



Thyroiditis

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Introduction

- The term thyroiditis encompasses many relatively common thyroid disorders, which have been classified according to various schemes (Table 1).
- In this article we review the diagnosis and treatment of the different types of thyroiditis.





Table 1. Terminology for Thyroiditis.

Type	Synonyms
Hashimoto's thyroiditis	Chronic lymphocytic thyroiditis Chronic autoimmune thyroiditis Lymphadenoid goiter
Painless postpartum thyroiditis	Postpartum thyroiditis Subacute lymphocytic thyroiditis
Painless sporadic thyroiditis	Silent sporadic thyroiditis Subacute lymphocytic thyroiditis
Painful subacute thyroiditis	Subacute thyroiditis de Quervain's thyroiditis Giant-cell thyroiditis Subacute granulomatous thyroiditis Pseudogranulomatous thyroiditis
Suppurative thyroiditis	Infectious thyroiditis Acute suppurative thyroiditis Pyrogenic thyroiditis Bacterial thyroiditis
Drug-induced thyroiditis (amiodarone, lithium, interferon alfa, interleukin-2)	
Riedel's thyroiditis	Fibrous thyroiditis

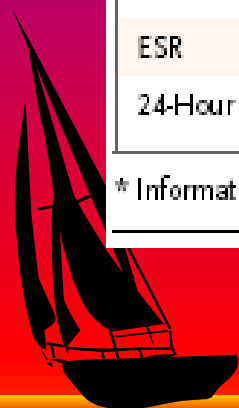




Table 2. Characteristics of Thyroiditis Syndromes.*

Characteristic	Hashimoto's Thyroiditis	Painless Postpartum Thyroiditis	Painless Sporadic Thyroiditis	Painful Subacute Thyroiditis	Suppurative Thyroiditis	Riedel's Thyroiditis
Age at onset (yr)	All ages, peak 30–50	Childbearing age	All ages, peak 30–40	20–60	Children, 20–40	30–60
Sex ratio (F:M)	8–9:1	—	2:1	5:1	1:1	3–4:1
Cause	Autoimmune	Autoimmune	Autoimmune	Unknown	Infectious	Unknown
Pathological findings	Lymphocytic infiltration, germinal centers, fibrosis	Lymphocytic infiltration	Lymphocytic infiltration	Giant cells, granulomas	Abscess formation	Dense fibrosis
Thyroid function	Hypothyroidism	Thyrotoxicosis, hypothyroidism, or both	Thyrotoxicosis, hypothyroidism, or both	Thyrotoxicosis, hypothyroidism, or both	Usually euthyroidism	Usually euthyroidism
TPO antibodies	High titer, persistent	High titer, persistent	High titer, persistent	Low titer, or absent, transient	Absent	Usually present
ESR	Normal	Normal	Normal	High	High	Normal
24-Hour ¹²³ I uptake	Variable	<5%	<5%	<5%	Normal	Low or normal

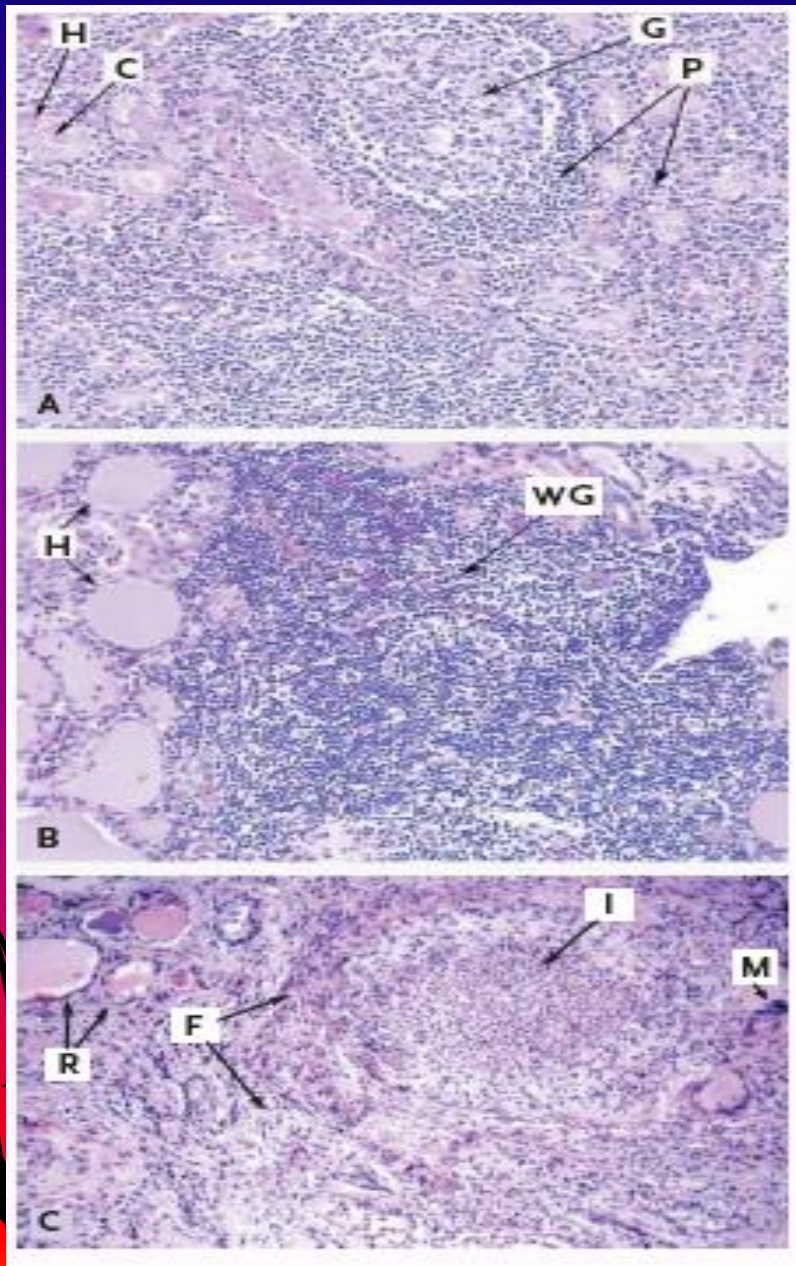
* Information is from Farwell and Braverman.¹ TPO denotes thyroid peroxidase, ESR erythrocyte sedimentation rate, and ¹²³I iodine-123.



Mechanisms of autoimmune thyroid destruction

- The mechanism for autoimmune destruction of the thyroid probably involves both cellular immunity and humoral immunity.
- Lymphocytic infiltration of the thyroid gland by equal numbers of B cells and cytotoxic T cells is a common histologic feature of all forms of autoimmune thyroiditis.





- **Figure 1. Specimens from Patients with Hashimoto's Thyroiditis (Panel A), Painless Postpartum Thyroiditis (Panel B), and Painful Subacute Thyroiditis (Panel C) (Hematoxylin and Eosin, .200).**
- The specimen in Panel A shows typical changes of Hashimoto's thyroiditis, including lymphoid follicles with germinal centers (G), small lymphocytes and plasma cells (P), thyroid follicles with Hürthle-cell metaplasia (H), and minimal colloid material (C). The specimen in Panel B, obtained from a patient with painless postpartum thyroiditis, shows normal follicles with minimal Hürthle-cell metaplasia (H) and dense lymphocytic infiltration (WG) without germinal centers. The specimen in Panel C, obtained from a patient with painful subacute thyroiditis, shows characteristic residual follicles (R), fibrotic bands (F), mixed inflammation (I), and a multinucleated giant cell (M).



Genetic susceptibility

- The genetics of autoimmune thyroid disease are complex.
- Association of Hashimoto's thyroiditis and painless postpartum thyroiditis with HLA-DR3, HLA-DR4, and HLA-DR5 has been reported in white persons, but other associations have been observed in other racial and ethnic groups.





- The cytotoxic-T-lymphocyte–associated protein 4 (CTLA-4) gene region may be associated with familial Hashimoto's thyroiditis, although a clear linkage has been difficult to demonstrate.
- Studies of the association between painless postpartum thyroiditis and the CTLA-4 gene have been negative.
- There is a higher incidence of subacute thyroiditis in those with the HLA-Bw35 haplotype.



Environmental factors



- Among patients with Hashimoto's thyroiditis, hypothyroidism is more likely to develop in **smokers than in nonsmokers**, a finding that may be related to the presence of thiocyanates in cigarette smoke.
- An increased prevalence of painless postpartum thyroiditis has also been noted among **smokers**.
- In addition, **geographic variations** in the incidence of Hashimoto's thyroiditis, painless postpartum thyroiditis, and painless sporadic thyroiditis suggest that **dietary iodine insufficiency** may be protective against autoimmune thyroiditis.



Clinical and biochemical changes in thyroiditis



- The various forms of thyroiditis may cause thyrotoxicosis, hypothyroidism, or both.



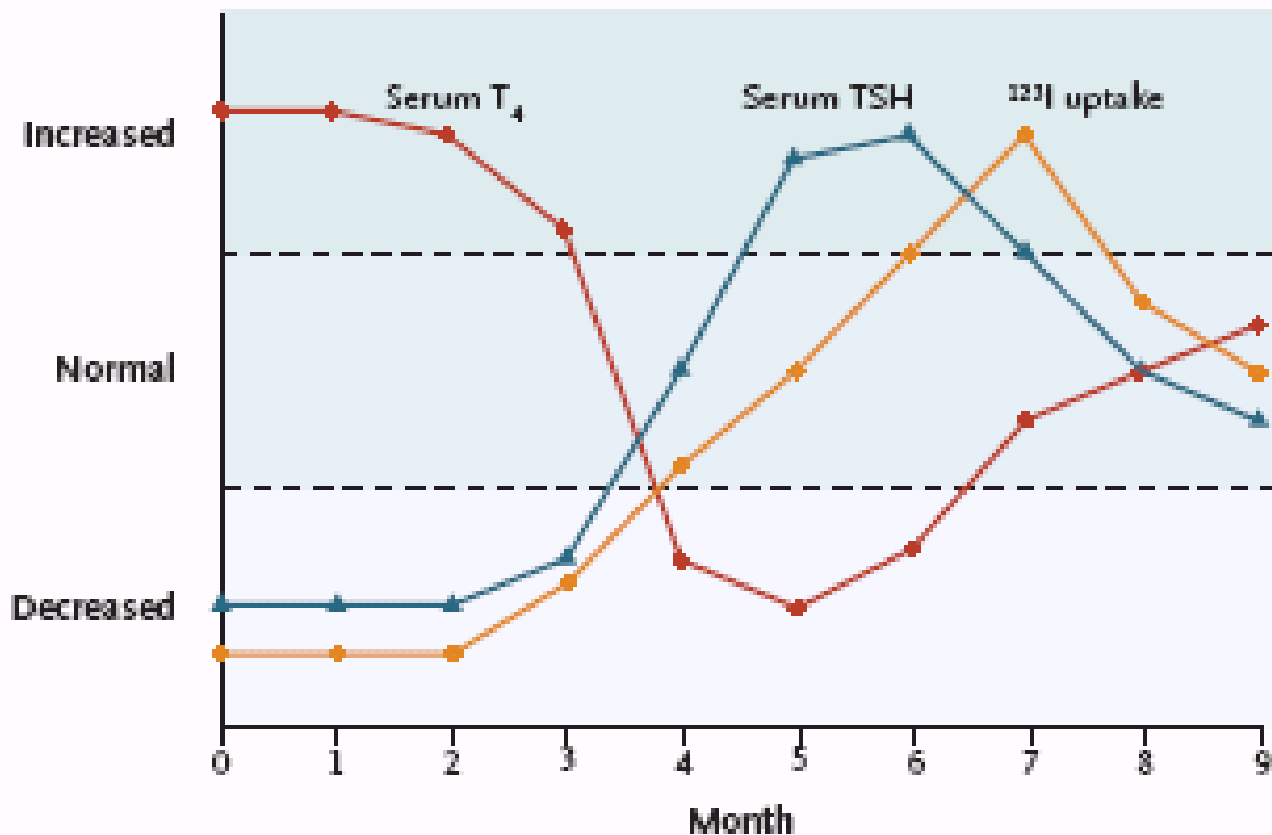


Figure 2. Clinical Course of Painful Subacute Thyroiditis, Painless Postpartum Thyroiditis, and Painless Sporadic Thyroiditis.

Measurements of serum thyrotropin (TSH) and iodine-123 (¹²³I) uptake show thyrotoxicosis during the first three months, followed by hypothyroidism for three months and then by euthyroidism. T₄ denotes thyroxine.



Thyrotoxicosis

- In painless sporadic thyroiditis, painless postpartum thyroiditis, and painful subacute thyroiditis, inflammatory destruction of the thyroid may lead to transient thyrotoxicosis as preformed thyroid hormones are released from the damaged gland.
- The first biochemical change in inflammatory thyroiditis before the onset of thyrotoxicosis is an increase in the serum concentration of thyroglobulin.





- As in other forms of thyrotoxicosis, the serum concentration of thyrotropin is suppressed, and concentrations of total and free triiodothyronine (T3) and thyroxine (T4) are elevated.
- The signs and symptoms of thyrotoxicosis due to thyroiditis are usually not severe.





Hypothyroidism

- The hypothyroid phase of thyroiditis results from the gradual depletion of stored thyroid hormones.
- Although chronic hypothyroidism is most closely associated with Hashimoto's thyroiditis, all types of thyroiditis may progress to permanent hypothyroidism.
- This outcome is more likely in patients with higher serum concentrations of thyroid antibodies or in patients in whom a more severe hypothyroid phase develops.





- The combination of elevated serum thyrotropin concentrations and normal free T4 and T3 concentrations is termed “subclinical hypothyroidism,” or “mild thyroid failure.”
- As thyroid failure progresses, serum T4 concentrations fall, and the combination of elevated thyrotropin concentrations and low T4 concentrations is termed “overt hypothyroidism.”
- In most patients, once the serum T3 concentrations fall below the normal level, the classic symptoms and signs of hypothyroidism appear.





Types of thyroiditis

- Hashimoto's thyroiditis
- Painless postpartum thyroiditis
- Painless sporadic thyroiditis
- Painful subacute thyroiditis
- Suppurative thyroiditis
- Drug-induced thyroiditis
- Riedel's thyroiditis



Hashimoto's thyroiditis



- Hashimoto's thyroiditis , which is characterized by the presence of **high serum thyroid antibody concentrations** and **goiter**, is the most common type of thyroiditis.
- A **firm, bumpy, symmetric, painless goiter** is frequently the initial finding in Hashimoto's thyroiditis.
- About 10 percent of patients with chronic autoimmune hypothyroidism have **atrophic thyroid glands (rather than goiter)**, which may represent the final stage of thyroid failure in Hashimoto's thyroiditis.





- High serum thyroid peroxidase antibody concentrations are present in 90 percent of patients with Hashimoto's thyroiditis, and high serum thyroglobulin antibody concentrations are present in 20 to 50 percent of these patients.
- The thyroid appears hypoechogenic on ultrasound examination.
- Once overt hypothyroidism is present, levothyroxine sodium is the treatment of choice for Hashimoto's thyroiditis.





- In patients with Hashimoto's thyroiditis and a large goiter, thyrotropin-suppressing doses of levothyroxine sodium can be given over the short term (i.e., six months) to decrease the size of the goiter.
- In most patients with Hashimoto's thyroiditis (whether their condition is euthyroid or hypothyroid), goiter size will decrease by 30 percent after six months of therapy with levothyroxine sodium.





- Although thyroid lymphoma is very rare, the risk of this disease is increased by a factor of 67 in patients with Hashimoto's thyroiditis.
- Patients with Hashimoto's thyroiditis and a dominant thyroid nodule should undergo fine-needle aspiration biopsy to rule out lymphoma and thyroid carcinoma.





Painless postpartum thyroiditis

- Painless postpartum thyroiditis causes lymphocytic inflammation of the thyroid within the first few months after delivery.
- The disease is most common in women who have high serum thyroid peroxidase antibody concentrations during the first trimester of pregnancy or immediately after delivery and in those with other autoimmune disorders, such as type 1 diabetes mellitus, or with a family history of autoimmune thyroid disease.





- In only one third of patients with painless post-partum thyroiditis will the classic triphasic thyroid hormone pattern develop .
- Thyrotoxicosis typically begins one to six months after delivery and lasts for one to two months.
- That phase may be followed by a hypothyroid phase starting four to eight months after delivery and lasting four to six months.
- Eighty percent of women recover normal thyroid function within a year; in one follow-up study, however, permanent hypothyroidism developed within seven years in 50 percent of the women studied.





- Chronic hypothyroidism is more likely in **multiparous women** or in those with a history of **spontaneous abortion**.
- After a first episode of painless postpartum thyroiditis, there is a **70 percent chance of recurrence with subsequent pregnancies**.
- In most cases of painless postpartum thyroiditis, a small, nontender, firm goiter is present.
- High serum concentrations of thyroid peroxidase antibodies, thyroglobulin antibodies, or both, are also present.





- The 24-hour ^{123}I uptake may be used to distinguish painless postpartum thyroiditis from postpartum Graves' disease; the uptake is low (<5 percent) in women with painless postpartum thyroiditis, whereas it is elevated in those with Graves' disease.
- Mild thyrotoxicosis rarely requires therapy, but when the disease is severe, it is treated with beta blockers.
- Antithyroid drug therapy is contraindicated, because there is no excess thyroid hormone production.





- Treatment of the hypothyroid phase may not be necessary, but if this phase is prolonged or if the patient is symptomatic, levothyroxine sodium should be given, then withdrawn after six to nine months to determine whether thyroid function has normalized.





Painless sporadic thyroiditis

- Painless postpartum thyroiditis and painless sporadic thyroiditis are **indistinguishable** except by the relation of the former to pregnancy.
- Painless sporadic thyroiditis may account for about **1 percent** of all cases of thyrotoxicosis.
- The clinical course is **similar** to that of painless postpartum thyroiditis.





- Although abnormalities in thyroid function resolve in most patients, 20 percent of patients will have residual chronic hypothyroidism.
- Symptoms are usually mild.
- A small, nontender, very firm, diffuse goiter is present in 50 percent of these patients.
- High serum thyroid peroxidase antibody concentrations are present in 50 percent of patients at the time of diagnosis, with lower titers, on average, than in Hashimoto's thyroiditis.





- A low or undetectable concentration of ^{123}I at 24 hours can be diagnostic, and the test should be performed when the cause of the thyrotoxicosis is unclear, in order to avoid inappropriate treatment with antithyroid drugs.
- Therapy is the same as that for painless postpartum thyroiditis.







Painful subacute thyroiditis

- Painful subacute thyroiditis , which is a **selflimited inflammatory disorder**, is the most common cause of thyroid pain.
- It occurs in up to **5 percent** of patients with clinical thyroid disease.
- It frequently follows an **upper respiratory tract infection**, and its incidence is highest in summer, correlating with the peak incidence of enterovirus.



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- Subacute thyroiditis begins with a prodrome of generalized myalgias, pharyngitis, low-grade fever, and fatigue.
 - Patients then present with fever and severe neck pain, swelling, or both.
 - Up to 50 percent of patients have symptoms of thyrotoxicosis.
 - In most patients, thyroid function will be normal after several weeks of thyrotoxicosis, and hypothyroidism will subsequently develop, lasting four to six months, as in painless sporadic thyroiditis and painless postpartum thyroiditis.



- The hallmark of painful subacute thyroiditis is a markedly elevated erythrocyte sedimentation rate.
- The C-reactive protein concentration is similarly elevated.
- The leukocyte count is normal or slightly elevated.
- Peripheral-blood thyroid hormone concentrations are elevated, with ratios of T4 to T3 of less than 20, reflecting the proportions of stored hormone within the thyroid, and serum concentrations of thyrotropin are low or undetectable.
- Serum thyroid peroxidase antibody concentrations are usually normal.



- The 24-hour ^{123}I uptake is **low (<5 percent)** in the toxic phase of subacute thyroiditis, distinguishing this disease from Graves' disease.
- The treatment for painful subacute thyroiditis is to **provide symptomatic relief only**. Nonsteroidal medications or salicylates are adequate to control mild thyroid pain.
- For more severe thyroid pain, **high doses of glucocorticoids** (e.g., 40 mg of prednisone daily) provide immediate relief; doses should be tapered over a period of four to six weeks.
- Corticosteroids should be **discontinued** when the ^{123}I uptake returns to normal. Beta-blockade controls the symptoms of thyrotoxicosis.





- Therapy with **levothyroxine sodium** is **rarely required**, because the hypothyroid phase is generally mild and transient, but it is indicated for symptomatic patients.





Suppurative thyroiditis

- Suppurative thyroiditis is usually caused by **bacterial infection**, but fungal, mycobacterial, or parasitic infections may also occur as the cause.
- The thyroid is resistant to infection, because of its encapsulation, high iodide content, rich blood supply, and extensive lymphatic drainage, and suppurative thyroiditis is therefore rare.





- It is most likely to occur in patients with **preexisting thyroid disease** (thyroid cancer, Hashimoto's thyroiditis, or multinodular goiter), those with **congenital anomalies** such as a pyriform sinus fistula (the most common source of infection in children), and those who are **immunosuppressed**, elderly, or debilitated; it is particularly likely to occur in patients with the acquired immunodeficiency syndrome (AIDS), in whom *Pneumocystis carinii* and other opportunistic thyroid infections have been reported.





- Patients with suppurative bacterial thyroiditis are usually acutely ill with fever, dysphagia, dysphonia, anterior neck pain and erythema, and a tender thyroid mass.
- Symptoms may be preceded by an acute upper respiratory infection. The presentation of fungal infection, parasitic infection, mycobacterial thyroiditis, and opportunistic thyroid infection in patients with AIDS tends to be chronic and insidious.





- Thyroid function is **generally normal** in patients with suppurative thyroiditis, but both thyrotoxicosis and hypothyroidism have been reported.
- Leukocyte counts and erythrocyte sedimentation rates are **elevated**.
- Suppurative areas appear “**cold**” on radioactive-iodine scanning. **Fine-needle aspiration biopsy** with Gram’s staining and culture is the diagnostic test of choice.
- The therapy for suppurative thyroiditis consists of appropriate antibiotics and drainage of any abscess.
- The disease may prove fatal if diagnosis and treatment are delayed.





Drug-induced Thyroiditis

- Many medications can alter thyroid function or the results of thyroid-function tests.
- However, only a few are known to provoke autoimmune or destructive inflammatory thyroiditis. (*Amiodarone; Lithium; Interferon Alfa and Interleukin-2*)



Lithium induced thyroiditis

- In patients with preexisting thyroid autoimmunity, lithium may increase the serum thyroid antibody concentrations and lead to subclinical or overt hypothyroidism.
- Estimates of the prevalence of high serum thyroid antibody concentrations in patients receiving long-term treatment with lithium range from 10 to 33 percent.
- In addition, thyrotoxicosis has been reported after long-term lithium use, possibly caused by lithium's direct toxic effects on thyroid cells or by lithium-induced painless sporadic thyroiditis.



Interferon Alfa and Interleukin-2 induced thyroiditis

- High serum thyroid peroxidase antibody concentrations in such patients and in patients receiving interleukin-2 therapy may be associated with overt or subclinical hyperthyroidism (Graves' disease) or hypothyroidism.
- Interferon alfa has also been reported to cause destructive inflammatory thyroiditis.





- The measurement of ^{123}I uptake helps to distinguish between drug-induced Graves' disease, in which the uptake is elevated, and **drug-induced inflammatory thyroiditis**, in which the uptake is **low**, in patients with thyrotoxicosis.
- When Graves' disease develops in patients receiving interferon alfa therapy, they should be treated with **antithyroid drugs**.
- While treatment with interferon alfa or interleukin-2 is continued, the thyrotoxic phase of inflammatory thyroiditis can be treated with **beta-blockers** and, if necessary, with **nonsteroidal antiinflammatory drugs** or **corticosteroids**, and the hypothyroidism can be treated with **levothyroxine sodium**.





- Although thyroid function usually normalizes when cytokine therapy is discontinued, affected patients are at increased risk for autoimmune thyroid dysfunction in the future.
- Thyroid-function tests and measurements of serum thyroid antibodies should be performed before therapy with interferon alfa or interleukin-2 is initiated and every six months thereafter.



Riedel's Thyroiditis



- Riedel's thyroiditis, a **local manifestation of a systemic fibrotic process**, is a progressive fibrosis of the thyroid gland that may extend to surrounding tissues.
- The prevalence of this disease is only **0.05 percent among patients** with thyroid disease requiring surgery, and its cause is unknown.
- High serum thyroid antibody concentrations are present in up to **67 percent of patients**, but it is unclear whether the antibodies are a cause or effect of the fibrotic thyroid destruction.





- Patients with Riedel's thyroiditis present with a **rock-hard, fixed, painless goiter**.
- They may have symptoms due to **tracheal or esophageal compression** or **hypoparathyroidism** due to extension of the fibrosis into adjacent parathyroid tissue.
- Most patients are **euthyroid at presentation** but become hypothyroid once replacement of normal thyroid tissue is nearly complete.





- A definitive diagnosis is made by open biopsy.
- The treatment is surgical, although therapy with glucocorticoids, methotrexate, and tamoxifen has been reported to be successful in the early stages of the disease.





The End

- Thank you for your attention.

