Chapter 10

Thyroid Hormones

Nam Deuk Kim, Ph.D.
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2700 BC</td>
<td>Emperor Shen Nung’s prescriptions (first published in Pen Tsao, the herbal of the Chinese pharmacopoeia, 1596) mentions the use of seaweed for the treatment of goiter</td>
</tr>
<tr>
<td>300 BC</td>
<td>Ayur Veda, Hindu holy text, discusses goiter.</td>
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<tr>
<td>40 BC</td>
<td>Pliny, Vitruvius, and Juvenal describe prevalence of goiter in the Alps and use of burnt seaweed for treatment.</td>
</tr>
<tr>
<td>138 AD</td>
<td>Greek physician, Soranus, mentions neck swelling following pregnancy</td>
</tr>
<tr>
<td>340</td>
<td>Ko-Hung, Chinese alchemist, recommends seaweed for treatment of goiter among people living in mountains</td>
</tr>
<tr>
<td>650</td>
<td>Sun Ssu-Mo, a Chinese physician, uses dried, powdered mollusc shells and chopped thyroid gland for the treatment of goiter</td>
</tr>
<tr>
<td>961</td>
<td>Abul Kasim, personal physician to Caliph El-Hakin III of Codoba, is first to describe thyroidectomy for goiter and to perform a needle biopsy of the thyroid.</td>
</tr>
<tr>
<td>1170</td>
<td>Roger of Salerno uses seaweed in the treatment of goiter</td>
</tr>
<tr>
<td>1200</td>
<td>Arnaldus de Villanova reports that marine sponges could be used to treat goiters of recent origin in the young</td>
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<tr>
<td>1475</td>
<td>Chinese physician, <strong>Wang Hei</strong>, recommends treatment of goiter with minced thyroid.</td>
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<tr>
<td>1500</td>
<td><strong>Leonardo da Vinci</strong> is first person to recognize and draw the thyroid gland</td>
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<tr>
<td>1543</td>
<td><strong>Andreas Vesalius</strong> provides first anatomic description and illustration of the thyroid gland</td>
</tr>
<tr>
<td>1563</td>
<td><strong>Eustachius</strong> introduces the term “isthmus” to describe tissue connecting the two lobes of the thyroid</td>
</tr>
<tr>
<td>1602</td>
<td>Felix Platter gives first description of cretins (see 1754) found in Valais region of Switzerland.</td>
</tr>
<tr>
<td>1656</td>
<td><strong>Thomas Wharton</strong> names gland “thyroid” after the shape of an ancient Greecian shield</td>
</tr>
<tr>
<td>1669</td>
<td>Albrecht van Haller describes constipation as a complication of cretinism</td>
</tr>
<tr>
<td>1754</td>
<td><strong>First use of the term “cretin” in the medical literature.</strong> The term is derived from the Latin “christianus” as affected individuals are incapable of committing a sin</td>
</tr>
<tr>
<td>1789</td>
<td>F.E. Fodere suggests an association between goiter and cretinism</td>
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<td>Year</td>
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<tr>
<td>1802</td>
<td>Giuseppe Flajani, personal physician to Pope Pius VII (1800-1823), described association of palpitations, goiter, and bulging of the eyes. This triad was known as Morbus Flajani.</td>
</tr>
<tr>
<td>1811</td>
<td>Bernard Courtois discovers iodine by oxidizing burnt seaweed (i.e. kelp 다시마류) with sulfuric acid</td>
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<tr>
<td>1813</td>
<td>Gay-Lussac names the vapor discovered by Courtois iodine, from the Greek word for violet</td>
</tr>
<tr>
<td>1818</td>
<td>Goiter reported in British Columbia</td>
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<tr>
<td>1820</td>
<td>Jean Francois Coindet concludes that iodine deficiency causes goiter and begins treatment of goiter with iodine.</td>
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<tr>
<td>1824</td>
<td>Alexander von Humboldt reports endemic goiter in Andes. He observes that goiter size decreases by 1/3 when an individual moves to an area where goiter is not endemic</td>
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<tr>
<td>1825</td>
<td>C. Parry describes exophthalmic goiter</td>
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<tr>
<td>1825</td>
<td>Boussonault detects iodine in the natural salt from mines in the northern Andes. Working in Bogota, he then recommends iodinated salt to prevent and treat endemic goiter</td>
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<tr>
<td>1829</td>
<td>LGA Lugol recommends use of aqueous solution of iodine made from KI for treatment of scrofula (a neck mass from a goiter and cervical adenopathy due to tuberculosis and lymphoma were considered identical processes)</td>
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<tr>
<td>1831</td>
<td>Francisco Freire-Allemao, a Brazilian physician, proposes iodine prophylaxis as a government-administered public health program, for goiter prevention.</td>
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<td>1834</td>
<td>Robert Graves describes a syndrome of palpitations, goiter, and exophthalmos in three women.</td>
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<tr>
<td>1848</td>
<td>C. von Basedow describes exophthalmic goiter</td>
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<tr>
<td>1849</td>
<td>J.L. Prevost adds iodine to food and water to prevent goiter</td>
</tr>
<tr>
<td>1850</td>
<td>T.B. Curling describes cretinism with athyreosis</td>
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<tr>
<td></td>
<td>A. Chatin detects iodine in freshwater plants and recommends these as prophylaxis for endemic goiter based upon his theory that goiter is due to low little iodine in drinking water</td>
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<tr>
<td>1851</td>
<td>T.B. Curling describes cretinism with athyreosis</td>
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<tr>
<td>1857</td>
<td>B. Niepce describes enlargement of sella turcica in cretins with hypothyroidism in Switzerland</td>
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<tr>
<td>1857</td>
<td>Maurice Schiff successfully performs total thyroidectomies in animals</td>
</tr>
<tr>
<td>1860</td>
<td>R. Virchow suggests that cretinism and goiter are related</td>
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<tr>
<td>1862</td>
<td>A. Trousseau introduces the term “Graves disease”</td>
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<tr>
<td>1864</td>
<td>Baillarger reports occurrence of goiter in animals where goiter and cretinism are widespread</td>
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<tr>
<td>1867</td>
<td>A. von Graefe describes lid lag in thyrotoxicosis (Basedow’s disease)</td>
</tr>
<tr>
<td>1873</td>
<td>Th. Billroth describes tetany following total thyroidectomy</td>
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<tr>
<td>1877</td>
<td>William Gull publishes “On a Cretinoid State Supervening in Adult Life in Women”</td>
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<tr>
<td>1882</td>
<td>William Ord coins term myxedema to describe middle aged women with cretinoid features</td>
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<tr>
<td>1883</td>
<td>J.L. Reverdin describes cretinism following thyroidectomy.</td>
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<tr>
<td>1883</td>
<td>Heinrich Bircher recognizes association of endemic goiter with geologic features characteristic of Quarternary glaciation</td>
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<tr>
<td>1883</td>
<td>E.T. Kocher calls attention to myxedema following thyroidectomy. He was awarded the Nobel Prize in 1909 for his work on the thyroid gland.</td>
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<tr>
<td>1886</td>
<td>Pierre Marie describes the characteristic tremor of hyperthyroidism</td>
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<tr>
<td>1888</td>
<td>Rogowitsch observes pituitary hyperplasia in rabbits following thyroidectomy</td>
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<tr>
<td>1891</td>
<td>F.D. von Recklinghausen reports on the occurrence of osteoporosis in hyperthyroidism</td>
</tr>
<tr>
<td>1891</td>
<td>Victor Horsley, using monkeys, shows that myxedema, cretinism, and post-thyroidectomy cachexia are all due to a deficiency of thyroid function.</td>
</tr>
<tr>
<td>1891</td>
<td>G.R. Murray introduces the use the thyroid extract to treat myxedema</td>
</tr>
<tr>
<td>1891</td>
<td>F.D. von Recklinghausen reports on the occurrence of osteoporosis in hyperthyroidism</td>
</tr>
<tr>
<td>1895</td>
<td>Aldolf Magnus Levy describes the influence of the thyroid on the basal metabolic rate</td>
</tr>
</tbody>
</table>
| 1896 | Eugen Baumann discovers iodine as a natural constituent of the thyroid and names it “iodothyrin”.
<p>| 1896 | B. Riedel publishes first description of chronic, fibrous thyroiditis. |
| 1897 | Pendred describes association of goiter with deaf-mutism. |
| 1898 | W. Osler publishes case reports of sporadic cretinism, some of whom had a family history of goiter. |
| 1898 | von Notthalt describes thyrotoxicosis factitia and suggests that excess thyroid hormone produces Graves disease. |</p>
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<td>1902</td>
<td>F. de Quervain describes subacute granulomatous thyroiditis</td>
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<tr>
<td>1905</td>
<td>Robert Abbe treats Graves disease by implanting radium into the patient’s goiter</td>
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<tr>
<td>1907</td>
<td>H.L. Wheeler and G.S. Jamieson show that gorgonia, from coral, is diiodotyrosine.</td>
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<tr>
<td>1907</td>
<td>David Marine publishes that iodine is necessary for thyroid function.</td>
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<tr>
<td>1907</td>
<td>David Marine recommends treating Graves disease with iodine</td>
</tr>
<tr>
<td>1910</td>
<td>Charles H. Mayo introduces term “hyperthyroidism” to describe the clinical conditions of primary exophthalmic goiter, toxic adenoma, and adenomatous goiter with hyperthyroidism.</td>
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<tr>
<td>1911</td>
<td>D. Marine and C.H. Lenhart describe hyperthyroidism due to Graves disease and concomitant functioning thyroid</td>
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<tr>
<td>1911</td>
<td>Henry Plummer from the Mayo Clinic distinguishes exophthalmic goiter from adenomatous goiter</td>
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<tr>
<td>1912</td>
<td>Kocher coins term Jod Basedow for iodine over-dosage.</td>
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<tr>
<td>1912</td>
<td>J.F. Gudernatsch observes that thyroid extract has a specific effect on accelerating the differentiation (metamorphosis) in amphibian larva.</td>
</tr>
<tr>
<td>1912</td>
<td>A. Seidell and F. Fenger describe the seasonal variation in thyroid iodine content.</td>
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<tr>
<td>1913</td>
<td>Massachusetts General Hospital establishes Thyroid Unit under the direction of J.H. Means.</td>
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<tr>
<td>1914</td>
<td>H. Hashimoto publishes 4 cases of a thyroid disorder characterized by a diffuse lymphocytic infiltration and fibrosis of the gland.</td>
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<td>1915</td>
<td>E.A. Kendall isolates thyroxine, a name he creates from a contraction of the term “thyroxindole”.</td>
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<tr>
<td>1916</td>
<td>Phillip E. Smith and Bennet M. Allen independently report that Hypophysectomized tadpoles show thyroid involution and do not undergo metamorphosis.</td>
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<tr>
<td></td>
<td>H. Hunziker proposes that endemic goiter is due to regional iodine deficiency, which in turn was the result of abundant precipitation in the mountains and alluvial loss of soluble iodine salts.</td>
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<td>1917</td>
<td>M. Seymour in Boston reports on the use of x-rays to treat Graves disease.</td>
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<td></td>
<td>Thyroxine introduced into commercial distribution in the United States for $350 per gram.</td>
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<tr>
<td>1920</td>
<td>Marine and Kimball successfully use iodine prophylaxis to prevent ovine and porcine athyreosis and trout goiter.</td>
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<tr>
<td>1923</td>
<td>P.E. Smith and I.P. Smith show that bovine pituitary extracts could stimulate the thyroid of a hypopituitary tadpole.</td>
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<tr>
<td>1924</td>
<td>H.S. Plummer at the Mayo Clinic report on the pre-operative use of iodine for the treatment of Graves disease.</td>
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<tr>
<td>1924</td>
<td>George Hevesy introduces concept of radioactive tracers for the study of metabolic pathways. He receives Nobel Prize for this work in 1943.</td>
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<tr>
<td>1926</td>
<td>McClendon reports that the iodine concentration in rainwater and in drinking water decreases as one travels from the Atlantic coast to the Great Lakes.</td>
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<tr>
<td>1927</td>
<td>Harington determines chemical structure of thyroxine.</td>
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<td>Year</td>
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<tr>
<td>1928</td>
<td>Harington and Barger synthesize thyroxine.</td>
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<tr>
<td>1930</td>
<td>A. Chesney, T. Clawson, and B. Webster show that vegetables can cause goiter by showing that rabbits fed cabbage develop enlarged thyroids.</td>
</tr>
<tr>
<td>1931</td>
<td>L. Loeb and R. Bassett extract and purify TSH from bovine pituitaries.</td>
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<tr>
<td>1932</td>
<td>Naffziger introduces orbital decompression for the treatment of exophthalmos.</td>
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<tr>
<td>1934</td>
<td>New Jones Motor Basal</td>
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<tr>
<td>1935</td>
<td>Roy O. Greep demonstrates that pituitary TSH differs from LH and FSH.</td>
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<tr>
<td>1936</td>
<td>Dr. Saul Hertz first proposes the use of radioactive iodine for the study of the thyroid.</td>
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<tr>
<td>1936</td>
<td>Marine describes cyanide goiter.</td>
</tr>
<tr>
<td>1936</td>
<td>Barker identifies goiter as a complication of thiocyanate treatment of hypertension.</td>
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<tr>
<td>1937-1943</td>
<td>Saul Hertz, working in the Massachusetts General Hospital’s Thyroid Unit under the direction of James Means, and Arthur Roberts, a physicist working in the laboratory of Robley Evans at MIT, are the first to use radioactive iodine to study thyroid physiology and treat hyperthyroidism.</td>
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<tr>
<td>1943</td>
<td>Kennedy observes that thiourea is goitrogenic</td>
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<tr>
<td>1946</td>
<td>A. Astwood used thiourea and thiouracil for the medical treatment of Graves disease.</td>
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<tr>
<td>1947</td>
<td>Cope, Rawson, and McArthur report first use of radioactive iodine to demonstrate a “hot” thyroid nodule</td>
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<tr>
<td>1948</td>
<td>H. Pemberton sends letter to The Lancet describing his eponymous sign for a substernal goiter.</td>
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<tr>
<td>1948</td>
<td>T. Tempka, J. Aleksandrowicz, M. Till publish the use of fine needle thyroid biopsy as a diagnostic method.</td>
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<tr>
<td>1949</td>
<td>R.G. Hoskins describes negative feedback of thyroid on pituitary, a mechanism which he termed “servo (feedback) mechanism”.</td>
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<tr>
<td>1949</td>
<td>J. Wolff and I. Chaikoff describe the regulatory effects of inorganic iodine on the thyroid.</td>
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<tr>
<td>1949</td>
<td>Jones, Kornfeld, McLaughlin and Anderson synthesize methimazole.</td>
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<tr>
<td>1949</td>
<td>J.B. Stanbury describes first case of a genetic abnormality of thyroid hormone synthesis.</td>
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<tr>
<td>1950</td>
<td>B. Duffy and P. Fitzgerald call attention to thyroid cancer in children following head and neck irradiation.</td>
</tr>
<tr>
<td>1951</td>
<td>J. Wolff and I. Chaikoff describe the regulatory effects of inorganic iodine on the thyroid.</td>
</tr>
<tr>
<td>1952</td>
<td>Lawson, Rimington, and Searle synthesize carbimazole.</td>
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<tr>
<td>1954</td>
<td>J.B. Stanbury, J.B. Wyngaarden, and A. Godley describe use of perchlorate in treatment of hyperthyroidism.</td>
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<td>1954</td>
<td>J.B. Stanbury provides definitive proof of Jod Basedown in course of treating endemic goiter in Menduza, Argentena.</td>
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<tr>
<td>1956</td>
<td>Goldschmidt, a Norweigen geochemist, identifies Quarternary glaciation as cause of iodine deficiency in soil.</td>
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<tr>
<td>1956</td>
<td>Roitt and Doniach demonstrate autoantibodies in Hashimoto’s disease.</td>
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<tr>
<td>1959</td>
<td>J.B. Hazard, W.A. Hawk, and G. Crile identify medullary thyroid cancer as a distinct entity.</td>
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<tr>
<td>1962</td>
<td>Robert Pendleton, a radiation ecologist at the University of Utah, provides first documentation of I-131 release from atmospheric nuclear testing.</td>
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<tr>
<td>1963</td>
<td>D.H. Copp, A.G.F. Davidson, and B. A. Cheney provide first description of calcitonin. Lewis Braverman MD, receives the 1963 Van Meter Award from Theodore Winship MD. Seated is Virginia Kneeland-Frantz MD</td>
</tr>
<tr>
<td>1965</td>
<td>E.D. Williams reports 17 cases of cancer of the thyroid and pheochromocytoma.</td>
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<tr>
<td>1966</td>
<td>R.F. Rohner, J.T. Prior, and J.H. Sipple describe the first cases of multiple endocrine neoplasia type 2.</td>
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<tr>
<td>1969</td>
<td>Neonatal screening for congenital metabolic disease introduced in Switzerland.</td>
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<tr>
<td>1970</td>
<td>A. Schally identifies TRH and receives Noble Prize for this work in 1977.</td>
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<tr>
<td>1972</td>
<td>S. Berens, J. Wolff, D. Murphy show that the thyroid concentrates lithium.</td>
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<tr>
<td>1974</td>
<td>S. Refetoff and L. DeGroot identify thyroid hormone resistance.</td>
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<tr>
<td>1977</td>
<td>J Ginsberg and PG Walfish recognize the classical thyrotoxic phase preceding the hypothyroid phase of postpartum thyroiditis.</td>
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<tr>
<td>1979</td>
<td>T.H. Liao and J. Pierce obtain first ultrapure TSH preparation and then demonstrate that TSH shares a common alpha subunit with LH and FSH.</td>
</tr>
<tr>
<td>1998</td>
<td>Recombinant human TSH approved for clinical use in the United States</td>
</tr>
<tr>
<td>2002</td>
<td>Thomas Scanlan discovers 3-iodo-thyronine (T1 amine).</td>
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</tbody>
</table>
1. The Thyroid Gland

• Consists of two lobes of endocrine tissue joined in middle by narrow portion of gland

• Follicular cells
  – Arranged into hollow spheres
  – Forms functional unit called a follicle
  – Lumen filled with colloid
    • Serves as extracellular storage site for thyroid hormone
  – Produce two iodine-containing hormones derived from amino acid tyrosine
    • Tetraiodothyronine (T\textsubscript{4} or thyroxine)
    • Tri-iodothyronine (T\textsubscript{3})

• C cells
  – Secrete peptide hormone calcitonin
Fig. 13-1. Structures of thyroxine \( (T_4) \) and triiodothyronine \( (T_3) \).
2. Synthesis and Chemistry

• Synthesis, storage, and secretion of thyroid hormone
  – Basic ingredients
    • Tyrosine
      – Synthesized in sufficient amounts by body
    • Iodine
      – Obtained from dietary intake
  – Synthesis
    • All steps occur on thyroglobulin molecules within colloid
    • Tyrosine-containing thyroglobulin is exported from follicular cells into colloid by exocytosis
    • Thyroid captures iodine from blood and transfers it into colloid by iodine pump
    • Within colloid, iodine attaches to tyrosine
    • Coupling process occurs between iodinated tyrosine molecules to form thyroid hormones
Tyrosine-containing Tg produced within the thyroid follicular cells is transported into the colloid by exocytosis.

Iodine is actively transported from the blood into the colloid by the follicular cells.

Attachment of one iodine to tyrosine within the Tg molecule yields MIT.

Attachment of two iodines to tyrosine yields DIT.

Coupling of one MIT and one DIT yields T₃.

Coupling of two DITs yields T₄.

On appropriate stimulation, the thyroid follicular cells engulf a portion of Tg-containing colloid by phagocytosis.

Lysosomes attack the engulfed vesicle and split the iodinated products from Tg.

T₃ and T₄ diffuse into the blood.

MIT and DIT are deiodinated, and the freed iodine is recycled for synthesizing more hormone.

Tg = Thyroglobulin
I = Iodine
MIT = Monoiodotyrosine
DIT = Di-iodotyrosine
T₃ = Tri-iodothyronine
T₄ = Tetraiodothyronine (thyroxine)

* Organelles not drawn to scale. Endoplasmic reticulum/Golgi complex are proportionally too small.
Fig. 13-4. Summary scheme of thyroid hormone biosynthesis and secretion. The actual oxidative coupling of iodinated tyrosine residues probably takes place at the apical surface of the follicular cell, rather than in the lumen.
Fig. 13-5. Hypothetical coupling scheme for iodothyronine formation.
- **Antithyroid drugs** can suppress thyroid hormone synthesis
  - Inhibit iodide transport (iodide trapping) into the thyroid gland and those that inhibit iodine incorporation into tyrosine.
  - Univalent inhibitors of iodide transport: thiocyanate and other monovalent anions (perchlorate, chlorate, periodate, etc.)
  - Iodide uptake inhibitors: antagonize iodide transport through competitive inhibition.
  - Other antithyroid compounds: thionamides, the sulfonamides (e.g., para-aminobenzoic acid), and the sulfonylureas (carbutamide, tolbutamide)

Fig. 13-6. Structures of some thionamide type antithyroid drugs.
• **Goitrogen**: substances that suppress the function of the thyroid gland by interfering with iodine uptake, which can, as a result, cause an enlargement of the thyroid, i.e., a goiter.

• **Goitrin**: a sulfur-containing oxazolidine, a cyclic thiocarbamate, that reduces the production of thyroid hormones such as thyroxine.

- found in cruciferous vegetables (십자화과 식물) such as **cabbage, brussels sprouts and oil-seed rape**, and is formed by the hydrolysis of a glucosinolate; 2-hydroxy-3-butenyl glucosinolate. The unstable isothiocyanate (2-hydroxy-3-butenyl isothiocyanate) derived from the latter glucosinolate spontaneously cyclizes to goitrin, because the hydroxy group is situated in proximity to the isothiocyanate group (allowing a five-membered ring to be formed).

![Chemical structure of goitrin](image)

**Fig. 13-7. Synthesis and structure of goitrin.**
Cruciferous (십자화과) vegetables

- Broccoli
- Brussels sprouts
- Cauliflower
- Watercress
- Turnips
- Mustard greens
- Kale
- Rutabaga
- Collard greens
- Kohlrabi (Nolkohl)
- Arugula
- White Radishes
3. Thyroid Hormone or Thyroid Hormone?

- **Storage**
  - Thyroid hormones remain in colloid until they are split off and secreted
  - Usually enough thyroid hormone stored to supply body’s needs for several months

- **Secretion**
  - Follicular cells phagocytize thyroglobulin-laden colloid
  - Process frees $T_3$ and $T_4$ to diffuse across plasma membrane and into blood
  - Regulated by negative-feedback system between hypothalamic TRH, anterior pituitary TSH, and thyroid gland $T_3$ and $T_4$
  - Feedback loop maintains thyroid hormones relatively constant
• Serum con. of **T4** is about 50x greater than the **T3** level.
• Conversion of **T4** → **T3**
• Activities: **T3** >>> **T4**

Chemistry and interconversions of the thyroid hormones
• Other iodothyronines in biological fluids (Fig. 13-8).

Fig. 13-8. Structural formulas of iodothyronines found in human plasma.
4. Control of Thyroid Hormone Secretion

- Stress
- Cold in infants

**Hypothalamus**
- Thyrotropin-releasing hormone (TRH)
  - Anterior pituitary
  - Thyroid-stimulating hormone (TSH)
  - Thyroid gland
  - Thyroid hormone (T<sub>3</sub> and T<sub>4</sub>)

↑ Metabolic rate and heat production; enhancement of growth and CNS development; enhancement of sympathetic activity

시상하부
뇌하수체
갑상샘

TRH
T<sub>3</sub>, T<sub>4</sub>
Pituitary

TSH
TSH receptor
G protein
GTP GDP
Thyroid hormone receptor

Gene expression

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5. Circulation and Metabolism

- Thyroid hormones: water-insoluble molecules
- Two major thyroxine-binding proteins:
  - **Transthyretin**: 55 kDa; four identical subunits; 127 aa per subunit
  - **Thyroxine-binding globulin (TBG)**: a single polypeptide chain
    - About 70-75% of T4: bound to TBG
    - About 20%: bound to transthyretin
    - 5-10%: bound to albumin
6. Physiological Roles of Thyroid Gland

• Effects of thyroid hormone: major
  – Main determinant of basal metabolic rate
  – Influences synthesis and degradation of carbohydrate, fat, and protein
  – Increases target-cell responsiveness to catecholamines
  – Increases heart rate and force of contraction
  – Essential for normal growth
  – Plays crucial role in normal development of nervous system
TABLE 13.1  Some physiological roles and actions of thyroid hormones in mammals

Feedback inhibition of hypothalamic TRH and pituitary TSH secretion
Permissive to the action of many other hormones:
  Enhances lipolytic response of adipose tissue to hormones
  Required for the growth-promoting activity of GH
Increases activity of the sympathoadrenal system
Regulates basal metabolic rate:
  Increases mitochondrial oxidative phosphorylation
Required for hepatic conversion of carotenes to vitamin A
Required for bone growth and maturation
Required for nervous system differentiation in early development
Required for pituitary prolactin and growth hormone synthesis
Increases the rate of intestinal glucose absorption
Increases human red blood cell Ca^{2+}-ATPase activity
Induces enzyme synthesis:
  Na^{+}/K^{+}-ATPase (or a protein component or activator of the sodium pump)
  Carbamoyl phosphate synthetase (a phosphotransferase)
  α-Lactalbumin (lactose synthetase system proteins)
  Hepatic pyruvate carboxylase (converts pyruvate to oxaloacetate)
  Chromatin protein kinase
  Mitochondrial α-glycerophosphate dehydrogenase
  Malic dehydrogenase (converts malic acid to oxaloacetate)
  Hyaluronidase (dissolves intercellular ground substance)
Induction of cellular proteins (other than enzymes):
  Prolactin, growth hormone, lung surfactants, brain nerve factor (NGF)
Fig. 13-10. **Model for the action mechanism of thyroid hormone on target tissues.** The active form of thyroid hormone, triiodothyronine (T<sub>3</sub>), is produced by deiodination of thyroxine (T<sub>4</sub>) by the enzymes T<sub>4</sub>5’-deiodinase (5’-D) types I and II. Type I T<sub>4</sub>5’-deiodinase is found predominantly in the liver and kidneys; its action is responsible for the production of two-thirds of the total T<sub>3</sub> in the body. Type II T<sub>3</sub>5’-deiodinase is responsible for most of the T<sub>3</sub> found in the pituitary, the brain, and brown fat. T<sub>3</sub> enters the cell or is produced locally and then transported into the nucleus. Transcriptionally active forms of thyroid hormone receptors (TR) include monomers, homodimers, and heterodimers with nuclear protein partners, such as the retinoid X receptor (RXR). The T<sub>3</sub>–receptor complex interacts with specific sequences in DNA regulatory regions and modifies gene expression. T<sub>3</sub> causes both increases and decreases in gene expression and may also influence the stability of messenger RNA (mRNA). 9-cis RA denotes 9-cis-retinoic acid, the ligand for RXR.
Thyroid Target Cell
(e.g., pituitary/brain, liver, muscle, heart)

**Fig. 5. Action of the thyroid hormones**

*Circulating T₄* - bound to TBG, Transthyretin, or TBPA

- **Circulating T₄**
  - Bound to TBG, Transthyretin, or TBPA
  - 5’ deiodination

- **New Proteins**
  - (enzymes)
  - Transcription
  - Translation
  - Mitochondria
  - G3PDH
  - Na⁺,K⁺-ATPase
  - UCP

- **Temp. homeostasis**
  - Heat generation from ATP used by Na, K-ATPase in liver and other tissues
  - ↑ O₂ consumption
  - ↑ BMR (liver)

- **Other effects of T₃**
  - ↑ brain development, myelination
  - ↑ Growth (GH transcribed in somatotrope; induction of anabolic enzymes)
  - ↓ TSH in thyrotrope (repressive pituitary effect)
  - ↑ β₁-adrenergic receptor

*UCP, uncoupling protein (Mitochondrial uncoupling proteins (UCPs) are transporters that are important for thermogenesis.*
NUTRITIONAL CORRELATE – IODINE DEFICIENCY

Plasma $T_4$: ↓

Weight of thyroid gland: ↑

Thyroid blood flow: ↑

**Goiter (샘종):** reversible hypertrophy/ hyperplasia of thyroid (intakes <10% of the RDA, Recommended Dietary Allowance, 1일 권장량)

**Thyromeegaly:**
- adaptation to lack of iodine for synthesis of thyroid hormone
- directly due to ↑TSH, due to low plasma thyroid hormones
- excessive TSH enhances number and size of thyroid cells

**Cretinism:**
- maternal iodine deficiency
- mental and physical impairments not reversible
- prevented by treating iodine-deficient mother with iodine early in pregnancy
비독성 갑상샘종(단순, 콜로이드 또는 다결절성 샘종
- 갑상샘의 비대
- 갑상선샘기능은 정상
- 남녀비 = 1:8
- 콜로이드형: 사춘기, 임신
- 다결절성: 50세 이상 노인
- 무게: 40g~수백g
- 자각증상 없음
- 원인: 요오드 이용 부족 및 결함, TSH에 과민 반응 등
Gross Pathology of Goiter (생종)

- Diffuse colloid goiter
- Nodular goiter
- Long-standing nodular goiter
Nontoxic Goiter

- *Thyroid* gland *enlarges* due to *excessive stimulation* by *TSH*
- *Treat* by supplying *thyroid hormone*
- *May need to remove surgically*
Etiology of Goiter

1. Iodine deficiency
   (요오드 부족)
2. Deficiency of enzymes required for synthesis of thyroid hormone or ingestion of substances that interfere with the function of these enzymes
   (효소 부족으로 인한 갑상샘 호르몬 합성계 이상)
3. Increased hormone requirements
   (호르몬 필요 증대): puberty, during pregnancy, and under conditions of stress
Treatment of Nontoxic Goiter

• Administration of thyroid hormone
Fig. 13-12. Various endocrine disorders relating to the overproduction or underproduction of TSH or to inadequate thyroid- or peripheral-tissue responses to TSH or thyroid hormones.
### TABLE 13.3  Pathophysiology of the human thyroid gland

**Hypothyroidism (hypothyroxinemia)**
- Primary hypothyroidism
  - Familial or congenital thyroid dysgenesis
  - Failure of thyroid hormonogenesis (usually of genetic origin)
- Secondary hypothyroidism
  - Hypothalamic hypothyroidism (tertiary hypothyroidism)
- Cretinism (childhood hypothyroidism)
  - Goitrous cretinism (endemic; lack of dietary iodide)
  - Athyreotic cretinism (congenital absence of thyroid; thyroid dysgenesis)
- Myxedema (adult hypothyroidism)
  - Simple goiter (endemic; lack of dietary iodide)
  - Primary myxedema
    - Idiopathic (atrophic thyroiditis of unknown origin)
    - Iatrogenic (surgical removal or chemical inactivation)
    - Spontaneous (autoimmune destruction: Hashimoto’s thyroiditis)

Familial peripheral (end-organ) resistance to thyroid hormones (e.g., lack of or defective T₃, T₄ receptors)
Familial thyroid hormone-binding protein defects or levels
Low T₃ syndrome (failure of peripheral conversion of T₄ to T₃)
Thyroid gland resistance to TSH

**Hyperthyroidism (thyrotoxicosis)**
- Primary hyperthyroidism
  - Neoplasia (adenoma, carcinoma producing excessive TSH)
- Secondary hyperthyroidism
  - Hypothalamic hyperthyroidism (tertiary hyperthyroidism)
  - TSH-dependent hyperthyroidism (pituitary thyrotroph unresponsiveness to T₃ feedback inhibition)
  - Ectopic TSH secretion (rare)
Thyroid-stimulating antibody (TSAb) (autoimmune agonistic antibodies of thyroid TSH receptors) (Graves’ disease) [9, 38]
## Table 13.2 Major physiological manifestations of hyperthyroidism and hypothyroidism

<table>
<thead>
<tr>
<th>Hyperthyroidism</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated $T_4$-$T_3$ levels</td>
<td>Decreased (or absent) $T_4$-$T_3$ levels</td>
</tr>
<tr>
<td>Elevated basal metabolic rate (BMR) (hypermetabolism)</td>
<td>Low basal metabolic rate (BMR) (hypometabolism)</td>
</tr>
<tr>
<td>Increased perspiration</td>
<td>Decreased perspiration</td>
</tr>
<tr>
<td>Rapid pulse (increased cardiac output, hypertension)</td>
<td>Slow pulse (decreased cardiac output, hypotension)</td>
</tr>
<tr>
<td>Increased body temperature (sensation of warmness)</td>
<td>Lowered body temperature (sensation of coldness)</td>
</tr>
<tr>
<td>Heat intolerance</td>
<td>Cold intolerance</td>
</tr>
<tr>
<td>Warm, moist palms</td>
<td>Coarse, dry skin, subdermal thickening</td>
</tr>
<tr>
<td>Nervousness, anxiety, excitability, restlessness, insomnia</td>
<td>Lethargy, decreased mentation, depression, paranoia, sleepiness, tiredness</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Muscle wasting</td>
<td>Loss of hair, dry and brittle texture</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>Edema of face and eyelids</td>
</tr>
<tr>
<td>Menstrual irregularities</td>
<td>Menstrual irregularities</td>
</tr>
<tr>
<td>Exophthalmos (in some individuals)</td>
<td>Carotenemia (increased plasma levels of carotenes)</td>
</tr>
<tr>
<td>Goiter (primary or secondary origin)</td>
<td>Goiter (may or may not be present)</td>
</tr>
</tbody>
</table>

Copyright © 2007 Pearson Prentice Hall, Inc.
<table>
<thead>
<tr>
<th>Symptom of Hyperthyroidism</th>
<th>Affected Enzyme, Receptor, Hormone, Antibody, etc.</th>
<th>Symptom of Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓Weight</td>
<td>Mitochondrial Uncoupling Protein (UCP), Oxidative Enzymes</td>
<td>↑Weight</td>
</tr>
<tr>
<td>↑BMR</td>
<td></td>
<td>↓BMR</td>
</tr>
<tr>
<td>Heat Intolerance</td>
<td>UCP, Na/K-ATPase</td>
<td>Cold Intolerance</td>
</tr>
<tr>
<td>↑Heart Rate</td>
<td>Cardiac $\beta_1$-Adrenergic Receptor</td>
<td>↓Heart Rate</td>
</tr>
<tr>
<td>Irritable</td>
<td>Central Sympathetic $\beta$-Adrenergic Receptor</td>
<td>Sluggish</td>
</tr>
<tr>
<td>Moist Skin</td>
<td>Fluid Imbalance</td>
<td>Dry Skin</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>Thyroid Stimulating Immunoglobulin (TSI)</td>
<td>-----</td>
</tr>
<tr>
<td>Goiter</td>
<td>TSI or TSH</td>
<td>Goiter</td>
</tr>
<tr>
<td>-----</td>
<td>Myelin</td>
<td>↓Mental Development</td>
</tr>
<tr>
<td>-----</td>
<td>Growth Hormone</td>
<td>↓Growth</td>
</tr>
</tbody>
</table>

Table 1. Biochemical Basis for the Symptoms of Hyper- and Hypothyroidism.
• Hypothyroidism
  • Causes
    – Primary failure of thyroid gland
    – Secondary to a deficiency of TRH, TSH, or both
    – Inadequate dietary supply of iodine
  • Cretinism
    – Results from hypothyroidism from birth
  • Myxedema
    – Term often used for myxedema in adults
  • Treatment
    – Replacement therapy
    – Dietary iodine
Causes of Hypothyroidism

• Primary
  a. Developmental (thyroid dysgenesis: PAX-8, TTF-2, TSH-receptor mutations)
  b. Thyroid hormone resistance syndrome (TRβ mutations)
  c. Postablative: surgery, radioiodine therapy, or external radiation
  d. Autoimmune hypothyroidism: Hashimoto thyroiditis
  e. Iodine deficiency
  f. Drugs (lithium, iodides, p-aminosalicylic acid)
  g. Congenital biosynthesis defect (dyshormonogenetic goiter)

• Secondary: Pituitary failure

• Tertiary: Hypothalamic failure (rare)
Adult: Myxedema
성인 갑상샘
기능 저하증

피부: 부풀어 오른 눈꺼풀, 손발 부종, 창백하고 찬 피부
신경계: 무기력증, 졸림, 기억상실, 느린 사고, 편집증, 우울증, 점액수종 정신착란
심장: 맥박수 및 박출량 감소, 심박출량 감소, 점액수종성 심장
위장관: 연동 감소로 인한 변비
허스키한 목소리
부종
월경불순 및 중단
쇠약감
Adult myxedema: Clinical manifestations and etiology

- 푸석한 얼굴, 두꺼운 입술, 건조한 피부, 두꺼운 눈꺼풀, 피곤한 표정, 푸석한 머리카락
- Megaloglossia (거대 혀)
- Pudgy hands (손 및 팔이 흉 부, 팔꿈치에 심한 과각화증)
갑상샘 유래 원인
• 갑상샘 절제술 후
• 갑상샘암 치료를 위한 방사선 치료
• 급성 갑상샘염 후
• 하시모토 갑상샘염 후
Adult : Secondary Myxedema (Pituitary Origin)
뇌하수체 유래 원인
Seehan 증후군에 의한 TSH 부족
Cretinism
선천성 갑상샘 기능 저하증

1. Young cretin with marked stigmata
2. Elderly cretin

- 풍토병, 산발적, 가족력
- 남녀비 = 1:2
- 90%가 갑상샘 발생 장애로 인함
- 어릴 때 나타남
- 무관심, 굶뜸
- 겉친 복부, 배꼽 탈장
- 낮은 체온(35°C) 이하
- 치료하지 않을 경우 난쟁이 및 지능저하 야기
Hyperthyroidism

- Most common cause is *Graves’ disease*
  - Autoimmune disease
  - Body erroneously produces thyroid-stimulating immunoglobulins (TSI)
  - Characterized by exophthalmos

- Treatment
  - Surgical removal of a portion of the over-secreting thyroid
  - Administration of radioactive iodine
  - Use of antithyroid drugs
Role of Thyroid-Stimulating Immunoglobulin in Graves’ Disease
Hyperthyroidism – Clinical course

• Hypermetabolic state
• Activated sympathetic nervous system
• Increase in the basal metabolic rate
• Cardiac manifestations are among the earliest and most consistent features of hyperthyroidism
• Diastolic dysfunction
• Thyrotoxic dilated cardiomyopathy

• Thyroid myopathy
• Ocular change
• Thyroid ophthalmopathy
• Gastrointestinal system: hypermotility, malabsorption, and diarrhea
• Skeletal system: stimulates bone resorption
• Atrophy of skeletal muscle
그레이브스병
임상 특징
- 초조, 감정적 변화
- 경련, 나약함
- 체중감소
- 추위에 약하고, 다한증
- 빈맥, 가슴 두근거림
- 무혈경
- 안구 돌출
- 습한 피부, 피부병
- 갈색
- Oligomenorrhea
- Localized myxedema
- Nervousness
- Excitability
- Restlessness
- Emotional instability
- Insomnia
- Exophthalmos
- Goiter
- Warm, velvety skin
- Palpitation, tachycardia
- Poor response to digitalis
- Increased appetite
- Diarrhea (occasional)
- Tremor
- Clubbing of fingers
- Muscular weakness, fatigability
Patients displaying exophthalmos.
Diffuse hyperthyroidism
(Graves’ disease)
Diffuse hyperthyroidism (Graves’ disease)

- **Breasts**
  - Gynecomastia in male
  - Breast enlargement in female

- **Reproductive System**
  - Oligomenorrhea or amenorrhea
Diffuse hyperthyroidism (Graves’ disease)
Diffuse hyperthyroidism (Graves’ disease)
Thyroid pathology in Diffuse hyperthyroidism (Graves’ disease)
Treatment of Hyperthyroidism

1. **Antithyroid drugs** can be administered to block the synthesis of hormone by the hyperactive gland.

2. A large portion of the gland can be removed surgically (**thyroidectomy**), reducing the source of the hormone.

3. A large dose of **radioactive iodine** can be administered to be taken up by the thyroid gland. The irradiation destroys part of the gland and reduces its hormone output.
Effects of therapy in diffuse hyperthyroidism (Graves’ disease)
Acute and Subacute Thyroiditis

- Malaise
- Dysphagia
- Pain radiating to ear
- Thyroid gland visibly enlarged (more on one side)
- Tender pretracheal lymph nodes
- Thyroid gland tender, palpable
Chronic Thyroiditis
(만성 갑상샘염)

• 갑상샘에 염증을 동반하면서 다양한 증상을 나타내는 질환

1. 하시모토 갑상샘염 (Hashimoto thyroiditis)

2. 아급성 갑상샘염 (Subacute thyroiditis)

3. 리델 갑상샘염 (Riedel thyroiditis)
Chronic Thyroiditis (Hashimoto’s Thyroditis)

- **Autoantibody destroys thyroid tissue**
- Often leads to **hypothyroidism**
- Cellular infiltration is the result of an **immunologic reaction** between antigen and antibody

Pathogenesis of Hashimoto thyroiditis. Three proposed models for mechanism of thyrocyte destruction in Hashimoto disease. Sensitization of autoreactive CD4+ T cells to thyroid antigens appears to be the initiating event for all three mechanisms of thyroid cell death. See the text for details.
Thyroid Tumors

• **Benign adenoma**

• **Carcinoma**
  – Well-differentiated
  – Undifferentiated
  – Medullary

• Papillary Carcinoma (유두암종)
  - 75% to 85% of cases

• Follicular carcinoma(여포암종)
  - 10% to 20% of cases

• Medullary carcinoma(속질암종)
  - 5% of cases

• Anaplastic carcinoma(미분화성암종)
  - <5% of cases
<성별 10대암 조발생률, 2010년>
(2013년 8월 현재)(단위: 명/10만명)

위(80.8) 대장(62.5) 폐(58.7)
간(47.3) 전립샘(31.4) 갑상샘(24.9)
방광(11.0) 담낭 및 기타 담도(10.1) 신장(10.1)
췌장(10.0) 갑상샘(119.6) 유방(57.1) 대장(40.8)
위(39.8) 폐(24.3) 간(16.5) 자궁경부(15.5)
담낭 및 기타 담도(9.4) 체장(8.6)
난소(8.0)
Symptoms(증상)

• 목 앞 부위에 혹
• 쉰 목소리
• 경부 림프절 종대
• 연하곤란, 호흡 곤란
• 목부위 압통

Diagnosis(진단)

• History & Physical Examination(조직 및 이화학적 검사)
• 갑상샘 기능 검사 및 호르몬 검사
• Laboratory Evaluation : blood test(혈액 검사)
• CT/Ultrasonography(초음파)
• Imaging Studies : Radionuclide Scanning (방사선 스캔 검사)
• Fine Needle Aspiration (FNA) Biopsy (세침흡인세포검사-결절의 악성도 검사)
Scintiscans of thyroid (방사선 스캔 검사)

- less radioactivity than the surrounding thyroid tissue (cold nodules -> benign or malignant)
- more radioactivity than the surrounding thyroid tissue (hot nodules -> usually benign)
(A) Benign epithelial cells, colloid, and occasional macrophages, typical of a "colloid nodule".

(B) Epithelial cells in a follicular arrangement suggesting adenoma, but which could be from a follicular carcinoma.

(C) Epithelial cells in a papillary formation from a papillary thyroid carcinoma. Nuclear grooves are also apparent.
유두암종

• 가장 흔한 갑상샘암
• 20세~50세 빈발
• 남녀비 = 1:3
• 병인:
  - 요오드 초과 투여 혹은 섭취
  - 방사능 노출
  - 유전적 요인: HLA-DR7
유두암종의 임상적 특징

• 유두암종은 대체로 림프관에 침투하여 경부 쪽 국부의 림프절에 퍼짐; 환자의 ¼ 경우

• 암의 말기 때에 씨름 목소리, 연하곤란, 기침, 호흡곤란 등의 증상이 동반됨

• 예후: 매우 좋음; 10년 생존율이 95%
  - 국소 재발: 5~20%
  - 원위부 재발: 10~20%
  - 환자 나이 (45세 이상), 감상선 외 조직 침투, 원위부 전이가 있을 경우 예후가 더욱 나쁨.
  - 폐, 뇌 전이 또는 식도나 기도 방해 등으로 사망
Follicular Carcinoma Of the Thyroid
(10% to 20%)

여포성 갑상샘암종
- 대부분 40세 이상
- 남녀비 = 1:3
- 손으로 만져지는 혹
- 10년 생존율 = 85%
수질의 갑상샘암종 (Medullary thyroid carcinoma)

- 갑상샘의 부여포 또는 C 세포에서 시작
- 칼시토닌을 분비하여 혈중 칼슘 농도 낮춤
- 갑상샘암의 5% 이하
- 악성종양증후군(세로토닌)과 쿠티징(Cushing) 증후군(부신피질자극호르몬) 같은 내분비물 증상을 앓고 있음
- 치료법: 완전갑상샘 절제술
- 5년 생존율: 75%
미분화성 갑상샘암종 (Anaplastic thyroid carcinoma)

- 매우 공격적이고 분화되지 않는 갑상샘암
- 급속하게 자라서 치명적
- 주로 여성에 발병(남녀비 = 1:4)
- 보통 60세 이상에서 발병
- 갑상샘암의 10%
- 대부분 장기간 지속되는 갑상샘종의 병력을 가졌음
- 국부조직을 억압하고 파괴시킴
- 연하곤란, 호흡곤란 야기
- 예후는 매우 나쁘고 전이가 잘 발생함
- 5년 생존율: 10% 이하

**Anaplastic thyroid cancer:** The 5-year relative survival rate for anaplastic (undifferentiated) carcinomas, all of which are considered stage IV, is around 7% (based on patients diagnosed between 1985 and 1991).
Tumors Metastatic To the Thyroid

1. Breast(유방)
2. Lung(폐)
3. Kidney(신장)
4. Rectum and sigmoid colon (직장, S상 결장)
### Survival rates by Stage of the Thyroid Cancers

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Stage</th>
<th>5-year relative survival rate(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>I</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>48</td>
</tr>
<tr>
<td>Follicular</td>
<td>I</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>47</td>
</tr>
<tr>
<td>Medullary</td>
<td>I</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>40</td>
</tr>
</tbody>
</table>

**Anaplastic thyroid cancer:** The 5-year relative survival rate for anaplastic (undifferentiated) carcinomas, all of which are considered stage IV, is around 7% (based on patients diagnosed between 1985 and 1991).
Treatment(치료)

... Depending on the type and stage of thyroid cancer

- Surgery (수술)
  (taking out the cancer)
- Radioactive Iodine (RAI) therapy(방사성 옥소 치료)
  (using radioactive iodine to destroy cancer cells)
- External radiation therapy (외인성 방사선 치료)
  (using high-dose x-rays or other high-energy rays to kill cancer cells)
- Hormone therapy (호로몬 억제제)
  (using hormones to stop cancer cells from growing)
- Chemotherapy(항암제 치료는 아주 특별한 경우에만 사용)
  (using drugs to kill cancer cells)
Surgery (수술법)

• Lobectomy removes only the side of the thyroid where the cancer is found. Lymph nodes in the area may be taken out (biopsied) to see if they contain cancer.

• Near-total thyroidectomy removes all of the thyroid except for a small part.

• Total thyroidectomy removes the entire thyroid.

• Lymph node dissection removes lymph nodes in the neck that contain cancer.

1. Partial Thyroid Lobectomy
2. Thyroid Lobectomy
3. Thyroid Lobectomy with isthmusectomy
4. Subtotal Thyroidectomy
5. Total Thyroidectomy
갑상샘암 결론

• 분화된 갑상샘암은 잘 치료됨
• 갑상샘암의 수술은 경험 있는 의사가 할 경우 큰 합병증 없이 잘 치료됨
• 재발된 경우에도 목 근처에서 재발하기 때문에 대부분 재수술로 치료 잘됨
• 비록 전이된 경우에도 치료 방법이 있음