Ray Peat's Newsletter

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Thyroiditis. Some confusions and causes of "autoimmune diseases"

Girls' thyroid glands usually enlarge during puberty, and in pregnancy it's entirely normal for the gland to enlarge and to become more active. Eighty years ago, when iodine deficiency was more common in the US and Europe, the idea of a "colloid goiter" was common. In certain regions, many people had enlarged thyroids that contained a large amount of colloid--colloid is the viscous protein (thyroglobulin) solution formed in tiny compartments in the thyroid gland, which can be broken down by "digestive" (proteolytic) enzymes of the cells that have secreted it, forming the thyroid hormones, and allowing them to be released into the blood stream. The hormones are formed as the accumulated protein is broken down; the hormone itself isn't stored in the gland.

The reason for the enlargement of the gland during puberty and in pregnancy, and during some kinds of stress, is that the colloid is formed faster than it is digested by the thyroid gland and secreted into the blood. If something, such as an excess of estrogen, is blocking the production of the thyroid hormone, the gland is likely to enlarge, because the pituitary secretes more thyroid stimulating hormone (TSH) when there is a deficiency of thyroid hormone.

In vitro experiments show that estrogen activates the formation of the colloid, but inhibits its breakdown into the hormones. Progesterone, on the other hand, activates the process of proteolytic digestion and so increases the release of hormones from the gland, decreasing the accumulation of the colloid.

Therefore, when progesterone is deficient or estrogen is present in excess, the colloid tends to accumulate (even to the point of causing a visible enlargement of the gland, a "colloid goiter"), at the same time that the person may be hypothyroid, because the hormone isn't being released from the stored colloid, into the blood stream. But, largely because no one wants to suggest that estrogen can

Injury to the thyroid apparently precedes the development of "autoimmune thyroiditis." There is evidence that tissue injury precedes the appearance of "autoantibodies" in other conditions, too.

Many people with metabolic problems, including hypothyroidism, are being told that they have "a genetic disease." This belief encourages both physicians and their customers to commit themselves to inappropriate treatments, and to misinterpret the results of tests.

Eating seaweed or other foods or supplements containing iodine can cause both hypothyroidism and thyroiditis. The iodate sometimes used as an oxidizing agent in breads have probably contributed to thyroid disease in the industrialized countries.

Dental x-rays, which can cause cancer of the thyroid, brain, and eye, certainly have increased the incidence of thyroiditis and hypothyroidism. The radioactive isotopes that are often foolishly used for supposedly "diagnostic" purposes probably contribute to the incidence and severity of hypothyroidism and thyroiditis.

Besides iodine, radioactive isotopes, and x-rays, other environmental toxins, including mercury and dioxins can cause thyroiditis, but diet and estrogens are probably the causes of most thyroid problems.

A generalized inflammatory state, rather than specific "autoimmunity," is responsible for thyroiditis and other "autoimmune degenerative" diseases.

A "respiratory defect" is behind the inflammatory condition.

Correcting a thyroid deficiency tends to gradually normalize the antibodies.

be pathogenic, an enlarged thyroid gland is now likely to be diagnosed as "Hashimoto's thyroiditis" (or Hashimoto's struma, or goiter, or disease).

Hashimoto's disease is clearly defined as the infiltration of the gland with lymphocytes, "causing destruction" of the gland's active tissue and leading to hypothyroidism. The only way to know that the gland is being invaded by large numbers of lymphocytes is by biopsy, but the condition is normally diagnosed by pure guesswork, without any biopsy. Sometimes "antithyroid antibodies" found in the blood are used to diagnose Hashimoto's disease, but the presence of those antibodies in the blood doesn't mean that they originated in the thyroid gland, and even though they have very specific names (e.g., "antithyroglobulin," "antithyroperoxidase") related to the thyroid gland, they aren't even specific for the thyroid gland. It has been suggested that similarities in molecular structure between thyroglobulin and connective tissue proteins could account for the finding of "antithyroid antibodies" **more frequently in rheumatoid arthritis and Sjogren's syndrome than in Hashimoto's disease and Graves' disease** (Ruggeri, et al, 2002).

In the last 60 years, most of estrogen's toxic effects have been hushed up by the drug industry, and estrogen's central antirespiratory and antithyroid actions are unknown to most contemporary endocrinologists. But endocrinologists often do know that estrogen causes the thymus gland to atrophy, and that the thymus gland is intimately involved in maintaining normal immune functions.

The degenerating thymus gland undergoes invasion by lymphocytes and the replacement of active tissue by fibrous tissue, under the influence of estrogen or stress. The process of cellular invasion in the thyroid gland probably develops more slowly than that in the thymus, because estrogen's effect on the thymus is very rapid.

The cells that make up the thymus are extremely varied, but a large portion of them are able to phagocytize other cells. This self-phagocytosis probably contributes to the gland's ability to shrink with such great rapidity. When other organs are damaged, the removal of debris can be delayed for days, as phagocytic cells gradually enter the tissues from the blood stream.

Hypothyroidism is an important cause of thymic atrophy, and a thyroid supplement can stimulate regeneration of the thymus.

This correction of the thymic portion of the "immune system" by the thyroid hormone is probably involved in the observation that the "antithyroid" autoantibodies decrease under the influence of supplemental thyroid hormone, but the supplement also affects the thyroid gland, by decreasing the thyroid stimulating hormone, TSH. Excess production of TSH causes an inflammation-like stress, that contributes to the production of the colloid goiter and eventually to disordered structural changes in the thyroid gland. A more efficient production and use of thyroglobulin will decrease the tendency of the overstimulated gland to produce a defective globulin that is antigenic.

So, rather than ignoring the frequency of the simple colloid goiter and calling everything "Hashimoto's autoimmune thyroiditis," if we look at the mechanisms involved in the production of autoantibodies, we will tend to see "thyroiditis" as, usually, the last stage in the development of a simple colloid goiter. The autoantibodies, in a healthy person, are probably part of a corrective repair process, rather than a simply pathogenic factor.

There is an almost obligatory medical genuflection toward "genetic causation" of disease, and especially of thyroid disease, autoimmune disease, and other chronic or degenerative diseases. **The fact that thyroid disease and autoimmune diseases are from five to ten times more frequent in women than in men somehow hasn't increased medical interest in the pathogenic role of estrogen,** and it doesn't prevent platoons of medical researchers from making claims to have discovered "which chromosome carries the disease."

This medical bias means that even the physicians who recognize that hypothyroidism is a condition that should be corrected are not likely to believe that it is important to modify the treatment according to changes in the patient's condition. Many doctors assume that a person never recovers

Part of the problem, Lewontin points out, is the casual way in which geneticists speak. "This is seen even in the naming of genes," he notes. "Geneticists speak casually of the 'gene for white eyes', but of course, there is no such gene. There is a variety of genes whose reading by the cell is proximally involved in the production of eye pigment and its deposition in the eye cells." He points out that genes are said to be "self-replicating," engaged in "gene action", "make" proteins and are "turned on " or "off" by regulatory DNA. "But none of this is true... DNA is among the most inert and non-reactive of organic molecules," he writes. S.W. Samuels, in Genes, Ethics & Environment!, an internet public policy journal.Vol.1, No. 1 October, 2000

from thyroiditis, but the evidence is clear that simply giving supplementary thyroid usually gradually corrects the problem. If other protective measures are taken, recovery will be quicker and more complete. When the diet is optimal, the TSH is likely to be "abnormally low," below 1.0 on the standard scale, even without use of a thyroid supplement. Keeping the level of TSH low contributes to the reduction of the generalized inflammatory state that characterizes hypothyroidism and autoimmunity. TSH should be considered to be one of the stress-related pro-inflammatory anti-respiratory hormones, along with serotonin, histamine, estrogen, parathyroid hormone, and prolactin.

The diet should be relatively free of antithyroid foods, especially legumes and polyunsaturated fats, and the foods of the cabbage family, such as broccoli, should be well cooked, and used no more often than once a week. The polyunsaturated fats interfere with the thyroid hormone, disturb the thymus and other immune functions, and increase the antigenicity of tissues.

A high protein diet, of about 100 grams of good protein daily, is protective, and protein deficiency is a common cause of hypothyroidism. But too much emphasis on the muscle meats, including fish fillets, chicken breast or legs, and the usual steaks and chops, can be antithyroid by providing too much tryptophan. That can be offset by using gelatin liberally (chicken soup and ox-tail soup contain lots of gelatin from the bones and connective tissues), because gelatin contains no tryptophan. Whey, which is sold as a protein supplement, and egg whites contain too much tryptophan, and can be antithyroid if used excessively.

Using large amounts of seaweed can cause hypothyroidism and can injure the thyroid cells, contributing to thyroiditis. Seaweed and other iodine-containing food supplements are often sold to improve thyroid function, but they usually have the opposite effect. An iodine deficiency used to cause goiters in some regions, but in the last 50 years most people in the US and Europe have been getting an excessive amount of iodine.

"We can recall when a TSH of 7.0 or below was considered normal. Years later, the TSH cutoff was 6.4, meaning that anything below that level was considered normal. Still later, the cutoff was moved to 5.5. Now, some labs are reporting a level of 4.2 as being the cutoff level, above which the patient may be hypothyroid." "...at our clinic, a TSH over 3 is considered suspicious...." (p. 75)

"Some doctors prefer the lower limit of a corrected TSH to be 1.0. Others are comfortable with a TSH of 0.5. Some thyroid specialists at the Universtiy of California Medical Center in San Francisco like to see the corrected level around 0.2 (slightly below the normal range of 0.4-5.0). That figure is generally considered by many nonuniversity doctors to be too low, suggesting to them that the patient is on too much thyroid medication.

"At our clinic, we have patients who do not feel well until they take enough medication to lower their TSH level to 0.1." (Page 79) R.L. Shames and K.H. Shames, *Thyroid Power,* 2001.

Endotoxin or other material absorbed from intestinal bacteria contributes to a variety of autoimmune problems, including thyroiditis (Penhale and Young, 1988). Combining an indigestible fiber, such as raw carrot, with mild germicides, such as vinegar and coconut oil, can improve the hormonal environment, while reducing the immunological burden.

Adequate light is another important factor in maintaining a high energy respiratory state and preventing the whole complex of inflammatory, autoimmune, degenerative diseases.

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Br J Psychiatry 1987 May;150:674-81. **Characteristic plasma hormone changes in Alzheimer's disease.** Christie JE, Whalley LJ, Bennie J, Dick H, Blackburn IM, Blackwood DH, Fink G. "A systematic endocrine investigation in dementia, depression and control subjects showed that plasma growth hormone (GH) was higher in the morning and **plasma TSH concentrations were higher throughout the day in Alzheimer-type dementia (ATD) than in age-matched depressed patients (MDD), and plasma TSH concentrations were also higher throughout the day in female ATD compared with** age-matched female control subjects. **The increased plasma TSH concentrations could not be due to reduced negative feedback** because plasma T3, T4 and rT3 were in the normal range."

Acta Cytol 1997 Jul-Aug;41(4 Suppl):1369-72. **Aspiration cytology of 131I-induced thyroiditis. A case report.** de la Roza GL, Burke KC, Dumler JS, Aisner SC. "Although 131I may induce morphologic changes similar to those associated with external radiation, a known diagnostic pitfall, the cytology literature on the subject is very sparse. This case exemplifies the thyroid cytologic changes associated with 131I exposure." "Review of the cytologic sample revealed follicular cells with focal, marked cytologic atypia, abundant colloid, stromal fragments, and lymphocytes."

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J Clin Endocrinol Metab 1996 Mar;81(3):990-4. **Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy.** Giani C, Fierabracci P, Bonacci R, Gigliotti A, Campani D, De Negri F, Cecchetti D, Martino E, Pinchera A. "**Hashimoto's thyroiditis was found in 13.7% of BC patients and in only 2% of the controls** ($P < 0.005$). Other thyroid disorders found in the BC group included 2 cases of Graves' disease, 2 of thyroid carcinoma, and 1 of subacute thyroiditis, whereas in the control group only 1 case of Graves' disease and none of the other disorders were found. Mean free T3, free T4, and TSH concentrations showed no difference between BC patients and controls. The prevalence of thyroperoxidase antibody was higher in BC patients than in controls (23.5% vs. 8%; $P < 0.005$), whereas the prevalence of thyroglobulin antibody was not different. In BC patients the presence of thyroid antibodies was more frequently associated with clinically detectable autoimmune thyroiditis (14 of 26, 51.8%; $P = 0.03$) and was more common in the younger group." "In conclusion, 1) the present study provides evidence that the overall prevalence of thyroid disorders is increased in patients with breast cancer, and 2) thyroid autoimmune disorders, especially Hashimoto's thyroiditis, account to a large extent for the increased prevalence of thyroid disease in patients with breast cancer."

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(beta-APP) is expressed, proteolytically cleaved and released into the extracellular space in a TSH-dependent fashion."

Lab Invest 1995 May;72(5):513-23. **Localization and regulated release of Alzheimer amyloid precursor-like protein in thyrocytes.** Graebert KS, Lemansky P, Kehle T, Herzog V. "Dysregulation in the processing of the Alzheimer precursor protein (APP) is thought to be central to the deposition of the beta-A4 peptide and to the pathogenesis of Alzheimer's disease. Expression and release of APP has also been known to mediate cell-matrix interactions and to participate in the regulation of cell proliferation." "Because of the specific processing of exportable proteins, thyrocytes represent a particularly useful cell type for the study of the processing of APP/APLP (especially proteolysis and iodination) as an indication of cell surface expression and for the study of the regulation of these functions." "The observations show the expression, maturation, and secretion of APP/APLP in **thyrocytes and the up-regulation of these processes by TSH.** Part of the immature APP/APLP appeared on the cell surface as indicated by its iodination. Apparently, this portion of immature APP/APLP escaped maturation during its transport to the cell surface."

Rinsho Shinkeigaku 1993 Sep;33(9):995-7. **[A case of Hashimoto's encephalopathy with a relapsing course related to menstrual cycle]** [Article in Japanese] Ishii K, Hayashi A, Tamaoka A, Mizusawa H, Shoji S. "Hashimoto's thyroiditis was diagnosed on the basis of high thyroid microsomal titer and mild hypothyroidism. Neurological findings in admission included action tremor in both hands, myoclonus in all extremities, cerebellar ataxia, confusion, and hyperreflexia." "Hashimoto's encephalopathy was diagnosed from these findings. These episodes of remission and exacerbation were observed during the admission. **Her symptoms started at ovulation, worsened during the luteal phase, and improved when menstruation started. After the third relapse, she was treated with oral thyroxine for hypothyroidism and with an estrogen and progesterone combination to regulate the menstrual cycle.** Her thyroid function gradually became euthyroid and she did not experience any subsequent relapses. **The relation between the relapsing course and menstrual cycle suggests that the periodic alteration of gonadotrophic and/or gonadal hormones or the menstrual regulating center itself in the brain may be an important factor of pathogenetic mechanism of the disorder."**

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Acta Med Austriaca 1999;26(4):126-8. **[Thyroid autoantibodies in depressive disorders]** [Article in German] Konig F, von Hippel C, Petersdorff T, Kaschka W. "We found autoantibodies (MAK, TAK, TRAK) in a high percentage (100 out of 144 = 70%) in severely depressed inpatients. Also we found a Hashimoto thyreoiditis in 5 patients." "We conclude that in cases of repeated depressive episodes especially depression of the elderly and in nonresponders it seems necessary not only to get lab for TSH, T3 and T4 but also to assess the autoimmune status of the thyroid gland (autoantibodies). There is further need for controlled studies whether there is a better outcome in nonresponders to antidepressive medical treatment and positive autoantibody status after supplementation with triiodothyronine."

Hokkaido Igaku Zasshi 1994 May;69(3):614-26. **[Screening for thyroid dysfunction in adults residing in Hokkaido Japan: in relation to urinary iodide concentration and thyroid autoantibodies]** [Article in Japanese] Konno N, Iizuka N, Kawasaki K, Taguchi H, Miura K, Taguchi S, Murakami S, Hagiwara K, Noda Y, Ukawa S. "The prevalence of thyroid dysfunction and its relation to thyroid autoantibodies (TAA) and urinary iodide concentration (UI) was studied in apparently healthy adults in Sapporo (n = 4110) (Sapporo group), and in five coastal areas of Hokkaido (n = 1061) (coastal group) which produce iodine-rich seaweed (kelp). The frequency of above normal UI (high UI) in the morning urinary samples of coastal group was 10.8%, significantly higher than that of Sapporo group (6.4%) ($p < 0.001$). Frequency of positive TAA in both groups were similar. In Sapporo group TAA was positive in 6.4% of males and 13.8% of females with an age-related increase." The overall prevalence of hyperthyroidism (TSH < 0.15 mU/L) in coastal group (0.6%) was similar to that in Sapporo group (1.1%), while that of **hypothyroidism (TSH > 5.0 mU/L) in coastal group (3.8%) was significantly higher than that in Sapporo group (1.3%) (P** < 0.001). The frequency of high UI correlated significantly with that of hypothyroidism with negative TAA ($r = 0.829$, $P < 0.05$), but not with positive TAA, or with that of hyperthyroidism. Hypothyroidism was more prevalent in TAA negative subjects with high UI than with normal UI. Moreover, serum TSH and thyroglobulin levels were higher and free T4 level was lower in former than in latter group. "These results indicate that 1) the prevalence of TAA negative hypothyroidism in iodine sufficient areas may be associated with the amount of iodine ingested, 2) **this hypothyroidism is more prevalent and marked in subjects consuming further excess amounts of iodine,** and 3) excessive intake of iodine should be considered an etiology of hypothyroidism in addition to chronic thyroiditis in these areas."

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Autoimmunity 1997;26(3):173-87. **Effects of HgCl2 on the expression of autoimmune responses and disease in diabetes-prone (DP) BB rats.** Kosuda LL, Greiner DL, Bigazzi "We found that DP rats treated with mercury or water for a period of 40-125 days developed autoantibodies to thyroglobulin, with a higher incidence in HgCl2-injected animals (92% vs. 56% in

H2O-injected controls). A novel finding of our study was the detection of autoantibodies to laminin in the same rats, again with an increased incidence after HgCl2 treatment (83% vs. 44%)." "... while mercury does not seem to recruit, induce or rescue regulatory T cell function in DP rats, it does stimulate autoantibody responses in these animals."

Life Sci 1999;64(12):1037-44. **Thyroid stimulating hormone-receptor overexpression in brain of patients with Down syndrome and Alzheimer's disease.** Labudova O, Cairns N, Koeck T, Kitzmueller E, Rink H, Lubec G.

Cytopathology 2002 Feb:13(1):31-9. **Aspiration cytology of Hashimoto's thyroiditis in an endemic area.** Kumar N, Ray C, Jain S. "Hashimoto's thyroiditis (HT) is the second most common thyroid lesion next to endemic goitre diagnosed on FNA in iodine (I2) deficient areas." "In the present study the patients presented with HT a decade earlier than reported in I2 sufficient areas. Presentation as a nodular thyroid is common. Diagnosis of HT is likely to be missed in smears showing cytological evidence of hyperplasia or abundant colloid. HT was concurrent in 20 cases of endemic goitre."

JAMA 1994 Aug 3;272(5):364-70. **Thyroid diseases among atomic bomb survivors in Nagasaki.** Nagataki S, Shibata Y, Inoue S, Yokoyama N, Izumi M, Shimaoka K. "A significant dose-response relationship was observed for solid nodules, which include cancer, adenoma, adenomatous goiter, and nodules without histological diagnosis, and for antibody-positive spontaneous hypothyroidism (autoimmune hypothyroidism) but not for other diseases. The prevalence of solid nodules showed a monotonic dose-response relationship, yet that of autoimmune hypothyroidism displayed a concave dose-response relationship reaching a maximum (+/- SE) level of 0.7 +/- 0.2 Sv." "The present study confirmed the results of previous studies by showing a significant increase in solid nodules with dose to the thyroid and demonstrated for the first time a significant increase in autoimmune disease among atomic bomb survivors. A concave dose-response relationship indicates the necessity for further studies on the effects of relatively low doses of radiation on thyroid disease."

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Acta Endocrinol (Copenh) 1978 Aug;88(4):703-12. **A case of Hashimoto's thyroiditis with thyroid immunological abnormality manifested after habitual ingestion of seaweed.** Okamura K, Inoue K, Omae T. "An interesting case of iodide induced goitre with immunological abnormalities is described. The patient who was sensitive to synthetic penicillin had previously been treated for exudative pleuritis, congestive heart failure and acute renal failure. Following recovery, he began to ingest large amounts of seaweed after which he developed goitrous hypothyroidism. It was of interest that the serum level of gamma-globulin increased, and subsequently the antithyroid microsomal antibody became strongly positive, suggesting that thyroidal autoimmune processes had been precipitated. Biopsy of the thyroid gland revealed chronic thyroiditis, with evidence suggesting extreme stimulation by TSH." "While there is evidence suggesting that increased iodide may be an important factor in the initiation of Hashimoto's thyroiditis, this may result from the marked increased sensitivity of Hashimoto's gland to the effects of iodine."

Thyroid 2001 Mar;11(3):249-55. **One-year prophylactic treatment of euthyroid Hashimoto's thyroiditis patients with levothyroxine: is there a benefit?** Padberg S, Heller K, Usadel KH, Schumm-Draeger PM. "After 1 year of therapy with LT4, TPO-Abs and B lymphocytes decreased significantly only in the treated group of euthyroid patients with HT ($p < 0.05$). In contrast, TPO-Abs levels did not change or even increased in untreated euthyroid patients with HT." "Prophylactic treatment of euthyroid patients with HT reduced both serological and cellular markers of autoimmune thyroiditis. Therefore, prophylactic LT4 treatment might be useful to stop the progression or even manifestation of the disease."

Free Radic Biol Med 1999 Oct;27(7-8):901-10. **Thyroid status modulates glycoxidative and lipoxidative modification of tissue Proteins.** Pamplona R, Portero-Otin M, Ruiz C, Bellmunt MJ, Requena JR, Thorpe SR, Baynes JW, Romero M, Lopez-Torres M, Barja G. **"The levels of the glycation product N(epsilon)-fructoselysine (FL) and those of the oxidation products, N(epsilon)-(carboxymethyl)lysine (CML) and malondialdehyde-lysine (MDA-lys), identified by GC/MS in liver proteins, decreased significantly in hyperthyroid rats,** as well as (less acutely) in hypothyroid animals." "Cytosolic proteolytic activity against carboxymethylated foreign proteins measured in vitro was significantly increased in hypo- and hyperthyroidism."

Eur J Endocrinol 2002 Jun;146(6):777-81. **Vitamin D 1alpha-hydroxylase (CYP1alpha) polymorphism in Graves' disease, Hashimoto's thyroiditis and type 1 diabetes mellitus.** Pani MA, Regulla K, Segni M, Krause M, Hofmann S, Hufner M, Herwig J, Pasquino AM, Usadel KH, Badenhoop K. **"The vitamin D endocrine system plays a role in the regulation of (auto)immunity and cell proliferation."**

Clin Exp Immunol 1988 May;72(2):288-92. **The influence of the normal microbial flora on the susceptibility of rats to experimental autoimmune thyroiditis.** Penhale WJ, Young PR. "Female PVG/c strain rats maintained under **specific pathogen-free conditions until weaning were found to be significantly less susceptible to the induction of autoimmune thyroiditis by thymectomy and irradiation** than conventionally reared rats of the same strain." "It was found that the oral administration of antibiotics followed by fresh, homogenized, intestinal contents obtained from conventionally reared rats to newly weaned SPF PVG/c rats significantly augmented their autoimmune susceptibility." **"It is proposed that the composition of the normal gastrointestinal flora of conventionally reared rats profoundly influences susceptibility to the induction of autoimmune thyroiditis in this particular experimental model, possibly by antigenic cross-reactivity with thyroid tissue."**

Radiats Biol Radioecol 1996 Jul-Aug;36(4):632-40. **[The probable sequelae of thyroid damage from radioactive iodine during the Chernobyl accident]** Poverennyi AM, Shinkarkina AP, Vinogradova IuE, Beziaeva GP, Podgorodnichenko VK, Tsyb AF. "The analysis of the situation when children's thyroids were subjected to irradiation shows that tumors can most frequently develop as late as 20-30 years after irradiation. There are reasons to believe that tumors are induced by low dose of irradiation. The most important factor in development of pathologies is for sure the

age of the children of the moment of irradiation. A well-known consequence of the impact of radiation on the thyroid is the lymphocyte thyroiditis."

Clin Immunol Immunopathol 1996 Dec;81(3):287-92. **Iodine-induced autoimmune thyroiditis in NOD-H-2h4 mice.** Rasooly L, Burek CL, Rose NR. "Excess iodine ingestion has been implicated in induction and exacerbation of autoimmune thyroiditis in human populations and animal models." "Levels of serum thyroxin (T4) were similar in the treatment and control groups. Thyroglobulin-specific antibodies were present in the iodine-treated group after 8 weeks of treatment but antibodies to thyroid peroxidase were not apparent in the serum of any of the animals. Levels of thyroglobulin antibodies increased throughout the 8-week iodine ingestion period; however, no correlation was seen between the levels of total thyroglobulin antibodies and the degree of thyroid infiltration at the time of autopsy."

J Endocrinol Invest 2002 May;25(5):447-54. **Thyroid hormone autoantibodies in primary Sjogren syndrome and rheumatoid arthritis are more prevalent than in autoimmune thyroid disease, becoming progressively more frequent in these diseases.** Ruggeri RM, Galletti M, Mandolfino MG, Aragona P, Bartolone S, Giorgianni G, Alesci D, Trimarchi F, Benvenga S. **"To verify the greater prevalence of circulating thyroid hormone autoantibodies (THAb) in primary Sjogren syndrome (SS) vs Hashimoto's thyroiditis (HT) and Graves' disease (GD),** we measured THAb in the serum of patients with these 3 diseases who were sampled from 1998-1999 (no.=20, 88, 25) and 1990-1992 (no.=13, 75, 31)." "We found that IgG antibodies against T3, T4 or both were present with these prevalences in the 1975-1982, 1990-1992 and 1998-1999 series: HT=1, 4, 20%; GD=2, 6, 32%; SS=20, 31, 50%; RA=0, 12, 26%; other collagenoses=0, 0, 0%. The majority of the Sjogren or arthritis cases positive for THAb were negative for TGAb, while the opposite was true for the 2 autoimmune thyroid diseases. We conclude that prevalence of THAb in the 2 non-thyroid autoimmune diseases is greater than in the 2 thyroid autoimmune diseases. In addition, prevalence of THAb is increasing over time regardless of disease. **Molecular similarity between extra-thyroid connective proteins (specifically associated to primary SS and RA) and iodinated regions of TG,** and an increased preponderance of environmental factors as triggers of autoimmune diseases might account for our findings."

Endocrinol Metab Clin North Am 1987 Jun;16(2):327-42. **Environmental factors affecting autoimmune thyroid disease.** Safran M, Paul TL, Roti E, Braverman LE. "Exposure to excess iodine, certain drugs, infectious agents and pollutants, and stress have all been implicated."

J Immunol 1994 Mar 1;152(5):2586-95. **Ionizing radiation and autoimmunity. Induction of autoimmune disease in mice by high dose fractionated total lymphoid irradiation and its prevention by inoculating normal T cells.** Sakaguchi N, Miyai K, Sakaguchi S. "Ionizing radiation can functionally alter the immune system and break self-tolerance."

J Clin Endocrinol Metab 1995 Dec;80(12):3513-9. **Thyroid epithelial cells produce large amounts of the Alzheimer beta-amyloid precursor protein (APP) and generate potentially amyloidogenic APP fragments.** Schmitt TL, Steiner E, Klingler P, Lassmann H, Grubeck-Loebenstein B. "In view of the known association between familial AD and thyroid autoimmune disease, the expression pattern and cellular processing of APP in human thyroid cells were investigated." "The results of these studies demonstrated that APP isoforms 770 and 751 were expressed in fresh thyroid extracts as well as in cultured thyroid epithelial cells, with APP 770 being the predominant form. Compared to other types of cells, such as lymphocytes and fibroblasts, thyroid epithelial cells produced larger amounts of APP." "Interestingly, thyroid epithelial cells also contained larger C-terminal APP fragments of 21, 35, and 41 kDa. From the sizes of these fragments it could be deduced that they contained the entire amyloid beta sequence and were thus potentially amyloidogenic. The 41-kDa fragment was unique to thyroid cells. These fragments may be released into the circulation after thyroid cell damage. Increased/altered thyroid APP expression in familiar AD may induce alterations in thyroid epithelial cells and cell damage, and thus explain the frequent occurrence of thyroid autoimmunity in this disease."

Radiats Biol Radioecol 1994 Jan-Feb;34(1):3-7. **[Antibodies to the thyroid microsomal antigen in children and adolescents subjected to radiation exposure as a result of the accident at the Chernobyl Atomic Electric Power Station]** Shinkarkina AP, Podgorodnichenko VK, Poverennyi AM. "There is significant difference in the frequency of the antibody appearance between persons suffered from radioactive iodine and unsuffered ones. Correlation between levels of antimicrosomal antibodies and radiation dose obtained from incorporated radioactive iodine was not estimated."

Verh Dtsch Ges Pathol 1996;80:297-301. **[Spontaneous Hashimoto-like thyroiditis in cats]** Schumm-Draeger PM, Langer F, Caspar G, Rippegather K, Herrmann G, Fortmeyer HP, Usadel KH, Hubner K. "A breeding line of domestic cats spontaneously developing symptoms of hypothyroidism between the 40th and 60th day of life (fur changes, loss of appetite, growth retardation), elevated levels of antibodies against microsomal structures and thyroglobulin, and lymphocytic thyroid infiltration has been recently established at our facility. Aim of our studies was to examine the effect of high iodine ingestion or prophylactic thyroid hormone therapy on functional and morphological characteristics of this Hashimoto-like thyroiditis in cat. From birth to day 80 of life cats were treated with iodine (n = 9; 0.1 mg/l) or thyroxin (n = 13; 2.0 micrograms/ kg/d) respectively. Untreated animals served as controls (n = 12). Cat-serum was tested for thyroid function (TT3, TT4). After 8 weeks the thyroid tissue was submitted to routine histological processing (H&E) and the inflammatory activity was scored." "Both untreated hypothyroid (UHC) as well as iodine-treated (IC) cats revealed a significantly higher degree of thyroid inflammation and higher tissue levels of IgM as the thyroxin-substituted animals (TC)." **"Early thyroid hormone therapy significantly decreases both incidence and activity of autoimmune thyroiditis in cats as measured by inflammatory infiltration, IgM production and epithelial proliferation. Animals with excess iodide intake, however, show an aggravation of the autoimmune inflammatory activity."**

Vnitr Lek 1999 Sep;45(9):527-31. **[Reactions to metals in patients with chronic fatigue and autoimmune endocrinopathy]** Sterzl I, Hrda P, Prochazkova J, Bartova J, Matucha P. "Our study was designed to assess the effect of heavy metals on the severity of fatigue in autoimmune thyroid disease associated with autoantibodies against other endocrine organs." "Fatigue regardless of the underlying disease is primarily associated with hypersensitivity to inorganic and organic mercury, nickel, and gold. The groups differed in their hypersensitivity to other metals. In the control group, hypersensitivity--mostly to cadmium and lead--was found in four of the examined individuals only. Statistical analysis of data obtained from professionals and controls revealed a higher incidence of positivity to organic and inorganic mercury and nickel in professionals."

Neuroendocrinol Lett 1999;20(3-4):221-228. **Mercury and nickel allergy: risk factors in fatigue and autoimmunity.** Sterzl I, Prochazkova J, Hrda P, Bartova J, Matucha P, Stejskal VD. We

have found that fatigue, regardless of the underlying disease, is primarily associated with hypersensitivity to inorganic mercury and nickel. The lymphocyte stimulation by other metals was similar in fatigued and control groups. To evaluate clinical relevance of positive in vitro findings, the replacement of amalgam with metal-free restorations was performed in some of the patients. At a six-month follow-up, patients reported considerably alleviated fatigue and disappearance of many symptoms previously encountered; in parallel, lymphocyte responses to metals decreased as well. We suggest that metal-driven inflammation may affect the hypothalamic-pituitary-adrenal axis (HPA axis) and indirectly trigger psychosomatic multisymptoms characterizing chronic fatigue syndrome, fibromyalgia, and other diseases of unknown etiology.

The New England Journal of Medicine Volume 326:513-518 February 20, 1992 Number 8. **Disappearance of thyrotropin-blocking antibodies and spontaneous recovery from hypothyroidism in autoimmune thyroiditis.** N Takasu, T Yamada, M Takasu, I Komiya, Y Nagasawa, T Asawa, T Shinoda, T Aizawa, and Y Koizumi. "We determined the frequency with which thyrotropin-blocking antibodies were present in 172 hypothyroid patients with goitrous autoimmune thyroiditis (Hashimoto's disease) and 64 hypothyroid patients with atrophic autoimmune thyroiditis (idiopathic primary hypothyroidism). For 6 to 11 years we then followed 21 of these patients who were found to have thyrotropin-blocking antibodies. They received levothyroxine therapy for 3.5 to 8 years, after which it was discontinued." **"Thyrotropin-blocking antibodies were detected in 9 percent of the patients with goitrous autoimmune thyroiditis and in 25 percent of those with atrophic autoimmune thyroiditis. Among the 21 patients studied serially while receiving levothyroxine, thyrotropin-blocking antibodies disappeared in 15 (group 1), 7 of whom had goiter initially, and persisted in 6 (group 2), none of whom had goiter initially.** Levothyroxine therapy was subsequently discontinued in these 21 patients. Six of those in group 1 (four with goiter) remained euthyroid (mean follow-up after discontinuation of therapy, 2.1 years), and nine became hypothyroid again within 3 months. All six patients in group 2 remained hypothyroid. CONCLUSIONS. Hypothyroidism in some patients with autoimmune thyroiditis may be due to thyrotropin-blocking antibodies. The production of thyrotropin-blocking antibodies may subside, producing remissions of hypothyroidism. Chronic autoimmune thyroiditis may therefore cause transient as well as permanent hypothyroidism."

Clin Exp Immunol 1993 Mar;91(3):442-8. **Gender-related influences on the development of chronic graft-versus-host disease-induced experimental lupus nephritis.** Treurniet RA, Bergijk EC, Baelde JJ, De Heer E, Hoedemaeker PJ, Bruijn JA. "Autoimmune diseases are far more common in women than in men. **In the incidence of systemic lupus erythematosus (SLE), the female-to-male ratio is as high as 10:1. This suggests that sex hormones may play a fundamental role in determining the susceptibility to these diseases."** "After four cell transfers, female recipients developed a significantly higher albuminuria than both male groups. Serum concentrations of autoantibodies against glomerular basement membrane (GBM), collagen IV, and laminin were significantly higher in females 2-4 weeks after induction." "These findings indicate that: (i) in this model of lupus nephritis, susceptibility to glomerulonephritis is strongly influenced by sex-related genes; and (ii) among the variety of autoantibodies occurring in this model of SLE, both anti-GBM and anti-RTE autoantibodies play a key role in the pathogenesis of glomerulonephritis."

J Immunol 2002 Mar 1;168(5):2470-4. **A unique combination of inflammatory cytokines enhances apoptosis of thyroid follicular cells and transforms nondestructive to destructive thyroiditis in experimental autoimmune thyroiditis.** Wang SH, Bretz JD, Phelps E, Mezosi E, Arscott PL, Utsugi S, Baker JR Jr. "Compared with control animals, mice treated with IFN-gamma and TNF-alpha showed significantly sustained lymphocytic infiltration in the thyroid, which was associated with the destruction of portions of the follicular architecture at wk 6 after initial immunization." "Minimal apoptosis of thyroid epithelial cells was observed unless the mice were pretreated with IFN-gamma and TNF-alpha. These data demonstrate that this unique combination of inflammatory cytokines facilitates the apoptotic destruction of thyroid follicular cells in experimental autoimmune thyroiditis, in a manner similar to what is observed in Hashimoto's thyroiditis in humans."

Presse Med 2002 Oct 26;31(35):1670-5. **[Hypothyroidism related to excess iodine]** Wemeau JL. "Iodine-induced hypothyroidism is observed in fetuses, newborn, adults and in the elderly. It is observed in individuals without underlying overt thyroid disorder, and specially in patients with autoimmune thyroiditis or those previously treated for thyroid diseases (Graves' disease, subacute or pospartum thyroiditis, iatrogenic thyroid dysfunction...)." "The hormone deficiency is of obvious clinical expression, or sometimes discreet and revealed by hormone exploration. It is usually temporary, regressing with a few days or weeks after iodine withdrawal. Nevertheless, some patients require transient hormone replacement therapy."

Clin Exp Immunol 1982 Apr;48(1):196-200. **Thyroid antibodies are produced by thyroid-derived lymphocytes.** Weetman AP, McGregor AM, Lazarus JH, Hall R. "The significance of the characteristic lymphocytic infiltrate in the target organ in organ-specific autoimmune disease is unknown." **"The thyroid appears to be an important site of thyroglobulin antibody production but the thyroid lymphocytes also contain many** IgG PFCs of non-thyroglobulin specificity."

Nephrol Dial Transplant 1993;8(5):402-6. **Increased prevalence of thyroid peroxidase antibodies (TPO-Ab) in women with Glomerulonephritis.** Westman KW, Erfurth EM, Hagmar L, Bygren PG, Ericsson UB, Landin-Olsson M. "Women with glomerulonephritis had both a significantly greater prevalence of thyroid peroxidase antibodies (odds ratio 3.85, 95% confidence interval 1.04-14.3) and an increased prevalence of elevated serum TSH values (P = 0.007). No such difference was found in men."

Baillieres Clin Rheumatol 1996 May;10(2):259-71. **Hormones and autoimmunity: animal models of arthritis.** Wilder RL. "Hormones, particularly those involved in the hypothalamic-pituitary-gonadal and -adrenal axes (HPG and HPA), play important roles in various animal models of autoimmunity such as systemic lupus erythematosus in mice and collagen-induced arthritis (CIA) in mice and rats, and the streptococcal cell wall, adjuvant and avridine arthritis models in rats. Intimately linked to the subject of hormones and autoimmunity are gender, sex chromosomes and age." **"Oestrogens stimulate higher corticosteroid responses in females. The animal model data have major implications for understanding autoimmunity in humans.** In particular, adrenal and gonadal hormone deficiency is likely to facilitate T-cell dependent diseases like rheumatoid arthritis, while high oestrogen levels or effects, relative to testosterone, are likely to promote B-cell dependent immune-complex-mediated diseases such as lupus nephritis."

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