Iodine:

Current, Historic and International Perspectives

A study in persistence and unanticipated Outcomes

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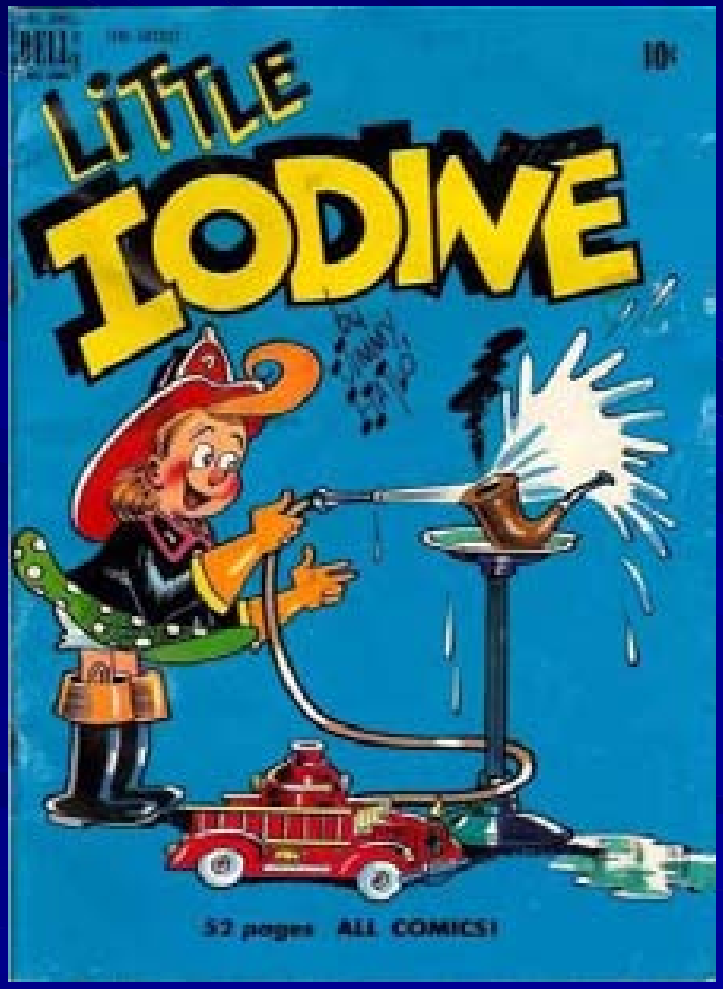
Medical Grand Rounds
Sarasota Memorial Hospital
May 1, 2009

This is Not about Little Iodine

They'll Do it Every Time
Jimmy Hatlo



Goals and Objectives

- What is iodine and where does it come from?
- What serious health problems are associated with dietary iodine deficiency?
- Who were the 20th century physicians who pioneered iodine supplementation; and why did they do it?
- Is there a world-wide problem with iodine deficiency diseases (IDD) now?
- Is dietary iodine intake adequate in the U.S. today?
- Why have topical iodine preparations disappeared from the OTC pharmacy shelves since August 2007?

Worldwide Health Problem

- “Iodine Deficiency Disorder Threatens Millions in China.” *Encarta July 1996*
- Iodine deficiency …affects 13% of the world’s population.” *JAMA, June 16, 2004*
- “Goiters Be Gone: Getting Rid of These Loathsome Lumps Has Been a Bumpy Road." *Doctor's Review, December 2007.*
- “In raising the World’s I.Q., the secret’s in the salt.” *N.Y. Times, Dec. 4, 2008*
- *“Iodine content of prenatal vitamins less than 50% of stated value in 10 of 27 RX brands.” N.E.J.M February 26, 2009*

What About Iodine?

- An element in the halogen (*salt former*) family.
- Atomic number 53, molecular weight of 126.9
  (53 protons and 74 neutrons in nucleus)
- Its symbol is I
- Other members of halogen group are fluorine, bromine , chlorine and astatine.
- It was first isolated from Seaweed residues in 1811 by Bernard Courtois, a French saltpeter manufacturer.
- Named “iodine” by Joseph Louis Gay-Lussac in 1813
- *iodes* is a Greek word for violet, the color of its vapor as it sublimates.

Iodine Crystals Sublimating

What About Iodine?

(Cont.)

- Relatively rare element, 62nd in abundance on our Earth.
- Present in seawater, brine, soil and rocks, Chilean nitrate ores and sea organisms, such as kelp and brown seaweeds.
- Essential for the production of thyroid hormones by the thyroid gland
- Thyroid hormones regulate somatic growth, intellectual development and metabolic functions
- 25% of total body iodine contained in thyroid gland
- Daily adult requirement is 100 to 220 *micrograms*/day, much more in pregnant and lactating women.

Table 1. Common Sources of Dietary Iodine

Breads	Iodized table salt
Cheese	Saltwater fish
Cow's milk	Seaweed (including kelp, dulce, nori)
Eggs	Shellfish
Frozen yogurt	Soy milk
Ice cream	Soy sauce
Iodine-containing multivitamins	Yogurt

Brochure from American Thyroid Association. 2009

Some Uses of Iodine

- Alcoholic tincture as antiseptic (Ouch!), Betadine, etc.
- OTC preparations being used for methamphetamine, production. 8/01/2007 DEA stopped OTC sales.
- Significant amounts of Iodine contained in Amiodarone* (37% I_2 by weight), i.v. radio contrast media for CT scans, kidney x-rays, etc.
- Radioactive labeled isotope for scans and treatments of the thyroid (I-131)

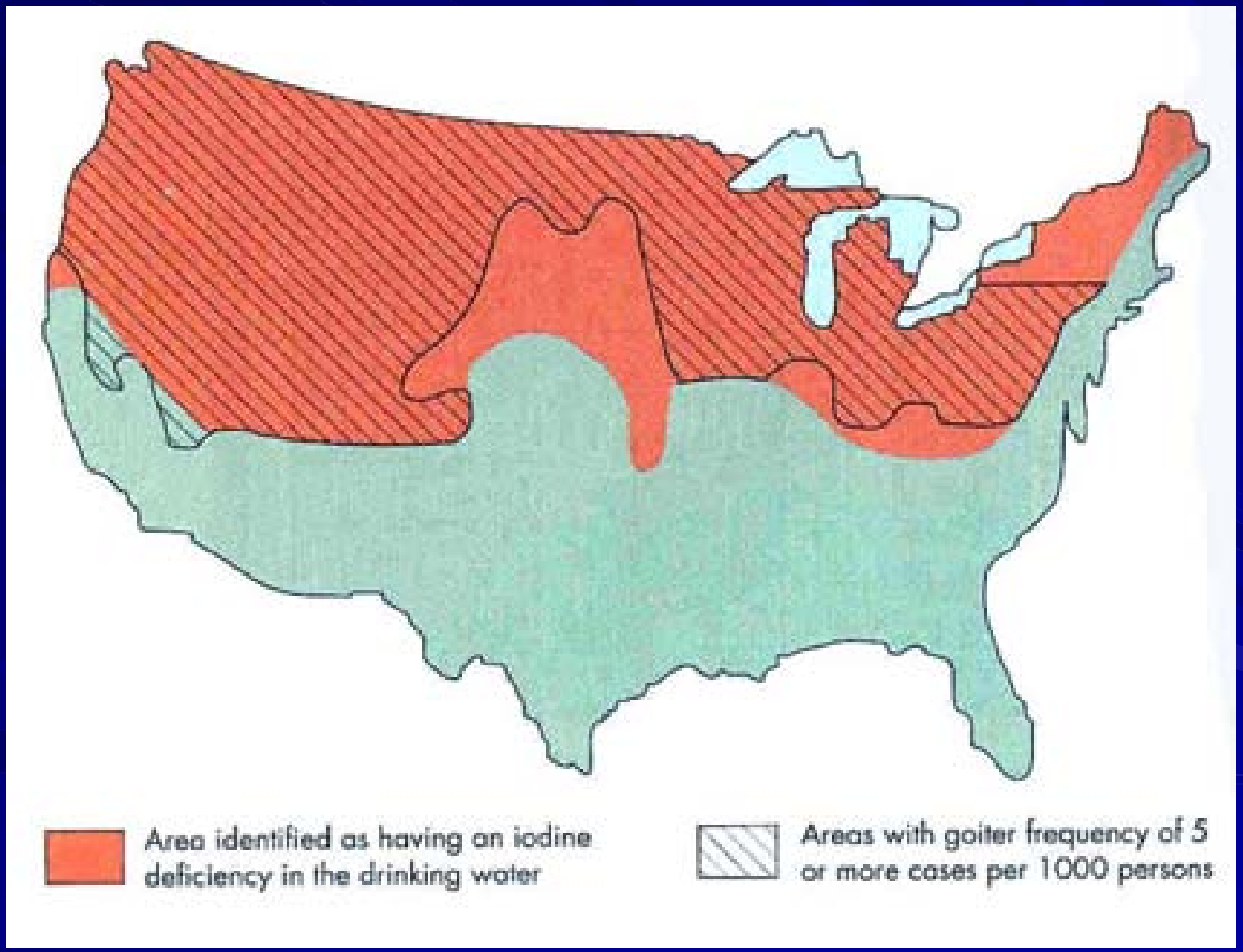
*Can cause hypo or hyperthyroidism, sometimes quite severe.

What About Iodine Deficiency?

- Iodine deficiency causes:
  - Enlargement of the thyroid gland, especially in teenage females, (*endemic goiter*)
  - Hypothyroidism with generalized lethargy and low metabolic rate
  - Mental retardation. (Greatest single and preventable cause of brain damage and mental retardation worldwide.) (Cretinism)
  - Stunted growth
  - “Diffuse toxic goiter with exophthalmos" (Grave’s disease)
  - “toxic nodular goiter.” (Plummer’s disease)
  - Possibly an increase in thyroid cancer?
- in US, Iodine is lacking in soil and water in areas around the Great Lakes (“*goiter belt*”) and upper Northwest.

The Goiter Belt

Relation of Iodine Deficiency to goiter by region



What Causes Iodine Deficiency?

- Iodine leached out of the soil by glacier melts and flooding.
- This results in inadequate amounts of iodine in the soil, water and food produced in these regions.
- Animals grazing in these areas have little or no naturally occurring iodine in their flesh and secretions such as milk.
- In these districts, humans subsisting only on locally produced nutrients often develop iodine deficiency disorders (*IDD*).

Iodine and the Thyroid Gland

What Does Iodine Do in Humans?

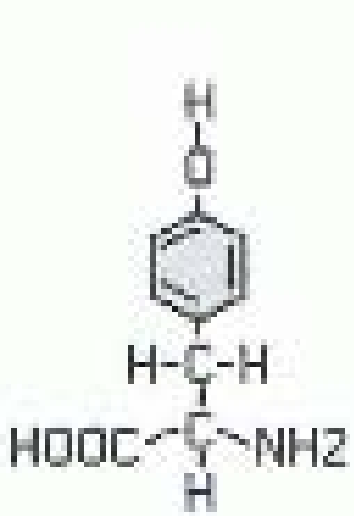
- Iodine's only known function in humans and animals is the synthesis of thyroid hormones by the thyroid gland in the neck. (Greek *thura* "door")
- Normal dietary intake of iodine is only 150 to 220 *micrograms* per day, but up to 290 ucg/day in lactating women.
- Four atoms of iodine are incorporated in each molecule of thyroxine (T4) and three in each molecule of triiodothyronine(T3).
- Thyroxines are stored in the thyroid gland in the neck in combination with a protein, thyroglobulin, as "colloid." (Greek *kolla* "glue")

Colloid in Thyroid Gland

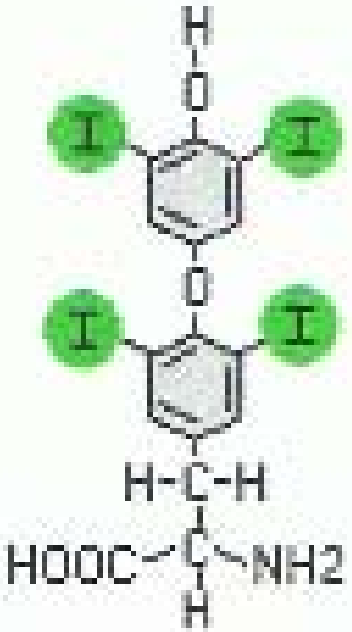
Regulation of T4 and T3

- Thyrotropin releasing hormone (TRH) in hypothalamus senses circulating T3 and T4 levels
- TRH controls release of thyroid stimulating hormone (TSH) by the anterior pituitary.
- TSH stimulates release of T4 and T3 by thyroid gland
- The serum T4 concentration is 50 times more than T3.
- But,T3 is 20 times more biologically active than T4.
- T4 is largely transformed to T3 in peripheral tissues, especially the liver.

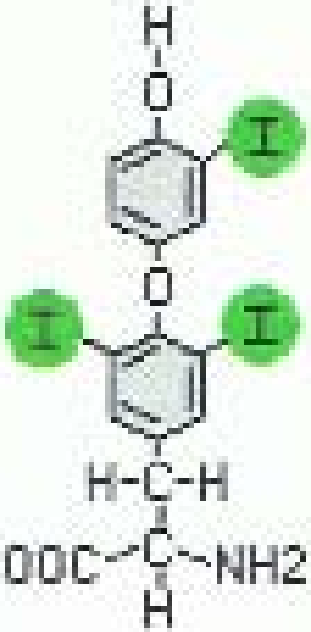
Thyroid Hormones



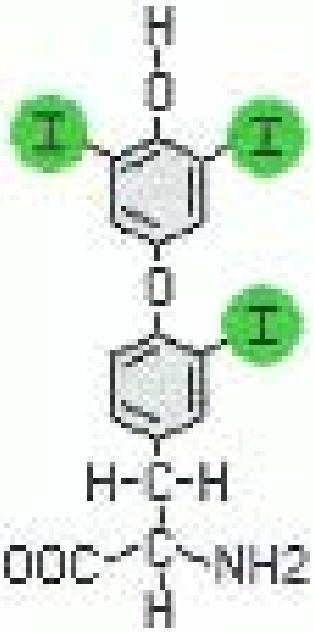
Tyrosine



Thyroxine (T4)



Triiodothyronine (T3)



"Reverse T3" (inactive)

What Does Iodine Do in Humans?

- T3 and T4 are responsible for neuronal and sexual development and growth
- T4 and T3 are also responsible for regulation of metabolic rate, the production of body heat and energy.
- When iodine intake is deficient, T3 and T4 are not produced in adequate quantities, but T3 production relatively increased. (Less iodine, more active)
- In an attempt to increase thyroid hormone production, the pituitary gland then releases more thyroid stimulating hormone (TSH) into the circulation.
- This causes the thyroid gland to increase in size and to increase its avidity for iodine.

What Happens Then?

- First, the thyroid gland increases in size, producing a goiter. (Latin word for throat, *guttur*, a diffuse enlargement of the thyroid gland in the neck.)
- Then, production of T3 and T4 hormones in the thyroid gland declines.
- If severe, this produces fatigue, slowing of intellect, intolerance to cold, generalized puffiness (*myxedema*), constipation, dry skin and depression. (*Hypothyroidism*)

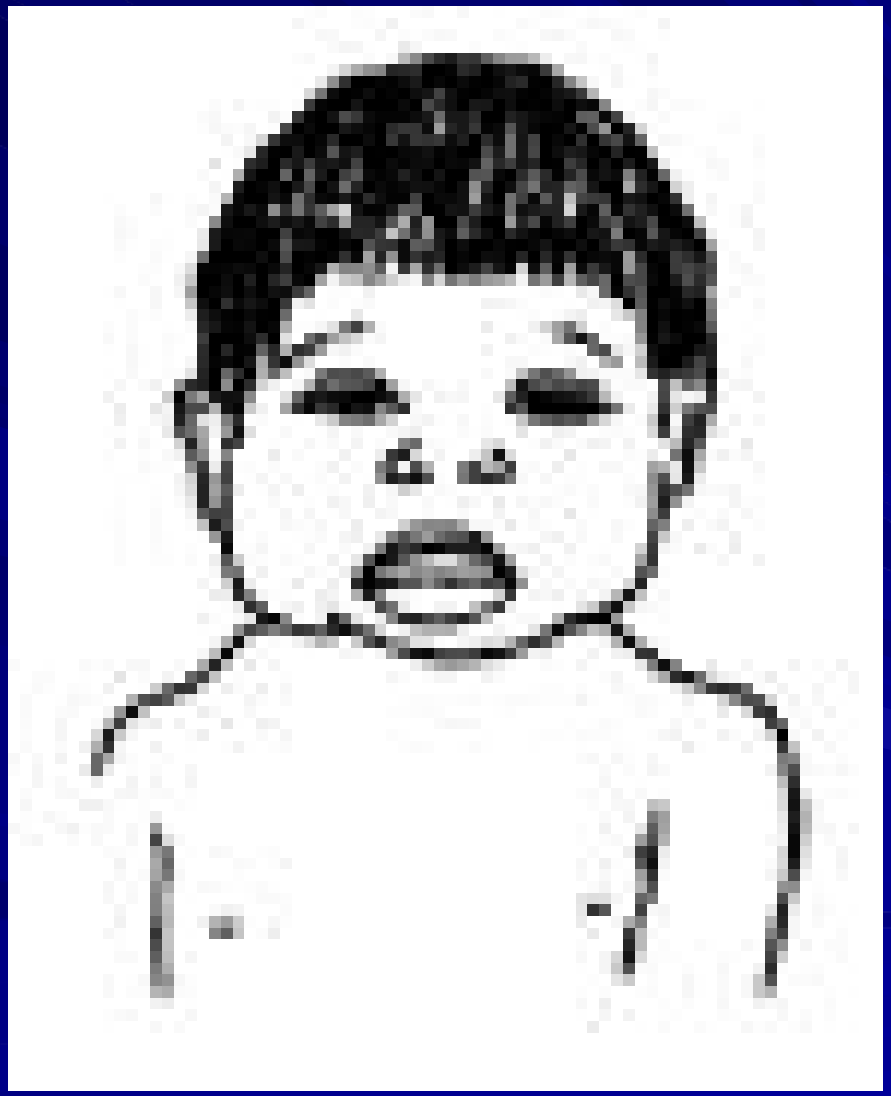
Consequences of Severe Iodine Deficiency

- Infants born to severely iodine deficient mothers may develop **cretinism**.

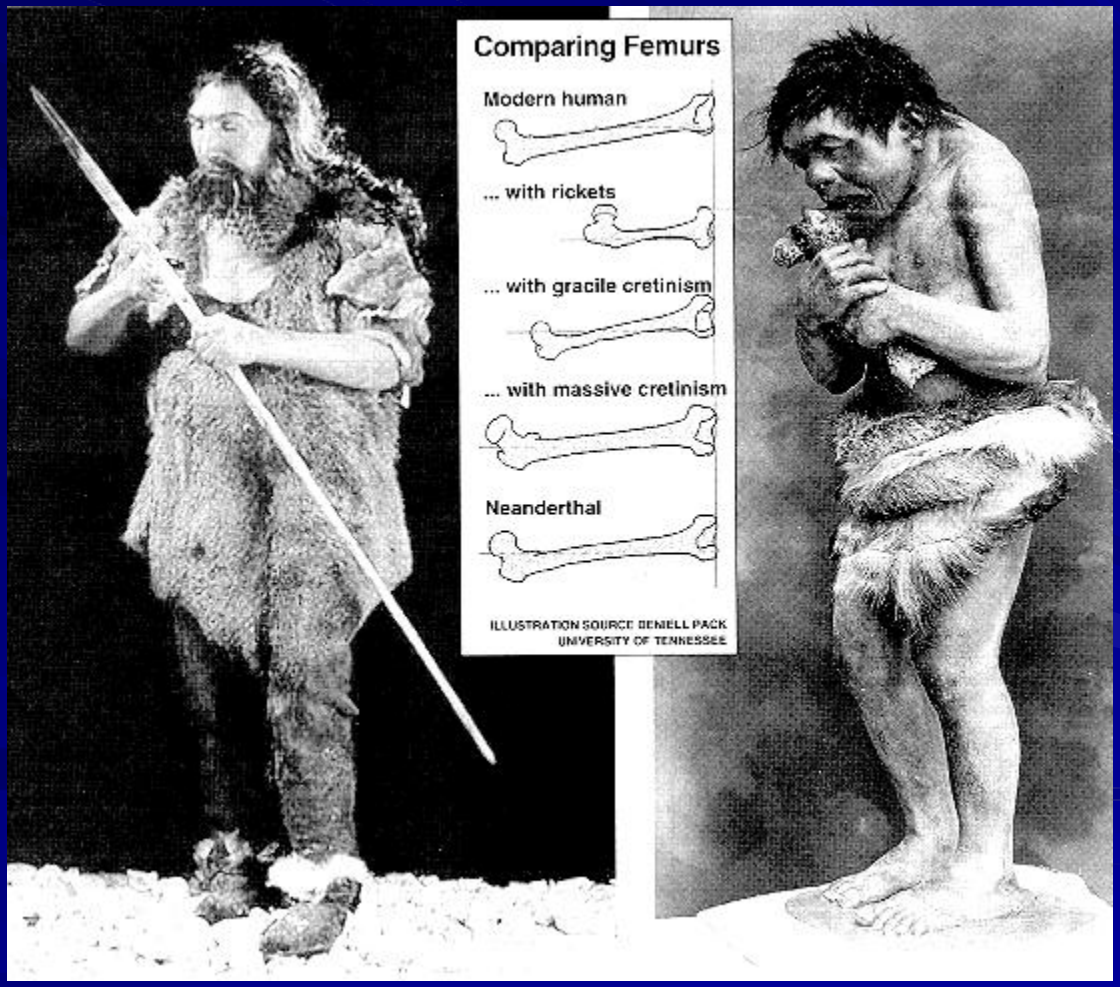
  ("*A mentally challenged person*." *French dialect.)*

  - Mental retardation
  - Abnormal gait
  - Deaf mutism
  - short stature
  - goiter and hypothyroidism

Infant with Cretinism



Were the Neanderthals Cretins?



What are the Historical Aspects of Iodine Deficiency?

Historical Aspects of Iodine Deficiency

- Ancient Chinese (1600 BC), Aurelius Celcus (25-50 BC), Pliny the Elder (23-79 AD) and Galen (129-200 AD) used burnt seaweed and sponges to treat goiters
- 1811-Bernard Courtois burned seaweed to make sodium carbonate and noted a purple vapor after adding too much sulfuric acid to the ashes
- 1814-Humphrey Davy named it *Iodine*, the Greek word for violet. It was another halogen.
- 1821-Jean Francois Coindet, in Switzerland, treated persons with goiters with iodine supplements (250 *milligrams*/day!) and it worked.
- 1821-Jean Baptiste Boussingault noted Columbian miners using iodine-rich salt were free of goiters, others not using this iodine rich salt had goiters.

Historical Aspects of Iodine Deficiency (cont.)

- This prompted widespread use of large doses of iodine to treat a ***whole variety*** of ailments.
- 1829-Jean Guillaume Auguste Lugol made up a solution of iodine and KI and used it to treat consumptives.#
- 1860s-French Academy declared that significant side effects occurred with use of large doses of iodine, *iodism*. (Law of unanticipated outcomes)
- 1872- Theodore Kocher* warned of the danger of making hyperthyroidism worse with iodine treatments. (Jod-Basedow phenomenon)
- That about ended the '*iodine therapy movement*' in Europe!

Lugol's iodine solution-130,000ucg/ml

* Nobel Prize winner in 1909 for Medicine or Physiology for work on the treatment of thyroid disorders. Student of Lister

What About Iodine Toxicity, '*Iodism*'?

- Usually occurs with large doses of iodine
- The symptoms and consequences are:
  - Soreness of the teeth and gums
  - Increased salivation
  - Coughing
  - Burning in the mouth and throat
  - Skin rash
  - Severe hyperthyroidism "**Jod-Basedow Phenomenon**".* ("The Law of Unexpected Consequences")
  - Jod-Basedow phenomenon is the induction of thyrotoxicosis in a previously normal individual as a result of exposure to large quantities of iodine.

*This is not a conjoint eponym, as there is no "Dr. Jod." Jod is the German word for iodine

20th Century Interest in Iodine Deficiency in the United States

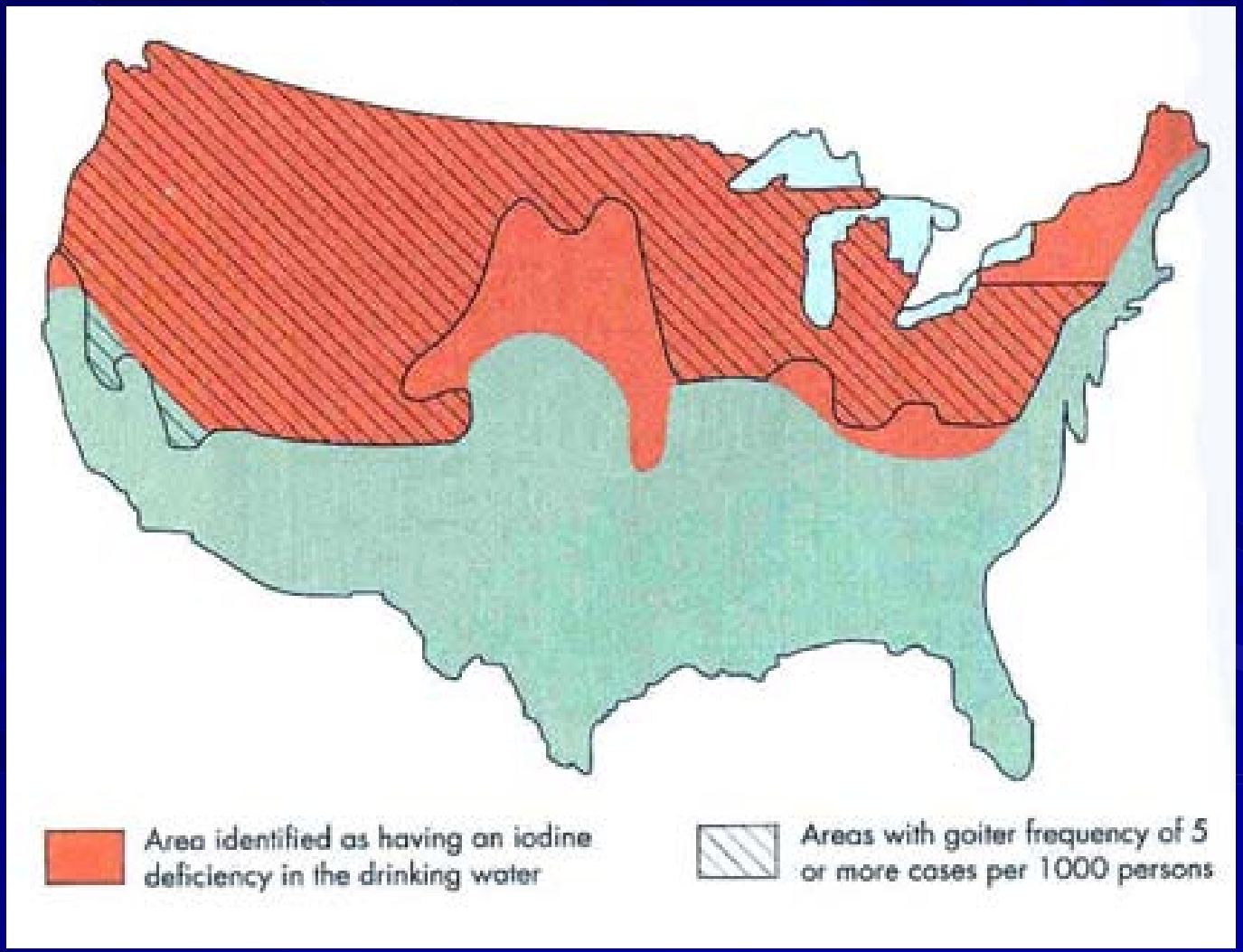
Medical Pioneers

In

The ‘Goiter Belt’

The Goiter Belt

Relation of Iodine Deficiency to goiter by region

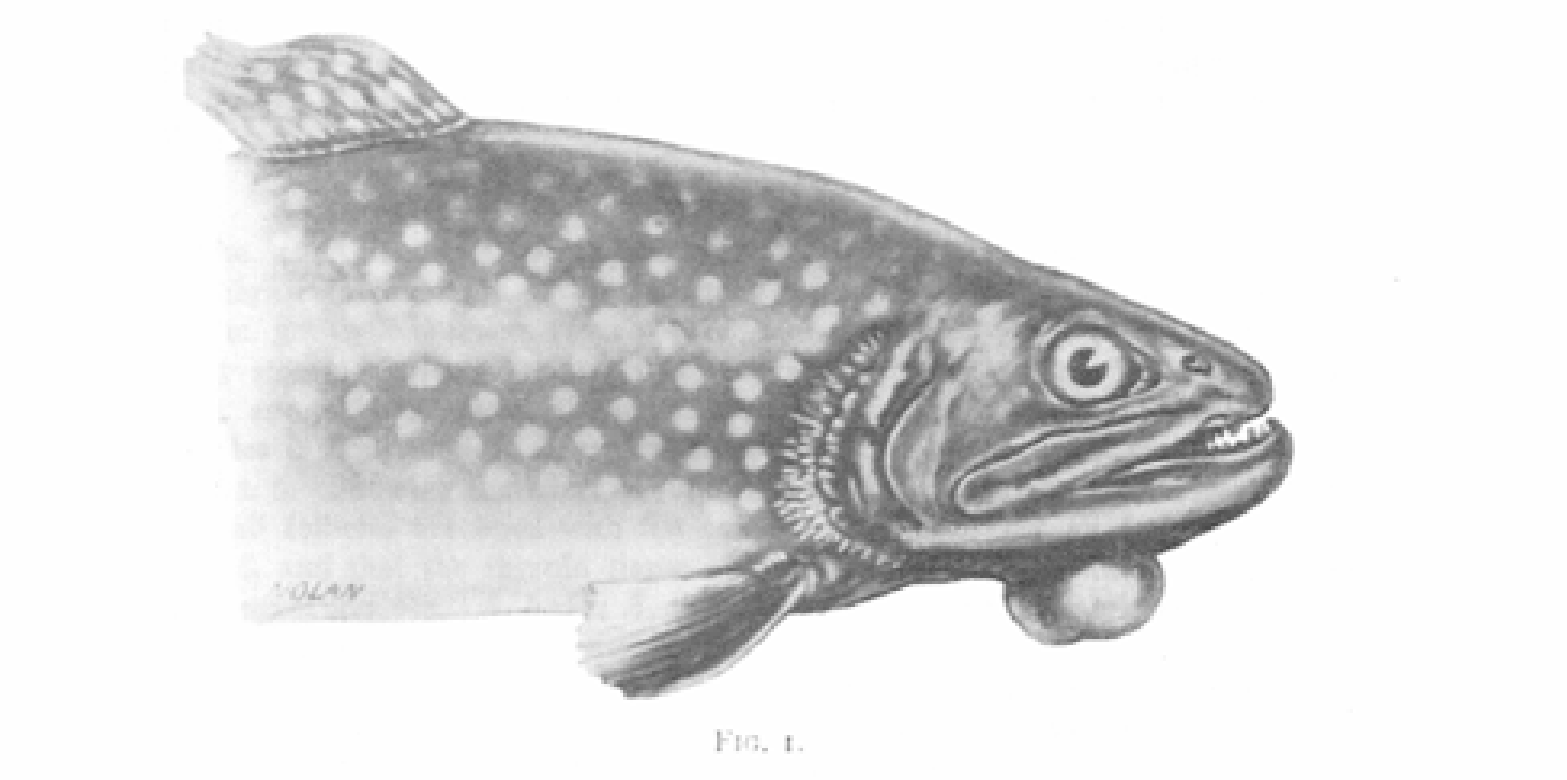


David Marine (1888-1976)

•David Marine (1888-1976)

- 1901 to1905-Johns Hopkins Medical School graduate
- 1905-Western Reserve University Residency
- 1906-Cleveland Clinic consultant
- 1909-1914-Goiters in iodine deficient trout, sheep and dogs
- Cured trout goiter by adding iodine to their water tanks

Trout with Iodine Deficiency Goiter



Marine and Kimball , J. Exp Med.1910; 12:311-337

David Marine (Cont.)

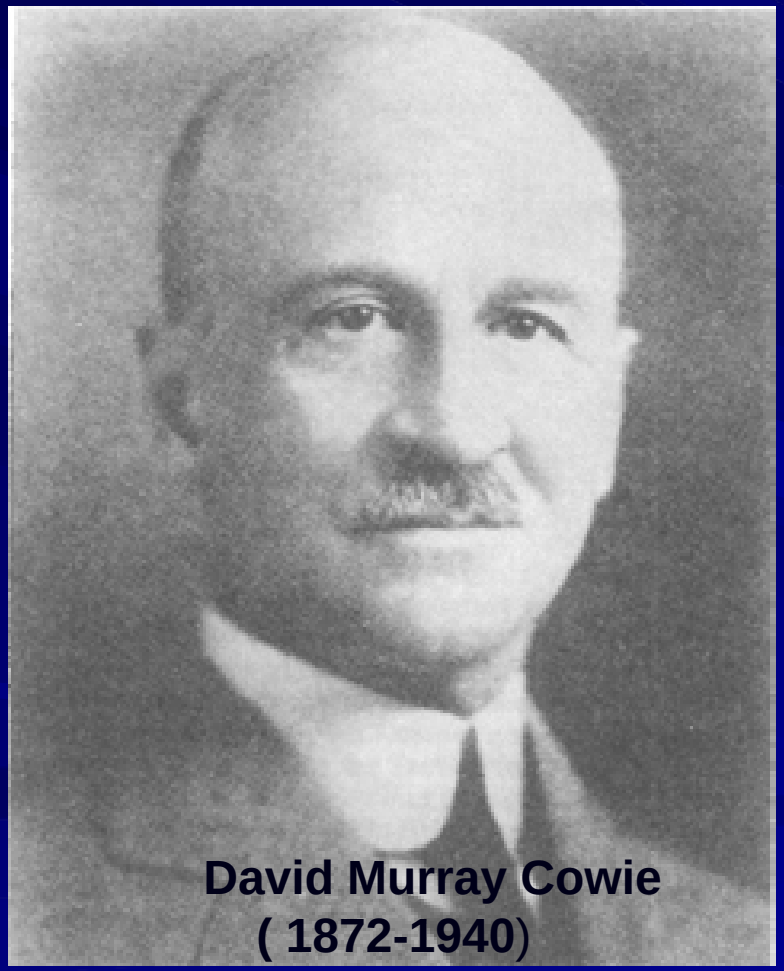
- 1917 to 1922-"The Akron Experiment."
  - Endemic goiters were prevalent in local school girls.
  - With the permission of the Akron, Ohio school Board, he recruited over 2000 teenage school girls for a trial of iodine supplementation as a preventive treatment for goiter.
    - 900 girls in the treated group received 200 mg. sodium iodide per day, by mouth, in water for ten days twice a year.
    - 1200 controls were those who declined iodine treatment
  - After 2 ½ years, known goiters improved in 56% of treated girls and in only 14% in the untreated group.
  - In the untreated group 14% had larger goiters and in only 0.2% in those treated with iodine supplement

George W. Goler (1864-1940)

- 1896-1932-Rochester, NY Public Health Officer
- He read about David Marine's 1922 "*Akron Experiment*" with iodine supplementation to prevent goiters
- 1923-Together with Mr. Beekman Little* they lowered a 16.6 pound bag of sodium iodide into the inflow of the Rochester, N.Y. water reservoir daily for three weeks, twice a year.
- The incidence of goiters decreased from 3,844 to 763 per year from 1923 to 1931 as reported in the Rochester school children
- However, there was a public outcry against "*Hemlock water" and* "*governmental control*." (Like the water fluoridation controversy)
- This plus budgetary problems ended the iodine-in-the-water-reservoir project in 1929

*Superintendant Rochester, N.Y. municipal waterworks, 1901-1926.

Iodized Salt and David Cowie 1872-1940



David Murray Cowie
(1872-1940)

- He was the first Professor of Pediatrics at U. of Michigan
- He was aware of the high incidence of goiters in the "goiter belt".
- He also knew about the *Akron Experiment* of David Marine and the *Rochester Experience* of George Goler with iodine supplementation

Iodized Salt and David Cowie (Cont.)

- 1922-He organized the Iodized Salt Committee of the Michigan State Medical society
- 1923-He promoted the "voluntary"* addition of iodine to table salt by Michigan salt manufacturers. (Morton Salt Company in Chicago resisted for awhile)
- 1924-Salt Producers Association recognized the promotional value of iodinating table salt as a "*public health issue*."
- May 1, 1924-Iodized salt first appeared on Michigan Grocers' shelves. (85 years ago today!)

* As opposed to a legislated mandate. Clyde Holmes, advising Attorney

Iodized Salt and David Cowie (Cont.)

- 1932- Eight years later, Iodized salt made up 90% of salt sales in Michigan
- 1925-A modest increase in hyperthyroidism noted, especially in those with "*toxic nodular goiters*". (*Jod-Basedow phenomenon.)*
- 1926-1932-Dramatic reduction in goiters in Detroit school children from 9.7 to 1.4%
- 1934-Another survey showed that the incidence of goiters was less than 2% in Michigan School children

Iodized Salt

- Technique of adding iodine to table salt.
  - Potassium iodate solution is sprayed on during production of edible salt (.01% KI).
  - Morton's Salt Company simply added potassium iodide to magnesium oxide, an agent that promoted less clumping of the salt. "*When it rains, it pours*."
  - The cost was estimated to be $1.15 per ton to iodize salt; 5 cents per person per year!
  - Estimated iodine content was 70 ucg. per gram of NaCl.

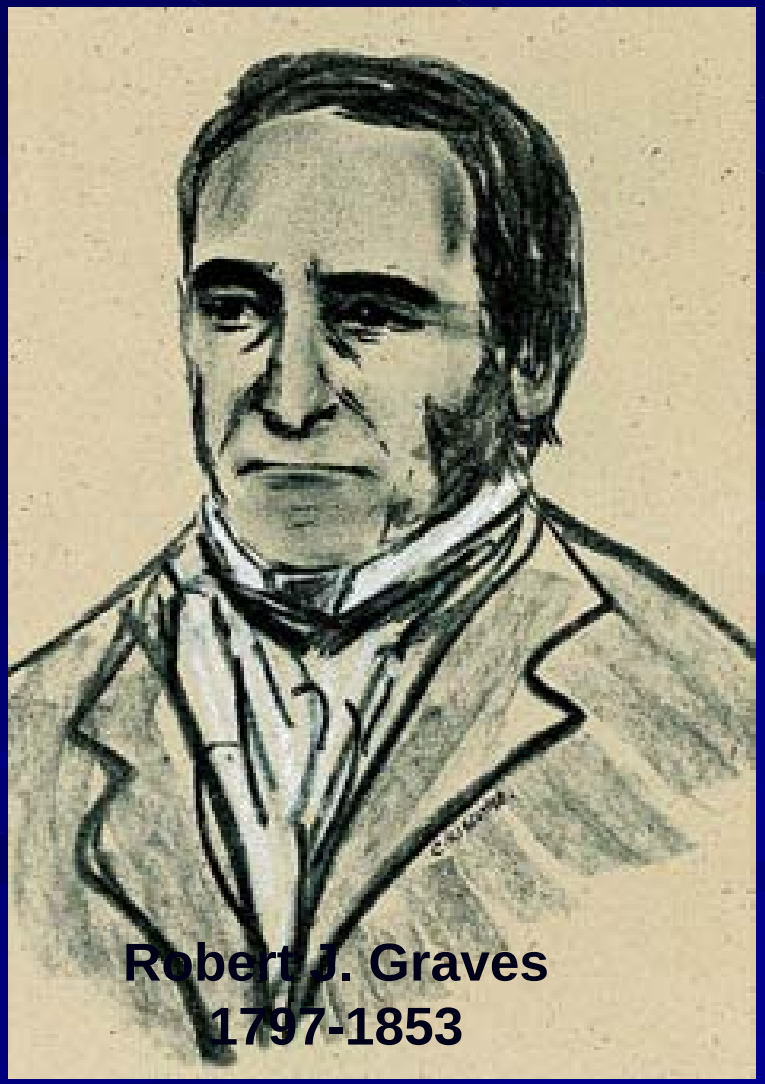
Henry Plummer and the Iodine treatment of Graves Disease*

*Hyperthyroidism with diffuse enlargement of the thyroid gland with exophthalmos

Diffuse Toxic Goiter

Grave's disease

Robert James Graves
1797-1853



- 1830- Robert J. Graves, in Dublin, described a condition with:*
  - diffuse enlargement of the thyroid gland
  - Weight loss
  - rapid heart beat
  - tremor
  - sweating
  - diarrhea.
  - protuberant eyes (Proptosis)

*Grave's Disease-1830, Basedow's Disease-1835

Proptosis in Grave's Disease

Grave's Disease

- It is the most common cause of hyperthyroidism. (?80 to 90%?)
- The cause is unknown, but is mediated by a "*thyroid stimulating immunoglobulin*", a thyroid stimulating hormone-like substance.
- When hyperthyroidism is extreme, it's called "thyroid storm."

Thyroid Storm and Iodine

- Thyroid storm consists of extremely rapid heart rate, high blood pressure, nausea, vomiting and coma
- In the past, when untreated, the mortality of thyroid storm was nearly 100%
- Until 1913, attempts to surgically remove the thyroid gland as a treatment for thyroid storm were more often fatal than not,
- In 1913 Dr. Henry Plummer at the Mayo clinic proposed a novel treatment for exophthalmic goiter with hyperthyroidism and storm.

Dr. Henry Stanley Plummer 1874-1936

Dr. Henry Stanley Plummer
1874-1936

-1901-He was the fourth physician recruited to the Mayo Clinic by W. J. Mayo.

-He had many interests, including thyroid diseases

-1907-He instituted a unified medical record and a patient numbering system at Mayo

-1929-He designed the Plummer Building in Rochester, Minnesota, a medical office structure with many innovations

Thyroid Storm, Plummer & Iodine

- 1913-Dr. Henry Plummer devised a program of the preoperative administration of Lugol's solution* to patients in thyroid storm.
- The symptoms of thyroid storm usually abated in 10-14 days after which surgical thyroidectomy was much safer.
- In February 1924 he published the results of 600 patients with Grave's disease treated with preoperative iodine.
- The death rate from this condition reduced from 15 per year to 4 per year at Mayo between 1918 and 1924!

* 5 grams iodine plus 10 grams potassium iodide in 85 mls of distilled water. Ten drops, two or three times a day by mouth or **by enema.**

The Value of Iodin in Exophthalmic Goiter

HENRY S. PLUMMER, M.D.
and
WALTER M. BOOTHBY, M.D.
Mayo Clinic, Rochester, Minnesota

Reprinted from
THE JOURNAL OF THE IOWA STATE MEDICAL SOCIETY
FEBRUARY, ISSUE, 1924

Surgical mortality Pre and Post iodine Treatment

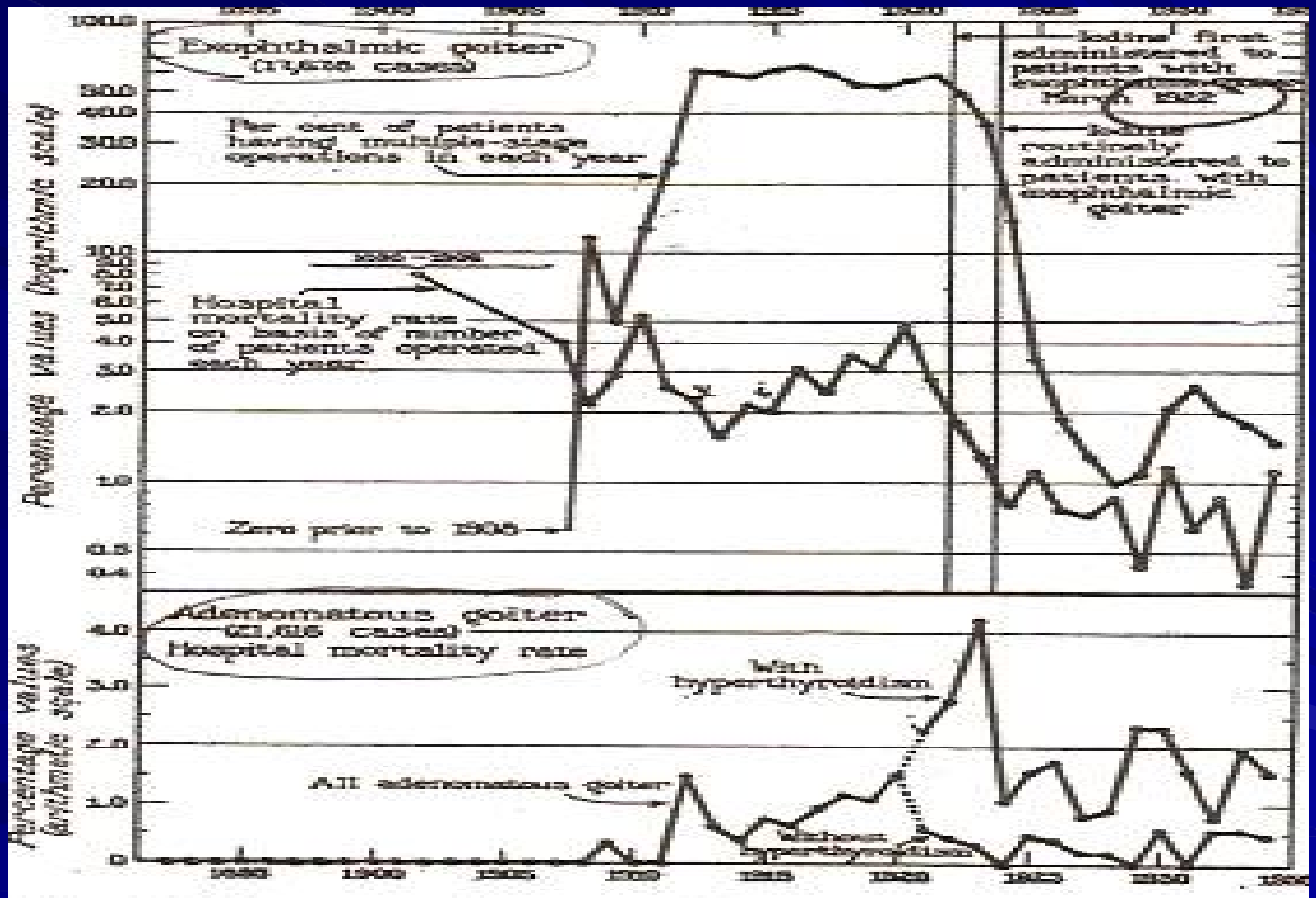


Fig. 1. Decrease in mortality with operation for goiter following introduction of the administration of iodine (C. H. Mayo and Pemberton.

Plummer’s Disease*

*Multiple Thyroid Nodules And Hyperthyroidism

Toxic Nodular Goiter

Plummer's disease

Toxic Nodular Goiter and Iodine

(Plummer's Disease)

- Plummer's Disease affects a *small number* of persons with hyperthyroidism.
- The thyroid gland contains one or more nodules of *hyperplastic* thyroid cells which seem to be "autonomously" producing excessive thyroid hormones
- Called "Plummer's Disease" in 1913
- The administration of exogenous iodine to some of these patients may "*paradoxicall*y" exacerbate the hyperthyroid symptoms. (Jod-Basedow phenomenon)
- He said that surgical removal of the thyroid, not iodine, seemed to be the best treatment

Worldwide Iodine Deficiency

A Major and Continuing
Health Problem

Worldwide Iodine Deficiency

- Endemic goiter secondary to iodine deficiency may now affect up to 13% of world's population, or 2.2 billion people
- Iodine deficiency is more common in Africa, the Middle East, South America and inland China.
- 30-70% of those with iodine deficiency have goiters, while1-10% of have cretinism

Worldwide Iodine Deficiency (cont.)

- In 1996, an estimated10 million persons in China suffered from some form of mental retardation because of iodine deficiency.
- Iodine replacement therapy is regarded as the single cheapest and most effective preventive treatment for correctable mental retardation worldwide.
- Since the late 1990s all table salt sold in China is iodized, but black market salt is cheaper.
- Guess what?

Australian Division of the World Action on Salt and Health

- AWASH: June 2007 recommendations
  - Salt reduction is a public health priority
  - Iodized table salt is not the best route for iodine supplementation (excess sodium)
  - Increasing iodine content in table salt is not a good response to reduced salt intake
  - Iodized salt in bread may not provide adequate iodine intake at present levels
  - Monitor iodine intake and look for better routes for iodine supplementation, i.e. iodized bread flour

Current Iodine intake in US

- The measurement of the urinary iodine concentration is the easiest way to estimate iodine intake. Normal concentration is between 150 and 300 micrograms per liter.
- In the US, iodine intake, estimated by urinary iodine concentration fell from 320 to 145 micrograms per day between 1970s and the 2002*
- The reasons for this:
  - Public information campaigns have recommended reducing salt and egg yolk consumption for blood pressure and cholesterol control
  - There is an increasing use of non-iodized salt in convenience foods
  - Bakeries are removing of iodate “stabilizers” in store-bought breads and substituting bromine.

* National Health and Nutrition Examination Survey 2001-2002 (NHANES)

Estimating iodine intake by Urinary Iodine Concentration

Table 2. Median Population Urinary Iodine Values and Iodine Nutrition

MEDIAN URINARY IODINE CONCENTRATION (µg/L)	CORRESPONDING IODINE INTAKE (µg/day)	IODINE NUTRITION
<20	<30	Severe deficiency
20-49	30-74	Moderate deficiency
50-99	175-149	Mild deficiency
100-199	150-299	Optimal
200-299	300-449	More than adequate
>299	>449	Possible excess

American Thyroid Association brochure 2008

Consequences of Iodine Deficiency

- In US, iodine deficiency increased in women of child bearing age from 4% in 1970s to 15% in 1990s.
- Infants borne to them are at risk for ‘cretinism’
- This could also play a role in an increased risk for thyroid cancers
- Are replacement strategies failing?

Radioactive Iodine (I-131) Exposure

I-131 is produced in large amounts with nuclear blasts

Radioisotopes of Iodine and the Atomic Bomb

Thyroid Cancer and I-131 Exposure

- 1951 to 1962-There were 90 above ground A-bomb tests in the Western US *.
- They produced large amounts of radioactive iodine (I-131)
- They caused radioactive iodine exposure of 95 million persons below 20 years of age during that era in the western United States
- Consumption of dairy products produced in those areas was a major source of I-131 ingestion
- 1986 The Chernobyl accident was followed by a dramatic increase in thyroid cancer in Belarus and Ukraine
- Oral iodine pills taken at the time of acute exposure can block thyroid uptake of radioactive iodine isotopes and may minimize thyroid cancer risk in exposed children. They did this in Poland after Chernobyl.

* National Cancer Institute release1997

Iodine in Health and Disease

Conclusions

- Iodine is an important element in human health and disease
- The thyroid gland is the sole utilizer of elemental iodine in humans and most animals
- Over the centuries recognition of the consequences of iodine deficiency has waxed and waned
- Dietary intake of iodine is inadequate in large parts of the world today

- In the 1920s **David Marine**, **David Cowie** and **George Goler** provided the impetus to correct iodine deficiency in segments of the US population
- Iodizing table salt then was an excellent way to correct iodine deficient diets with few side effects
- Current campaigns to reduce dietary salt use may be limiting this route of iodine supplementation

- in the 1920s Henry Plummer devised a life-saving preoperative treatment for *thyroid storm* with large dose iodine supplementation.
- Iodine deficiency remains the leading preventable cause of mental retardation worldwide *
- We may need devise another way to provide adequate iodine in the diet.

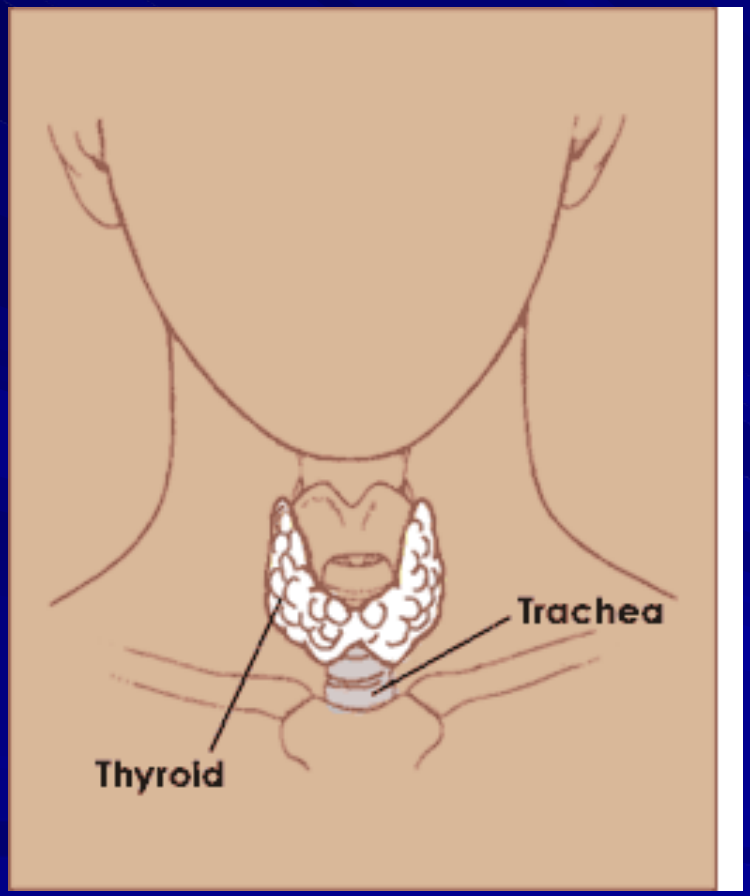
New York Times Dec. 16, 2006 & December 4, 2008

Conclusions

- Multivitamin preparations are often lacking in iodine content, even in prescription prenatal vitamins.*
- Topical iodine was removed from stores by the DEA in August 2007. (It was being used to make methamphetamines in illegal laboratories.)

Wal-Mart Prenatal vitamin preparation has 0 ucg. of iodine!

Thank You for Your Attention



The End