in the thyroid structure.²⁷

Endemic Goiter

Absolute Iodine Deficiency. Absolute iodine deficiency is the dominant cause of endemic goiter in the world. The measurement of iodine in food is difficult, and the 24-hour collection of urine is often unreliable. Therefore, the severity of endemic, iodine-deficient goiter is classified according to the urinary excretion of iodide in micrograms per gram creatinine in a casual specimen of a representative sample of the population in the area.²⁷

- Grade I. Goiter endemias with an average of more than 50 $\mu\text{g I}^-$ per g creatinine in the urine. The thyroid hormone supply is adequate for normal physical and mental development.
- Grade II. Goiter endemias with urinary excretion between an average of 25 to 50 μg iodide per gram creatinine. The secretion of thyroid hormone may not be adequate, and these individuals are at risk of hypothyroidism, but not of overt cretinism.
- Grade III. Goiter endemias with an average urinary excretion of iodide below 25 μg per g creatinine. The population is at serious risk of cretinism.²⁷

Adaptation to iodine deficiency is a dynamic process that starts after a few weeks of negative iodine balance. At first, an increase in all thyroid functions and a slight, diffuse enlargement of the thyroid gland, due to hypertrophy and hyperplasia of thyroid cells, represent an increased response to the stimulation by the normal amount of TSH. If that mechanism fails to preserve the normal serum level of T_4 and T_3 , an increase in secretion of TSH will further augment the above compensatory mechanisms. Thereafter, chronic high stimulation by TSH will cause a relative increase in secretion of T_3 over T_4 , accompanied by continuous, at first patchy and later overt, nodular thyroidal hyperplasia in one area, as well as degenerative exhaustion and atrophy of thyroid tissue in another area. The advantages of relatively higher secretion of T_3 over T_4 are that: 1) T_3 contains 25 percent less iodine than does T_4 , 2) T_3 is three to four times more potent than T_4 and 3) the half-lives of T_3 and T_4 are one and seven days, respectively. Therefore, the relative increase in secretion of T_3 represents a further modality of adaptation to severe iodine deficiency.

The beginning of iodine deficiency is characterized by a compensatory increase in excretion of stored thyroid hormone and a normal excretion of urinary iodide. As the stores of thyroid hormone continue to deplete, the thyroidal clearance of plasma inorganic iodide increases, with a commensurate decrease of iodide excretion in the urine. After that, the thyroidal uptake of stable iodide is equal to the amount of iodine excreted in the form of thyroid hormone. The plasma inorganic iodide concentration is decreased, as is the thyroidal iodine content. At this time, iodine deficiency either may be relieved or may progress into a chronic stage. It is during the chronic iodine deficiency that the metabolism of iodine is greatly altered. According to the model of Riggs,¹⁹ under conditions of severe iodine deficiency only one-third or less of iodine requirement is supplied in food; the major fraction of iodine in the iodide pool is derived from catabolism of thyroid hormone. Therefore, the plasma inorganic iodide concentration is less than 4.7 μg per liter, and the inorganic iodide pool is very small. Because the renal clearance of iodide is constant, the urinary excretion of iodide, under conditions of low serum iodide concentration, is also very low.

Conditioned Iodine Deficiency

Under conditions of equal iodine supply or action of goitrogens, the age, sex, body build and functions, as well as genetic abnormali-

ties or acquired disorders, can contribute to a higher prevalence and larger size of goiter in certain individuals. The most important are increased requirement for thyroid hormone and mild genetic disorders of the thyroid.

Some fast-growing children, as well as some pregnant and lactating women, develop goiter due to a relative iodine deficiency produced by an increased requirement of thyroid hormone.

Statistical studies of the prevalence of and freedom from goiter in homozygous and heterozygous twins, respectively, suggest that genetic factors do affect goiter development. The higher prevalence of goiter in some families may be partly due to a "lower biological efficiency" of the thyroid. About 3 to 4 percent of otherwise healthy individuals with persistent Wolff-Chaikoff effect manifest an oversensitivity to the goitrogenic action of excessive pharmacological doses of iodine (discussed later in this chapter). About 30 percent of humans and chimpanzees lack the taste for bitter phenylthiocarbamates. In the white race, this taste deficiency can also extend to some antithyroid compounds such as methylthiouracil. This anomaly occurs more frequently in some individuals with either sporadic nodular non-toxic goiter or with endemic goiter of any type.²⁸ Individuals with latent Hashimoto's thyroiditis can develop goiter when exposed to either mild iodine deficiency or iodine excess.¹²

Natural Goitrogens

Recently Gaitan²⁹ observed a great disparity in goiter prevalence in several neighboring communities in various countries, despite the fact that the severe iodine deficiency was the same (that is, urinary iodine excretion of less than 25 µg per gram creatinine). The following are examples of this phenomenon with respective goiter prevalence: 1) Alto Ventuary and Bailadores, Venezuela, 5 and 55.8 percent; 2) Tiom and Mulia, Western New Guinea, 5 and 58.04 percent; 3) South-West Idjwi Island and North Lake Kivu, Zaire, 5.3 and 54.0 percent; 4) Guangaje, Cumbaya and Pisticulla, 12.4, 16.3 and 26.1 percent, versus Penipe, La Esperanza and Tucachi, 49.0, 51.0 and 54.4 percent in Ecuador. These observations suggest that iodine deficiency in some areas is only the permissive factor, and the natural goitrogens in feed and food are the significant determinants in the prevalence and severity of endemic goiter.

Furthermore, natural goitrogens are probably the dominant cause of goiter in some localities where iodine intake is abundant. In 1963-64, Indian Creek, Kentucky had a goiter prevalence of 33.1 percent. Similarly, in Richmond County, Virginia, goiter prevalence in school children was 29.0 percent; the average daily iodine intake was 165 to 384 µg per day. Goiter prevalence in children drinking artesian waters was 9.8 ± 2 percent. In contrast, 28.4 ± 2.8 percent of children drinking water from surface springs and shallow wells were goitrous. Endemic goiter in school children in 37 communities in the Cauca Valley in Western Colombia belongs in a similar category. After ten to 20 years of goiter prophylaxis with iodized salt, the goiter prevalence in school children was 1 to 42 percent, and the average daily urinary iodine excretion was in the range of 65 to 295 µg. In a prospective study started in 1959, goiter prevalence in school children decreased from 82 percent to 30 percent in Candellaria, but had remained at that level for 15 years; in Zarza, Colombia only 80 km away, goiter prevalence had decreased from 16 percent to less than 9 percent.²⁹

Natural goitrogens vary by origin and by their adverse mechanism of action. The most important goitrogenic substances of natural origin will be briefly mentioned.

The tubers and leaves of cassava are the staple source of carbohydrates for about 300 million people in tropical countries. During processing of cassava, the plant enzyme, linamarase, liberates hydrocyanic acid (HCN) from the cyanogenic glucoside linamarin. The consumer's procedures for removal of the HCN from the cassava dishes are relatively effective. The body's impressive number of detoxifying mechanisms change HCN into thiocyanate (SCN⁻), which is a strong goitrogen under conditions of moderate to severe iodine deficiency. SCN⁻ can cross the placenta and can disturb the transplacental transport of iodine to the fetus. It reaches milk, however, only by diffusion. The ratio of urinary SCN⁻ (mg) to ¹²⁷I (µg) is the best available indicator of this goitrogen.

Cabbage, rape and mustard, which belong to the genus *Brassica* and the family of *Cruciferae*, are important as foods, feed and condiments. Today these plants are enormously important sources of rapeseed meal for animal feed and purified proteins in food, as well as rapeseed oil in the food industry.

The major technical and nutritional problem with roots, leaves and especially seeds of domesticated and wild *Cruciferae* is their

high content of glucosinolates, which during processing of the plant are hydrolyzed by their myrosinase (thioglucosylase EC 3.2.3.2). This reaction releases glucose, sulfate and an aglucon molecule which is further converted into thiocyanate, nitriles, sulfur and isothiocyanates. The allyl-, 3-butenyl-, 4-pentenyl-, benzyl-, phenylethyl and 4-methyl-3-butenyl glucosinolates are converted into isothiocyanates (that is, steam-volatile mustard oils). Some of these isothiocyanates degrade further to thiocyanate ion. More importantly, some isothiocyanate intermediates, also called progoitrins, by spontaneous cyclation form 5-vinyl-2-thioxazolidones, also known as goitrins.^{30,31} The latter compounds are by action and potency similar to the synthetic thionamide antithyroid drugs. They inhibit both the iodination and coupling processes in the synthesis of thyroid hormone, and addition of iodine to food does not relieve their goitrogenic effect.

Disulfides of saturated and unsaturated aliphatic hydrocarbons from sedimentary rock drained by waters into deep wells were identified as the cause for an unsatisfactory reduction of endemic goiter in Candellaria, in the Cauca Valley, Colombia. Experimentally, the ether-methanol extracts from the charcoal filters kept at the outlets of those wells caused inhibition in rats of thyroidal ¹³¹I uptake and synthesis of thyroid hormone; enlargement of the thyroid also occurred.

High goiter prevalence with abundant iodine intake was observed in eastern Kentucky³² and northern Virginia,³³ where the drinking water came from shallow wells and was bacteriologically polluted. The cell-free filtrates of cultures of *E. coli* from these waters contained a substance with molecular weight 10⁵ which had an inhibitory effect on the thyroid uptake of ¹³¹I in the rat.^{34,35}

Soybean, which for 5000 years has been the principle crop of the warm and tropical areas of the Orient and today is an important crop in the United States, was first identified as a goitrogen in rats in the 1930s. By adding more iodine to the diet, its goitrogenic effect could be eliminated.³⁶

Uptake of ¹³¹I increases in the soybean goiter of the rat. Van Middlesworth³⁶ injected ¹³¹I-thyroxine intraperitoneally in the rat and observed that soybean-fed animals wasted large amounts of ¹³¹I-thyroxine in the stool. The goiter development in soybean-fed rats is secondary to a relative iodine deficiency (1 mg T₄ contains 0.68 mg iodine). Although this type of goitrogenesis is characteris-

of the rat, blood-biliary turnover in humans is generally too small for such a pathogenic mechanism.

Rats fed peanuts develop goiter.³⁷ Phenolic derivatives are active goitrogens in the peanut and in several similar nuts. An unknown compound in the Persian walnut, similar to soybean, produces a waste of thyroxine in the feces of the rat.

The small, seed-pine nuts of the female cones of the pinon are important in the diets of Indians in southwestern United States and South America. The unknown goitrogenic substance inhibits thyroidal uptake and organification of ¹³¹I in the rat. Administration of iodine does not reverse the effects.

Iodine Excess in Food and Feed as Goitrogen

In contrast to all other goitrogens, iodine in large amounts disturbs all thyroid functions, starting from the transport of iodine and continuing to the synthesis and secretion of the thyroid hormone.

Iodide in large doses (that is, usually more than 50 mg per day, or at serum iodide concentration of 20 µg per deciliter) inhibits the thyroidal transport of ¹³¹I-iodide. The thyroid hormone synthesis at all steps, starting with iodination of tyrosyl residues up to the formation of T₄ and T₃, is progressively more inhibited by acute and chronic intake of large amounts of iodine. This phenomenon, known as the Wolff-Chaikoff effect, is persistent in only 3 to 4 percent of otherwise healthy individuals, for whom iodine in large doses is a goitrogen. In other individuals, an escape from or adaptation to this mechanism occurs after 48 hours, because of a more efficient hormone synthesis caused by a drop in intrathyroidal iodine concentration, which in turn is due to a persistent reduction of iodide transport into the thyroid cell.³⁸

Iodine in large doses is the only constituent of food which can inhibit the secretion of thyroid hormone by preventing hydrolysis of thyroglobulin. Excess iodine acts directly on the thyroid cell, but it also inhibits the normal stimulating effect of TSH on the proteolysis of thyroglobulin, thus interrupting the secretion of thyroid hormones. Whether excess iodide intake can be a goitrogen in man is at present controversial.³⁹

Synthetic Goitrogens

Some of the synthetic goitrogens are PCBs, fire retardants (PBBs), organochlorine insecticides (DDT, DDD and Dieldrin), fungicides (ethylenbidithiocarbamates, EBDCs), bacteriostatic agents (sulfonamides) and antibiotics (tetracyclines).¹²

The first three groups of goitrogens act mostly by inducing the thyroxine uridine diphosphate (UPD) glucuronyl transferase activity of the liver. This activity leads to an excessive biliary excretion of T₄-glucuronate in the bowel which is beyond the capacity of intestinal reabsorption of thyroxine. The high fecal loss of thyroxine results in the lowering of serum level of thyroxine. In a servo-mechanism type of reaction, the pituitary, sustained by the hypothalamic TRH, augments the excretion of TSH which in turn stimulates simultaneously an increase in function and size of the thyroid gland. Concurrent severe iodine deficiency or abundant supply of iodine, respectively, can increase or prevent the goitrogenic effect of these compounds. In addition, these chemicals in larger concentration can directly damage the thyroid gland.

The fire retardants (PBBs) and the organochlorine insecticides disturb the iodine metabolism and produce goiter in essentially the same way as the PCBs. The fungicides in question, under the influence of heat, are degraded to ethylthiourea, which like thionamide inhibits iodination and coupling of iodotyrosines. The sulfonamides are similar to thionamide goitrogens, but are less potent. Their effect, however, is increased in the presence of iodine. The tetracyclines act as antithyroid agents because they specifically disturb the coupling of iodotyrosines.

Summary

Iodine is essential for the biosynthesis of the thyroid hormones. The RDA is 2 µg per kg body weight in adults and somewhat more in children. Endemic goiter caused by iodine deficiency is a world wide problem. Public health policy should ensure optimal iodine intake throughout the world. The prevention of both iodine deficiency and excess, combined with prevention of effects of natural and synthetic goitrogens, should be a continuing public health goal.

REFERENCES

- 1 J.O. Orr and I. Leitch. *Iodine in Nutrition: A Review of Existing Information Up to 1927*. Special Report No. 123. Medical Research Council, London, 1929.
- 2 P. Richter. *Wer Hat Zuerst Die Spongia Usta Gegen Kropf Emphohien*. *Arch. Klin. Chir.* 82: 951-952, 1907.
- 3 J. Von Schroeter. *Die Entdeckung des Jods*. *Ciba Ztschr.* 10: 4342-4434, 1949.
- 4 W. Prout. *Chemistry, Meteorology and the Function of Digestion*. W. Pickering, London, 1934.
- 5 J.D. Coindet. *Nouvelles Recherches sur les Effets de Mode, et sur Les Precautions a Suivre dans le Traitement du Goitre par ce Nouveau Remede*. *Ann. de Chim. et Phys. Paris* 16: 252-266, 1821.
- 6 J. Matovinovic, M.A. Child, M.Z. Nicholas and F.L. Trowbridge in *Endemic Goiter and Cretinism: Continuing Threats to World Health*. J.T. Dunn and G.A. Medeiros-Neto, Editors. Scientific Publication No. 292, pp. 67-94. Pan American Health Organization, Washington DC, 1974.
- 7 C. Hunniken and F.O. Wood in *Endemic Goiter and Endemic Cretinism*. J.B. Stanbury and B.S. Hetzel, Editors, pp. 497-506. J. Wiley and Sons, Inc., New York, 1980.
- 8 D. Koutras, J. Matovinovic and R. Vought in *Endemic Goiter and Endemic Cretinism*. J.B. Stanbury and B.S. Hetzel, Editors, pp. 185-195. J. Wiley and Sons, Inc., New York, 1980.
- 9 W. Etkin. *The Thyroid—A Gland in Search of a Function*. *Perspect. Biol. Med.* 22: 19-30, 1978.
- 10 F.C. Kelly and W.W. Snedden in *Endemic Goitre*. WHO Monograph, Ser. 44, pp. 27-233. World Health Organization, Geneva, 1960.
- 11 H.T. Suzuki, K. Higuchi, K. Sawa, S. Ohtaki and H. Horiuchi. *Endemic Coastal Goitre in Hokkaido, Japan*. *Acta Endocrinol. (Kbh)* 50: 161-176, 1965.
- 12 J. Matovinovic and F.L. Trowbridge in *Endemic Goiter and Endemic Cretinism*. J.B. Stanbury and B.S. Hetzel, Editors, pp. 37-67. J. Wiley and Sons, Inc., New York, 1980.
- 13 W.C. Miller. *Iodine*. *Mineral Yearbook* 1: 471-474, 1965.
- 14 W.J. Weber in *Towards Cleaner Water: Studies in Toxic Substances and Other Contaminants*. J. Wei, Editor, vol. 3, pp. 26-33. Research News, University of Michigan, Ann Arbor, 1978.
- 15 R. Sonstegard and J.F. Leatherland. *The Epizootiology and Pathogenesis of Thyroid Hyperplasia in Coho Salmon (Oncorhynchus Kisutch) in Lake Ontario*. *Cancer Res.* 36: 4461-4773, 1976.
- 16 C. Allen-Rowland, V.D. Castracane and J. Seifter in *Programs and Abstracts of the Endocrine Society*. P. 301. The Endocrine Society, Anaheim, 1979.
- 17 I.J. Selkoff and H.A. Anderson. *A Survey of the General Population of Michigan for Health Effects of Polybrominated Biphenyl*. Exposure Report to the Department of Public Health, Sept. 30, 1979. Environmental Science Laboratory, Mt. Sinai School of Medicine, New York, 1979.
- 18 J.K. Stross, I.A. Smokier, J. Isbister and K.R. Wilcox. *The Human Health Effects of Exposure to Polybrominated Biphenyls*. *J. Toxicol. Appl. Pharmacol.* 58: 145-150, 1981.
- 19 D.S. Riggs. *Quantitative Aspects of Iodine Metabolism in Man*. *Pharmacol. Rev.* 4: 284-370, 1952.

- 20 H N Wagner, Jr., W B Nelp and J H Dowling: Use of Neutron Activation Analysis for Studying Stable Iodine Metabolism in Man *J Clin Invest* 40: 1984-1992, 1961
- 21 *Iodine Nutrition in the United States*. Summary of a Conference, Oct. 31, 1970, p 51. Food and Nutrition Board, National Academy of Sciences, Washington, DC, 1971
- 22 Food and Nutrition Board, National Research Council. *Recommended Dietary Allowances* Ninth Edition, pp 147-151. National Academy of Sciences, Washington, DC, 1980
- 23 S H Ingbar: Autoregulation of the Thyroid: The Response to Iodide Excess and Depletion *Mayo Clinic Proc* 47: 814-823, 1972
- 24 L J DeGroot and J B Stanbury: *The Thyroid and Its Diseases*, Fourth Edition, pp 37-109. J. Wiley and Sons, Inc., New York, 1975
- 25 S H Ingbar: Clinical and Physiological Observations in a Patient with Idiopathic Decrease in Thyrosine-Binding Globulin of Plasma *J Clin Invest* 40: 2053-2063, 1961
- 26 C. Perez, N J Scrimshaw and J A Munoz in *Endemic Goiter*. Pp. 369-378. WHO Monograph Ser. No. 44, Geneva, 1960
- 27 A. Querido, F. Delange, J. Dunn, R. Fierro-Benitez, H.K. Ibertson, D.A. Koutras and H. Perinetti in *Endemic Goiter and Cretinism. Continuing Threat to World Health*. J T. Dunn and G A Medeiros-Nero, Editors, Scientific Publication No. 292, p 267. Pan American Health Organization, Washington, DC, 1974
- 28 D A Koutras in *Endemic Goiter and Endemic Cretinism*. J.B. Stanbury and B.S. Hetzel, Editors, pp 255-268. J. Wiley and Sons, Inc., New York, 1980
- 29 E. Gaitan in *Endemic Goiter and Endemic Cretinism*. J.B. Stanbury and B.S. Hetzel, Editors, pp 219-236. J. Wiley and Sons, Inc., New York, 1980
- 30 C H Van Elten in *Toxic Constituents of Plant Foodstuffs*. I.E. Liener, Editor, pp 103-134. Academic Press, New York, 1969
- 31 C.H. Van Elten and I.A. Wolff in *Toxicants Occurring in Foods*. Second Edition, Publication No. 73, pp 210-234. National Academy of Sciences, Washington, DC, 1973
- 32 W.T. London, D.A. Koutras, A. Pressman and R.L. Vought: Epidemiologic and Metabolic Studies of a Goiter Endemic in Eastern Kentucky. *J Clin Endocrinol Metab* 25: 1091-1097, 1965
- 33 R.L. Vought, W.T. London and G.E.T. Stebbing: Endemic Goiter in Northern Virginia. *J Clin Endocrinol Metab* 27: 1381-1389, 1967
- 34 E. Gaitan, P. Medina, T.A. De Rouen and M.S. Zia: Goiter Prevalence and Bacterial Contamination of Water. *J Clin Endocrinol Metab* 51: 957-961, 1980
- 35 R.L. Vought, F.A. Brown and K.H. Sabinovic: Antithyroid Compound(s) Produced by *Escherichia coli*. Preliminary Report. *J Clin Endocrinol Metab* 38: 861-865, 1974
- 36 L. Van Middlesworth: Re-Evaluation of Certain Aspects of Iodine Metabolism. *Rec Progr Hormone Res* 16: 405-431, 1960
- 37 V. Srinivasan, N.R. Moudgal and P.S. Sarma: Studies on Goitrogenic Agents in Food. *J Nutr* 61: 87-95, 1957
- 38 J. Wolff: Iodine-Goiter and the Pharmacological Effects of Excess Iodine. *Am J Med* 47: 101-124, 1969
- 39 J. Matovinovic in *Annual Review of Nutrition*. W J Darby, H P Broquist and R.L. Olson, Editors, vol 3, pp 341-412. Annual Reviews Inc., Palo Alto, California, 1983

Other Trace Elements

Evidence for the essentiality of molybdenum first appeared in 1953 when xanthine oxidase was identified as a molybdenum metalloenzyme.¹ Reports suggesting that arsenic, cadmium, lead, nickel, tin and vanadium are essential have appeared since 1970. Those relating to cadmium, lead and tin have come from one laboratory,² however, and have not been confirmed by others. Dietary supplements of cadmium, lead or tin improved the growth of sub-optimally growing rats slightly, but did not give optimal growth;² the evidence of a growth effect was not confirmed independently. Nielsen critically reviewed those findings and concluded that on the basis of present knowledge, cadmium, lead and tin should not be included in the list of essential trace elements.³ For those elements, the evidence did not fulfill the requirements for essentiality as defined by Mertz.⁴ Thus, the following discussion will be limited to aspects of arsenic, molybdenum, nickel and vanadium nutrition.

Arsenic

Metabolism. Absorption, retention and excretion of arsenic are influenced by the chemical form and level in which it is ingested. Rats, unlike other mammals, concentrate arsenic in their blood⁵ and appear unique in the metabolic management of arsenic. Thus, metabolic findings from rats may not be applicable to other species.

All forms of arsenic are well-absorbed. Organo-arsenic, however, may be less well-absorbed than is inorganic arsenic. Human subjects who ingested tissues of chickens fed arsenic-⁷⁴As acid rapidly

EFFECTS OF TIME OF ADMINISTRATION AND DIETARY IODINE LEVELS ON POTASSIUM IODIDE (KI) BLOCKADE OF THYROID IRRADIATION BY ^{131}I FROM RADIOACTIVE FALLOUT

Pat B. Zanzonico* and David V. Becker†

Abstract—Radioiodines, particularly ^{131}I , may be released into the environment in breach-of-containment nuclear reactor accidents and localize in and irradiate the thyroid with an attendant risk of neoplastic growth and other adverse health effects. Pharmacologic thyroid blockade by oral potassium iodide (KI) (50–100 mg in adults) can substantially reduce thyroid uptake of and irradiation by internalized radioiodine. In the current analysis, computer modeling of iodine metabolism has been used to systematically elucidate the effects of two practically important but highly variable factors on the radioprotective effect of KI: the time of administration relative to exposure to radioiodine and the dietary level of iodine. In euthyroid adults receiving iodine-sufficient diets (250 $\mu\text{g d}^{-1}$ in the current analysis), KI administered up to 48 h before ^{131}I exposure can almost completely block thyroid uptake and therefore greatly reduce the thyroid absorbed dose. However, KI administration 96 h or more before ^{131}I exposure has no significant protective effect. In contrast, KI administration after exposure to radioiodine induces a smaller and rapidly decreasing blockade effect. KI administration 16 h or later after ^{131}I exposure will have little effect on thyroid uptake and absorbed dose and therefore little or no protective effect. The ^{131}I thyroid absorbed dose is two-fold greater with insufficient levels of dietary iodine, 2,900 cGy/37 MBq, than with sufficient levels of dietary iodine, 1,500 cGy/37 MBq. When KI is administered 48 h or less before ^{131}I intake, the thyroid absorbed doses (in cGy/37 MBq) are comparably low with both sufficient and insufficient dietary iodine levels. When KI is administered after ^{131}I intake, however, the protective effect of KI is less and decreases more rapidly with insufficient than with sufficient dietary iodine. For example, KI administration 2 and 8 h after ^{131}I intake yields protective effects of 80 and 40%, respectively, with iodine-sufficient diets, but only 65 and 15% with iodine-deficient diets. In conclusion, whether exposed populations receive sufficient or insufficient dietary iodine, oral KI is an effective means of reducing thyroid irradiation from environmentally dispersed radioiodine but is effective

only when administered within 2 d before to ~8 h after radioiodine intake.

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Key words: ^{131}I ; dosimetry; thyroid; fallout

INTRODUCTION

RADIOISOTOPES of iodine are produced in abundance in fission reactions, and significant amounts of radioiodine can be released into the environment in breach-of-containment nuclear reactor accidents. The potential adverse health effects of environmentally released radioiodines lie in the fact that iodine is readily absorbed into the circulation following ingestion or inhalation, rapidly concentrated by and stored in the thyroid, and only slowly secreted in organified form as thyroid hormones resulting in high thyroid absorbed doses. Thyroid irradiation at sufficiently high absorbed doses from internally deposited radioiodine can cause the late appearance of thyroid nodules and/or cancer (NCRP 1985) and, at higher absorbed doses, destroy follicular cells and thereby induce hypothyroidism (Wolf 1980). Following the Chernobyl nuclear reactor accident in 1986, for example, an early and dramatic increase in the incidence of pediatric thyroid cancer ensued in Byelorussia and Ukraine, presumably as a result of environmental dispersion and ingestion and inhalation of radioiodine and, in particular, ^{131}I (Astakhova et al. 1998; Baverstock et al. 1992; Becker et al. 1996; Goslings 1989; Kazakov et al. 1992; Sobolev et al. 1997; Williams 1996).

Radioactive fallout in the immediate vicinity of the reactor, the so-called near-field, is introduced into the body predominantly through inhalation but also is deposited upon vegetation, which is consumed directly as food or indirectly by consuming milk from cows that have grazed on radioactively contaminated fodder. At later times and greater distances, ingestion is the primary pathway into the body (Becker 1987; Eisenbud and Wrenn 1963; Holland 1963; Zanzonico and Becker 1993).

There are 24 isotopes of iodine, ^{127}I to ^{140}I , all of which except ^{127}I are radioactive. Although ^{132}I , ^{133}I , ^{134}I , and ^{135}I are actually produced in greater yields than ^{131}I in thermal neutron fission of ^{235}U (Holland 1963), thyroidal

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radiation off-site following breach-of-containment nuclear reactor accidents is ascribed almost entirely to ^{131}I because of its relatively long half-life (Holland 1963). The current analysis is therefore restricted to ^{131}I .

Most reactor accident scenarios are envisioned as developing over many hours, providing some time to implement protective actions to reduce intake of radionuclides. Since the initial near-field exposure is primarily through inhalation, air filtration, sheltering, and evacuation are particularly important early protective measures. Even minimal respiratory protection with a moistened handkerchief can filter out some particles and significantly reduce inhalation of radioactivity. Sheltering, which includes closing of windows, doors, and ventilation systems, can provide non-disruptive protection when exposure is expected to be of short duration. In high-level or continuing releases, evacuation of populations in the immediate vicinity of reactor accidents may be prudent. Interdiction of contaminated foods, particularly milk and water, can be immediately effective in preventing ingestion of fallout. Radioiodines can appear in cow's milk within 5 to 10 h of ingestion of contaminated fodder, with peak concentrations by 36 to 48 h post-ingestion (Becker 1987; Zanzonico and Becker 1993).

In addition to the foregoing physical measures, a number of biologic measures can interfere with the absorption and internal deposition of some radionuclides. Pharmacologic thyroid blockade by oral potassium iodide (KI) is perhaps the most efficient and practical of these protective measures (Becker 1987; Becker et al. 1984; NCRP 1977; Robbins 1983; Rubery and Smales 1990; Stanbury 1990; VanMiddlesworth 1987; Zanzonico and Becker 1993). Iodine is rapidly and completely absorbed by the upper gastrointestinal tract within 30 to 60 min of ingestion. Inhaled radioiodines reach equilibrium in the blood within about 30 min. Iodide is rapidly concentrated by the thyroid with maximum accumulation reached by 36 to 48 h in euthyroid individuals receiving sufficient dietary iodine. In iodine deficiency, uptake is more rapid, and a higher peak uptake is reached earlier, at 12 to 24 h. Intrathyroidal iodine is slowly secreted into the circulation in organic form as the thyroid hormones, tetra-iodothyronine (T₄, thyroxine), and tri-iodothyronine (T₃). The biologic half-life of the organified thyroidal iodine is 60 to 100 d. Because of its rapid uptake and long retention, the radioiodine thyroid dose is proportional to the uptake (Berman et al. 1968; Wolff 1980; Zanzonico and Becker 1993; Zanzonico et al. 1995).

Potassium iodide, given in adequate quantities (50–100 mg in adults) at the appropriate times, can almost completely block thyroidal uptake of radioiodide (Becker 1987; Becker et al. 1984; Il'in et al. 1972; NCRP 1977; Robbins 1983; Rubery and Smales 1990; Stanbury 1990; Sternthal et al. 1980; VanMiddlesworth 1987; Wolff 1980; Zanzonico and Becker 1993). Although the predominant mode of action is not well established, several mechanisms have been postulated. These include isotope dilution, saturation of the iodide transport mechanism, interference with intrathyroidal organification of iodide, and inhibition of hormone release (Dumont et al. 1990;

Sternthal et al. 1980; Wolff 1980). The time of administration of the KI relative to radioiodine intake is the critical determinant of effectiveness of blockade, with KI administration coinciding with radioiodine intake providing the greatest protective effect, that is, the greatest reduction in thyroid uptake of and irradiation by radioiodine (Blum and Eisenbud 1967; Il'in et al. 1972; Lengemann and Thompson 1963; Stanbury 1990; Zanzonico and Becker 1993). Practically, however, given the vagaries of environmental release and dispersion of radioiodine in breach-of-containment nuclear reactor accidents, it is probably impossible to time KI administration to coincide exactly with radioiodine intake.

Besides the time of KI administration relative to radioiodine exposure (Zanzonico and Becker 1993), the effectiveness of KI blockade is affected by dietary levels of iodine. For the purposes of the current analysis, restricted to euthyroid adults, a dietary intake $100 \mu\text{g d}^{-1}$ less than and greater than the recommended dietary intake of $150 \mu\text{g d}^{-1}$ (NRC 1989) was defined as iodine deficiency ($50 \mu\text{g d}^{-1}$ overall) and iodine sufficiency ($250 \mu\text{g d}^{-1}$ overall), respectively. In the current paper, computer modeling of iodine metabolism has been used to systematically elucidate the effectiveness of thyroid blockade as a function of dietary iodine status as well as of the time of KI administration relative to radioiodine intake.

MATERIALS AND METHODS

Compartmental model of iodine metabolism

Whole-body iodine metabolism was simulated using the compartmental model in Fig. 1 and Berman's SAAM program (Berman et al. 1962; Boston et al. 1981). In Fig. 1, PBI, or protein-bound iodine, corresponds to circulating thyroid hormone. This standard model is essentially a simplification of the detailed model of Berman et al. (1968).

Using the analytic fit of Blum and Eisenbud to their measurements of suppression of the 24-h thyroid uptake of ^{131}I as a function of serum concentration of iodide (Adams and Bonnell 1962; Blum and Eisenbud 1967; Ramsden et al. 1967), the following formula relating the iodide-to-thyroid exchange rate to the serum iodide concentration was derived and used in the foregoing compartmental model (Zanzonico and Becker 1993):

$$k(\text{thyroid, iodide}) = 0.37k(\text{thyroid, iodide})_0[\text{Iodide}]^{-0.9} \quad (1)$$

where

$k(\text{thyroid, iodide})$ = the iodide-to-thyroid exchange rate (h^{-1});

$k(\text{thyroid, iodide})_0$ = the maximum iodide-to-thyroid exchange rate (h^{-1}); that is, the theoretical iodide-to-thyroid exchange rate (h^{-1}) at a serum iodide concentration of zero,
= 0.0456 h^{-1} ; and

[Iodide] = the concentration of iodide in serum ($\mu\text{g}/100 \text{ mL}$).

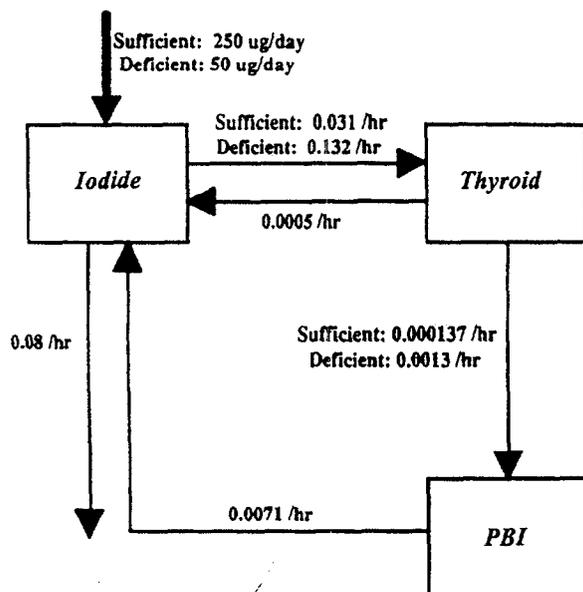


Fig. 1. Simplified whole-body compartmental model of iodine metabolism. Inter-compartment exchange rates are indicated, including the iodide-to-thyroid and thyroid-to-PBI (protein-bound iodine) exchange rates for iodine sufficiency ($250 \mu\text{g d}^{-1}$) and deficiency ($50 \mu\text{g d}^{-1}$). The clearance exchange rate from the iodide compartment, 0.08 h^{-1} , corresponds to urinary excretion.

Using eqn (1), the model is quantitatively adaptable to the entire range of dietary iodine levels, from deficiency (assumed to correspond to $50 \mu\text{g d}^{-1}$ ingested) to sufficiency (assumed to correspond to $250 \mu\text{g d}^{-1}$ ingested), and to KI blockade (corresponding to oral administration of 100 mg of KI). The pertinent concentrations of iodide in serum were determined using the compartmental model in Fig. 1 to determine the steady-state amount (in μg) of iodide for a daily intake of 50 or $250 \mu\text{g}$ and a Reference Man serum volume of $3,000 \text{ mL}$ (ICRP 1975).

Thyroid cumulated activity

The time-dependent radioiodine activity and the resulting cumulated activity in the thyroid were estimated using the foregoing model. The effect of radioactive decay was introduced by appending a "clearance" exchange rate to each compartment i equal to the physical decay constant (λ_p) of ^{131}I , $k(0,i) = \lambda_p = 0.00359 \text{ h}^{-1}$. Assuming an internalized activity of 37 MBq (1 mCi), the cumulated activity of inhaled/ingested radioiodide in the thyroid was determined by integrating the decayed activity in each compartment using the method of Sgouros et al. (1987).

Thyroid mean absorbed dose

A standard methodology widely used for internal radionuclide absorbed dose calculations is the "MIRD formalism," developed by the Medical Internal Radiation

Dose Committee (MIRD) of the Society of Nuclear Medicine (SNM) (Loevinger et al. 1991; Zanzonico et al. 1995). The *DOSCAL* program (Sgouros et al. 1988), a computerized version of the MIRD formalism, was used in the current analysis.

For internal radionuclides in general and radioiodine in the thyroid in particular, self-irradiation accounts for nearly the entire absorbed dose to any given target region primarily because of the contribution from particulate radiations (such as beta-rays). Beta-rays are assumed to be completely or almost completely absorbed *in situ* since the dimensions of human organs are typically much greater than the ranges in tissue of particulate radiations. The thyroid absorbed dose may be equated with the mean self-irradiation absorbed dose (Zanzonico et al. 1995):

$$\bar{D}(\text{thy}) \approx \bar{D}(\text{thy} \leftarrow \text{thy}) \quad (2)$$

$$= \bar{A}_{\text{thy}} S(\text{thy} \leftarrow \text{thy}), \quad (3)$$

where

$\bar{D}(\text{thy})$ = the mean absorbed dose to the thyroid;

$\bar{D}(\text{thy} \leftarrow \text{thy})$ = the mean self-irradiation absorbed dose to the thyroid;

\bar{A}_{thy} = the cumulated activity in the thyroid; and

$S(\text{thy} \leftarrow \text{thy})$ = the thyroid-to-thyroid S factor.

= $22 \text{ cGy}/37 \text{ MBq h}^{-1}$ for ^{131}I in the adult 20-g thyroid.

As noted, an inhaled and/or ingested activity of 37 MBq (1 mCi) of ^{131}I was assumed for the current analysis.

Protective effect

The reduction in thyroid irradiation achieved with oral KI blockade was expressed as the "protective effect," defined below (H'in et al. 1972):

Protective effect

$$\begin{aligned} & \frac{\text{Thyroid absorbed dose without blocking} \\ & - \text{Thyroid absorbed dose with blocking}}{\text{Thyroid absorbed dose without blocking}} \\ & \times 100\%. \quad (4) \end{aligned}$$

Protective effects were determined and presented separately for sufficient and for deficient dietary levels of iodine (250 and $50 \mu\text{g d}^{-1}$, respectively) and as a function of time of KI administration relative to radioiodine intake.

RESULTS

In Figs. 2 and 3, thyroid uptake, in decay-corrected percentage of ingested and/or inhaled activity, is plotted against the time interval between KI administration and intake of ^{131}I ; the data in Figs. 2 and 3 have been

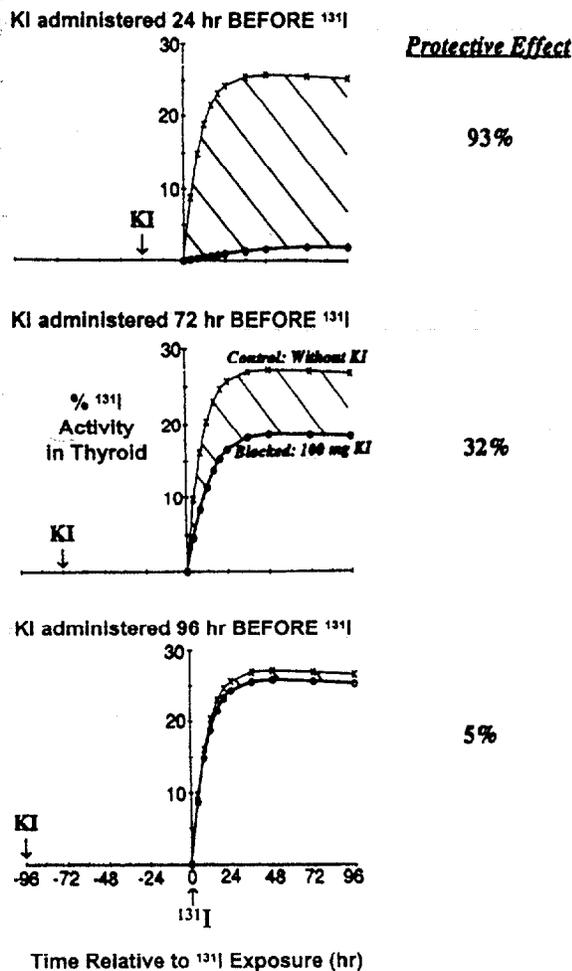


Fig. 2. Thyroid uptake of radioiodine in percentage of administered activity vs. time for different time intervals between a single KI administration (100 mg) and exposure to ¹³¹I for KI administration before ¹³¹I exposure. The top, middle, and bottom graphs correspond to KI administered 24, 72, and 96 h before exposure to ¹³¹I, respectively. The upper curves (X) correspond to the control, or unblocked, time-dependent thyroid uptake; the lower curves (O) are the corresponding data for KI blockade. The corresponding protective effects of KI, related to the crosshatched area between the two curves in each graph, are specified.

calculated for euthyroid adults on iodine-sufficient diets. KI administration before ¹³¹I exposure (Fig. 2) corresponds to negative time intervals (to the left of the ordinate axis) and KI administration after ¹³¹I exposure (Fig. 3) corresponds to positive time intervals (to the right of the ordinate axis). As indicated on the middle graph in Figs. 2 and 3, the upper curves in each graph correspond to the unblocked, or control, time-dependent thyroid uptake; the lower curves are the corresponding data for KI blockade. In Figs. 2 and 3, the corresponding protective effects, related to the difference between the

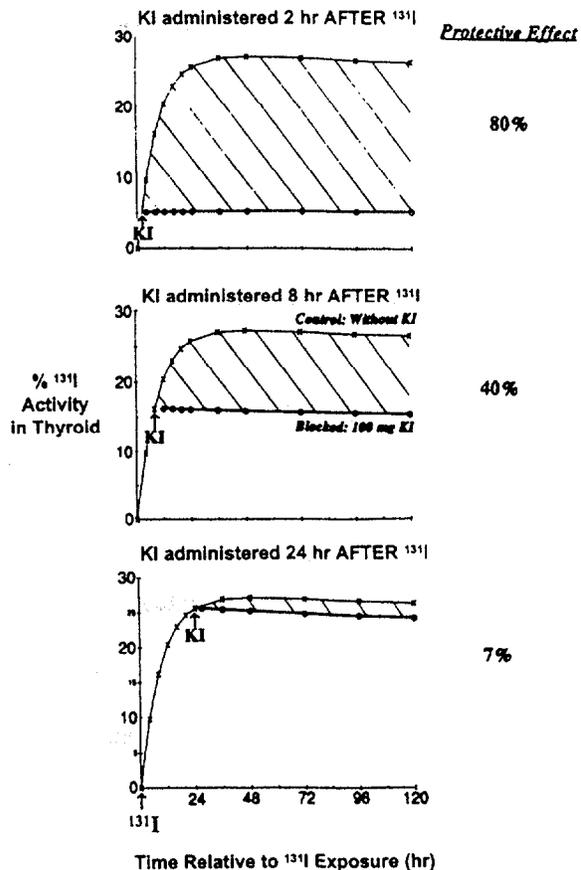


Fig. 3. Thyroid uptake of radioiodine in percentage of administered activity vs. time for different time intervals between a single KI administration (100 mg) and exposure to ¹³¹I for KI administration after ¹³¹I exposure. The top, middle, and bottom graphs correspond to KI administered 2, 8, and 24 h after exposure to ¹³¹I, respectively. The upper curves (X) correspond to the control, or unblocked, time-dependent thyroid uptake; the lower curves (O) are the corresponding data for KI blockade. The corresponding protective effects of KI, related to the crosshatched area between the two curves in each graph, are specified.

areas under the blocked and unblocked thyroid time-activity curves (represented by the crosshatched region between the curves), are also presented.

Fig. 4 illustrates the differences between sufficient and deficient dietary levels of iodine in terms of thyroid kinetics and the protective effect of KI; in this illustration, it was assumed that KI was administered 8 h after ¹³¹I intake. In iodine deficiency, the model-derived thyroid uptake rises more rapidly to a higher maximum (60%) at an earlier time (12 h) than in iodine sufficiency (26% at 36 h). As a result of the approximately two-fold higher thyroid uptake, the thyroid absorbed dose is approximately two-fold greater in iodine deficiency, 2,900 cGy/37 MBq, than in iodine sufficiency, 1,400 cGy/37 MBq (assuming no significant difference in the effective half-time of thyroïdal radioiodine).

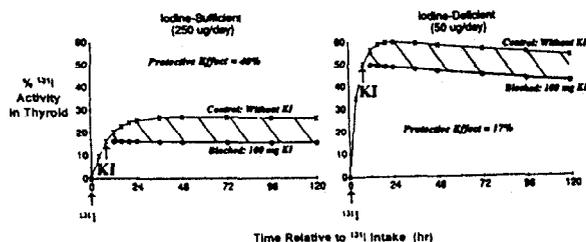


Fig. 4. Protective effect of KI blocking in iodine sufficiency and deficiency illustrated for KI administration 8 h after exposure to ^{131}I . The upper curves (X) correspond to the control, or unblocked, time-dependent thyroid uptake; the lower curves (O) are the corresponding data for KI blockade. The protective effect of KI is proportional to the crosshatched area between the two curves expressed as the fraction of the area under the control thyroid uptake curve and thus is greater for iodine sufficiency than iodine deficiency.

Fig. 5 graphically summarizes the effect on ^{131}I thyroid uptake (Fig. 5a), absorbed dose (Fig. 5b), and protective effect (Fig. 5c) of the time interval between KI administration and ^{131}I intake and of the level of dietary iodine. As in Figs. 2 and 3, KI administration before ^{131}I exposure (Fig. 2) corresponds to negative time intervals (to the left of the ordinate axis), and KI administration after ^{131}I exposure (Fig. 3) corresponds to positive time intervals (to the right of the ordinate axis). KI administration up to 48 h before ^{131}I exposure can almost completely block thyroid uptake (Fig. 5a) and therefore greatly reduce the thyroid absorbed dose (Fig. 5b), regardless of the dietary iodine level. For example, KI administration 24 and 48 h before ^{131}I exposure yields a protective effect of 90 and 75%, respectively, in iodine sufficiency and 95 and 85%, respectively, in iodine deficiency (Fig. 5c). KI administration even 72 h before ^{131}I exposure will reduce 24-h thyroid uptake from 26 to 19% (Fig. 5a) and yield a protective effect of 32% in iodine sufficiency (Fig. 5c). In iodine deficiency, KI administration at this time will reduce 24-h thyroid uptake from 60 to 25% (Fig. 5a) and yield a protective effect of 55% (Fig. 5c). However, as indicated in Fig. 5c, KI administration 96 h or more before ^{131}I exposure has no significant protective effect (less than 10%).

In contrast, KI administration after exposure to radioiodine induces still marked but less, and rapidly decreasing, blockade (Fig. 5). Once ^{131}I is incorporated into the thyroid, its slow discharge cannot be significantly accelerated except perhaps with thyroid stimulating hormone (TSH), but further accumulation can be blocked by KI. KI administered up to 2 h after ^{131}I exposure can almost completely block thyroid uptake (Fig. 5a) and therefore greatly reduce the thyroid absorbed dose (Fig. 5b), yielding protective effects of 80 and 65% in iodine sufficiency and iodine deficiency, respectively (Fig. 5c). However, later KI administration, even as soon as 8 h after ^{131}I intake, will only modestly reduce uptake (Fig. 5a) and dose (Fig. 5b), yielding a protective effect of only 40% in iodine sufficiency and

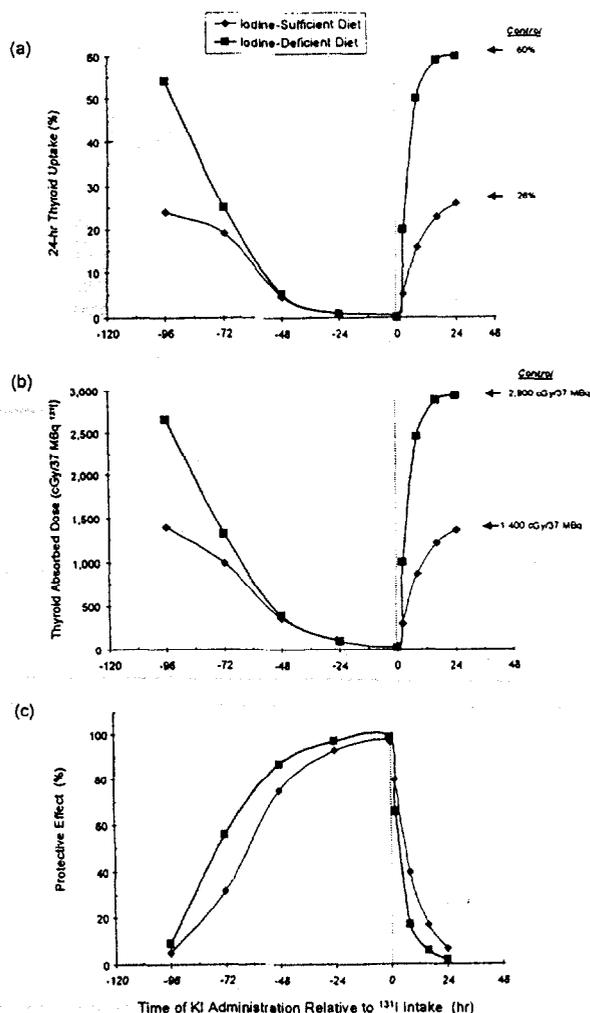


Fig. 5. Decay-corrected 24-h percent thyroid uptake, thyroid absorbed dose per unit activity inhaled and/or ingested (cGy/37 MBq), and KI protective effect (%) as function of time of KI administration relative to ^{131}I exposure for iodine sufficiency (\diamond) and iodine deficiency (\blacksquare). Time "0" represents the time of ^{131}I intake.

even less, 15%, in iodine deficiency (Fig. 5c). KI administration 16 h or later after ^{131}I exposure will have little effect on uptake (Fig. 5a) and dose (Fig. 5b) and therefore little or no protective effect (Fig. 5c).

Because the ^{131}I thyroid absorbed dose is essentially proportional to the 24-h thyroid uptake, the curves representing the 24-h thyroid uptake (Fig. 5a) and the ^{131}I thyroid absorbed dose (Fig. 5b) as functions of the time of KI administration relative to ^{131}I exposure are parallel. Note that the 24-h thyroid uptake (Fig. 5a) and therefore the ^{131}I thyroid absorbed dose (Fig. 5b) for iodine deficiency are always greater than or equal to the corresponding values for iodine-sufficient diets. As further indicated in Fig. 5c, for KI administered before

exposure to ^{131}I , the protective effect is greater in iodine deficiency than in iodine sufficiency, and the earlier KI is administered before ^{131}I intake the greater the protective effect (as discussed above). However, when KI is administered after ^{131}I intake, its protective effect is less and decreases more rapidly in iodine deficiency than in iodine sufficiency. For example, KI administration 2 and 8 h after ^{131}I exposure yields protective effects of 80 and 40%, respectively, in iodine sufficiency, but only 66 and 17%, respectively, in iodine deficiency (Fig. 5c).

DISCUSSION

The results of the current model-based analysis are qualitatively and quantitatively similar to the experimental results of Il'in et al. (1972) in human subjects. These results indicate that KI is more effective in reducing the absorbed dose of ^{131}I to the thyroid when it is administered prior to or at the same time as ingestion or inhalation of the radioiodine (Figs. 2 and 3), and its effectiveness in iodine deficiency may be comparable to or somewhat greater than that in iodine sufficiency (Fig. 5). Since logistical issues such as distribution may make administration of KI before or coincidental with the radioiodine exposure unlikely, the effectiveness of KI given following exposure is of considerable practical importance. Clearly, the earlier the KI is given, the better, but it is still useful in reducing thyroid dose if administered up to 8 h and to a lesser extent even 12 h after a single exposure to fallout. Importantly, however, the protective effect is less and decreases more rapidly in iodine deficiency than in iodine sufficiency when KI is administered after ^{131}I intake (Fig. 5c).

It is important to note that in the absence of KI blockade the ^{131}I 24-h thyroid uptakes and absorbed doses and, therefore, radiogenic risks are two-fold greater in iodine deficiency than in iodine sufficiency. Accordingly, in the event of breach-of-containment nuclear reactor accident, KI administration and the promptness of administration are actually more important among iodine-deficient than among iodine-sufficient populations. Endemic iodine deficiency persists in parts of Europe, where nuclear power reactors are rather numerous, and in other heavily populated areas of the world (Delange et al. 1993).

The results of the current analysis apply to a single blocking dose of KI before or after a single exposure to ^{131}I . With continuing or subsequent exposure to ^{131}I , however, the effects of even a single administration of KI may still be significant because of its persistent though decreasing blockade of uptake for as long as 72 h. For example, 48 h after KI, there is still a 75 and 87% protective effect in iodine sufficiency and deficiency, respectively, and at 72 h a 32 and 56% protective effect in iodine sufficiency and deficiency, respectively, against "new" ^{131}I exposures (Fig. 5c).

The issue of the optimum oral dosage of KI for thyroid blockade has been addressed by a number of different investigators (Blum and Eisenbud 1967; Sternthal et al. 1980; WHO 1989). Sternthal et al. (1980)

showed that 10 mg of KI given in a single dose simultaneously with a tracer of radioiodine will decrease uptake from 25 to 16% of control and thus provide a 35% protective effect. However, KI in amounts of 30 mg or more will reduce the 24-h uptake from 25 to 1% and provide a 95% protective effect. Although 100 mg is only slightly more protective than 30 mg, there are substantial pharmacokinetic advantages to a larger amount: it will provide an elevated iodide blood level, which is directly related to both blocking effectiveness and the duration of effect. The U.S. Food and Drug Administration has recommended 100 mg of iodide (130 mg of KI) as the "standard" adult dose. The recommended dose for children is 65 mg. This is the same order of magnitude as Poland's selection of 70 mg for children ages 2-16 y; Poland gave children from 3 to 12 y 50 mg of iodine and children under 3 received 25 mg (Nauman 1990, 1991). By these measures, Poland was able to reduce the projected thyroid absorbed doses from radioactive Chernobyl fallout by an estimated 40% (Nauman 1990, 1991).

With continuing exposure, it is desirable to administer KI daily for the duration of the exposure and perhaps for several days longer. Continued administration of KI, however, may produce significant physiological effects. In the study of Sternthal et al. (1980), most individuals who received KI in amounts greater than 30 mg a day for 8 d had a significant fall in serum thyroid hormone levels. Three of the five subjects who received 100 mg a day for 8 d had elevated TSH levels and biochemical hypothyroidism. Also noted was a considerable individual variation in response which potentially could be a major problem in large populations.

The World Health Organization (WHO), in their extensive examination of KI administration (WHO 1989), concluded that iodide prophylaxis was not generally justified in the far-field for adults (except for pregnancy), where the main route of exposure is ingestion and where embargo of contaminated food can be used to limit the thyroid dose. In the near field, however, where thyroid doses in adults as well as children may be high and inhalation the more likely route of exposure, more rapid action is required. Infants, children, and adolescents up to 16 y should be given KI in both near-and far-fields (as was done in Poland). For pregnant women in the first trimester, the fetal thyroid is not yet functioning, but in second and third trimesters stable iodine should be given to protect both the fetal and maternal thyroids. In all cases, administration should be determined by projected dose estimates when such projections exceed the intervention level for the country and community involved. The oral dose for adults is generally recommended to be 100 mg of iodide (130 mg of potassium iodide). Neonates should have doses preferably not to exceed 12.5 mg and children not to exceed 50 mg (NCRP 1977; WHO 1989).

Considerable attention has been given to the possibility of adverse reactions to KI, but wide experience prior to Chernobyl has been limited (Becker et al. 1984; NCRP 1977; Robbins 1983; Wolff 1985). The primary

reactions from single or several doses of KI given over a short period have been dose-dependent non-thyroidal effects (Wolff 1985). The greatest concern, therefore, is related to iodine sensitivity, where a small dose may possibly trigger a pronounced response. Although rare, such effects have been reported and include dermatologic reactions (eczema) and sensitivity reactions (edema of the face and, at worst, glottis) as well as asthma.

The experience in Poland, where 10.5 million children and adolescents were given a single dose of 70 mg of KI, showed reactions to be uncommon (overall ~4.5%) (Gembicki et al. 1991; Nauman 1990, 1991). Somewhat surprisingly, the most common reaction in children was that of vomiting (2.4%). This could have been a psychological effect of stress rather than a direct toxic effect. Other reported side effects include dermatologic effects in 1.1% and abdominal pain in 0.36%.

As illustrated by the experience in Poland following the Chernobyl nuclear reactor accident, rapid distribution of KI to a very large population requires an extraordinary degree of organization and centralized authority. Ideally, KI should be administered prior to exposure, but the practical aspects of such administration to large populations raise many difficult questions. These center on the near impossibility of distributing KI to an entire population, including transients, over a wide and varied geographic area in a timely fashion. If predistribution is elected, special efforts must be made with regard to the safety of storage in the home to avoid premature, inappropriate or accidental ingestion (Becker 1987).

The decision as to whether KI should be recommended for an exposed population is based upon projections of the radiation dose (Meck et al. 1985). These in turn depend upon the immediate availability of expert technical assessment of the reactor, the nature of the accident, its rate of progress, geographic distribution of populations at risk, and the prevailing meteorological conditions. Based upon radiogenic cancer risk estimates, different local, national, and international bodies have recommended intervention at somewhat different projected radiation dose levels. For adults, these range around 25 rem (250 mSv) with a smaller dose limit (~5 rem) for children (WHO 1989). It should be realized, of course, that KI provides protection only for the thyroid and only against the radioiodine component of fallout. Risks from other radionuclides must be incorporated into a comprehensive emergency response plan.

REFERENCES

- Adams, C.; Bonnell, J. Administration of stable iodine as a means of reducing thyroid irradiation resulting from inhalation of radioactive iodine. *Health Phys.* 7:127-149; 1962.
- Astakhova, L.; Anspaugh, L.; Beebe, G.; Bouville, A.; Drozdovitch, V. V.; Garber, V.; Gavrillin, Y. I.; Khrouch, V. T.; Kuvshinnikov, A. V.; Kuzmenkov, Y. N.; Minenko, V. P.; Moschik, K. V.; Nalivko, A. S.; Robbins, J.; Shemiakina, E. V.; Shinkarev, S.; Tochitskaya, S. I.; Waclawiw, M. A. Chernobyl-related thyroid cancer in children of Belarus: A case-control study. *Rad. Res.* 150:349-356; 1998.
- Baverstock, K.; Egloff, B.; Pinchera, A.; Ruchti, C.; Williams, D. Thyroid cancer after Chernobyl. *Nature* 359:21-22; 1992.
- Becker, D.; Robbins, J.; Beebe, G.; Bouville, A.; Wachholz, B. Childhood thyroid cancer following the Chernobyl accident. *Endocrinol. Metab. Clin. North Am.* 25:197-211; 1996.
- Becker, D. V. Reactor accidents. Public health strategies and their medical implications. *JAMA* 258:649-654; 1987.
- Becker, D. V.; Braverman, L. E.; Dunn, J. T.; Gaitan, E.; Gorman, C.; Maxon, H.; Schneider, A. B.; Van Middlesworth, L.; Wolff, J. The use of iodine as a thyroidal blocking agent in the event of a reactor accident. Report of the Environmental Hazards Committee of the American Thyroid Association. *JAMA* 252:659-661; 1984.
- Berman, M.; Hoff, E.; Barandes, M.; Becker, D. V.; Sonenberg, M.; Benua, R.; Koutras, D. A. Iodine kinetics in man—A model. *J. Clin. Endocr. Metab.* 28:1-14; 1968.
- Berman, M.; Shahn, E.; Weiss, M. The routine fitting of kinetic data to models: A mathematical formalism for digital computers. *Biophys. J.* 2:275-316; 1962.
- Blum, M.; Eisenbud, M. Reduction of thyroid irradiation from ¹³¹I by potassium iodide. *JAMA* 200:1036-1040; 1967.
- Boston, R. C.; Greif, P. C.; Berman, M. Conversational SAAM—an interactive program for kinetic analysis of biological systems. *Computer Programs Biomed.* 13: 111-119; 1981.
- Delange, F.; Dunn, J.; Glinoe, D. Iodine deficiency in Europe: A continuing concern. NATO Advanced Science Institutes (ASI) Series, volume 241. New York: Plenum Press; 1993.
- Dumont, J.; Corvilain, B.; Coclet, J.; Raspe, E.; Reuse, S. Recent progress in fundamental thyroidology with relevance to the prevention of medical consequences of a nuclear accident. In: Rubery, E.; Smales, E., eds. Iodine prophylaxis following nuclear accidents. Proceedings of a Joint WHO/CEC Workshop, July 1988. Oxford: Pergamon Press; 1990: 33-37.
- Eisenbud, M.; Wrenn, M. Biological disposition of radioiodine—A review. *Health Phys.* 9:1133-1139; 1963.
- Gembicki, M.; Sowinski, J.; Ruchala, M.; Bednarek, J. Influence of radioactive contamination and iodine prophylaxis after the Chernobyl disaster on thyroid morphology and function of the Poznan region. *Endokrynol. Pol.* 42: 273-298; 1991.
- Goslings, B. Chernobyl fallout and the thyroid gland: A review of radioiodine exposure in Europe and its potential carcinogenic effect on the thyroid. In: Nagataki, S., ed. Radiation and the Thyroid. Tokyo: Excerpta Medica; 1989: 25-35.
- Holland, J. Physical origin and dispersion of radioiodine. *Health Phys.* 9:1095-1103; 1963.
- ICRP. Report of the Task Group on Reference Man. Oxford: Pergamon Press; ICRP Publication 23; 1975.
- Il'in, L.; Arkhangel'skaya, G.; Konstantinov, Y.; Likhtarev, I. Radioactive iodine in the problem of radiation safety. Atomizdat 1972. (Springfield, VA: Translation series US-AEC 7536, National Technical Information Service; 1972: 208-229.)
- Kazakov, V.; Dimidchik, E.; Astakhova, L. Thyroid cancer after Chernobyl [letter]. *Nature* 359:21; 1992.
- Lengemann, F.; Thompson, J. Prophylactic and therapeutic measures for radioiodine contamination—A review. *Health Phys.* 9:311; 1963.
- Loevinger, R.; Budinger, T.; Watson, E.; Atkins, H. L.; Blau, M.; Lathrop, K. A.; Poston, J. W.; Robertson, J. S.; Thomas, S. R.; Weber, D. A. MIRD primer for absorbed dose

- calculations. New York: Society of Nuclear Medicine; 1991.
- Meck, R. A.; Chen, M. S.; Kenny, P. J. Criteria for the administration of KI for thyroid blocking of radioiodine. *Health Phys.* 48:141-157; 1985.
- Nauman, J. Potassium iodide prophylaxis in Poland: Review of far field experience. In: Rubery, E.; Smales, E., eds. Iodine prophylaxis following nuclear accidents, Proceedings of a Joint WHO/CEC Workshop, July 1988. Oxford: Pergamon Press; 1990: 135-140.
- Nauman, J. Study of the effects of some prophylactic measures and radiological contamination in Poland after the Chernobyl accident; Introduction to the research program MZ-XVII. *Endokrynol. Pol.* 42:153-158; 1991.
- National Council on Radiation Protection and Measurements. Protection of the thyroid gland in the event of releases of radioiodine. Bethesda, MD: NCRP; NCRP Report No 55; 1977.
- National Council on Radiation Protection and Measurements. Induction of thyroid cancer by ionizing radiation. Bethesda, MD: NCRP; NCRP Report No 80; 1985.
- National Research Council. Recommended dietary allowances, Iodine, 10th ed. Washington, DC: National Academy Press; 1989.
- Ramsden, D.; Passant, F. H.; Peabody, C. O.; Speight, R. G. Radioiodine uptakes in the thyroid. Studies of the blocking and subsequent recovery of the gland following the administration of stable iodine. *Health Phys.* 13:633-646; 1967.
- Robbins, J. Indications for using potassium iodide to protect the thyroid from low level internal irradiation. *Bull. NY Acad. Med.* 59:1028-1038; 1983.
- Rubery, E.; Smales, E. Iodine prophylaxis following nuclear accidents, Proceedings of a Joint WHO/CEC Workshop, July 1988. Oxford: Pergamon Press; 1990.
- Sgouros, G.; Bigler, R.; Zanzonico, P. Techniques for the direct determination of cumulated activity from computer simulations of linear and non-linear compartmental models (Abstract). *J. Nucl. Med.* 28:617; 1987.
- Sgouros, G.; Bigler, R.; Zanzonico, P. *DOSCAL*: A tumor-incorporating mean absorbed dose calculation program. *J. Nucl. Med.* 29:874; 1988.
- Sobolev, B.; Heidenreich, W. F.; Kairo, I.; Jacob, P.; Goulko, G.; Likhtarev, I. Thyroid cancer incidence in the Ukraine after the Chernobyl accident: comparison with spontaneous incidences. *Radiat. Environ. Biophys.* 36:195-199; 1997.
- Stanbury, J. The physiological basis for blockade of radioiodine retention by iodine. In: Rubery, E.; Smales, E., eds. Iodine prophylaxis following nuclear accidents, Proceedings of a Joint WHO/CEC Workshop, July 1988. Oxford: Pergamon Press; 1990: 57-63.
- Sternthal, E.; Lipworth, L.; Stanley, B.; Abreau, C.; Fang, S. L.; Braverman, L. E. Suppression of thyroid radioiodine uptake by various doses of stable iodide. *N. Engl. J. Med.* 303:1083-1088; 1980.
- VanMiddlesworth, L. Nuclear reactor accidents and the thyroid. *Thyroid Today* 10:1; 1987.
- World Health Organization. Guides for iodine prophylaxis following nuclear accidents. Copenhagen: WHO; 1989.
- Williams, D. Thyroid cancer and the Chernobyl accident. *J. Clin. Endocrinol. Metab.* 81:6-8; 1996.
- Wolff, J. Physiological aspects of iodide excess in relation to radiation protection. *J. Mol. Med.* 4:151; 1980.
- Wolff, J. Risks for stable and radioactive iodine in radiation protection of the thyroid. In: Hall, R.; Kobberling, J., eds. *Serono Symposia*, Vol 22. New York: Raven Press; 1985: 11.
- Zanzonico, P.; Becker, D. Use of potassium iodide to minimize thyroid radiation from radioactive fall-out. In: Delange, F.; Dunn, J.; Glinoe, D., eds. *Iodine deficiency in Europe: A continuing concern*. New York: Plenum Press; 1993: 243-253.
- Zanzonico, P.; Brill, A.; Becker, D. Radiation dosimetry. In: Wagner, H.; Szabo, Z.; Buchanan, J., eds. *Principles of nuclear medicine*. Philadelphia, PA: WB Saunders Company; 1995: 106-134.
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