



Hypothyroidism: An Overview of Contemporary Understanding and Management

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Teaching Objectives

- To review hypothyroidism, its clinical syndromes, its etiologies, its diagnosis and its management
- To provide a special focus on the management of hypothyroidism, a state commonly encountered in clinical medical practice





Ancient relief depicting Cleopatra with a goiter.





Sacro monte of Varallo. Terracotta figure. Negroid henchman with a giant goitre.



Domenico Fetti , *Giovane mendicante.*



Goitre operation in the Turkish manuscript of CHARAF ED-DIN. Bibliothèque Nationale, Paris (Ms. Suppl. turc. 693, Fol. 85).



Sketches by MICHELANGELO in the margin of his Sonnet V. Ironically he portrays himself with a large goitre and his head bent back, painting a grotesque figure on the ceiling.



HANS WEIDITZ. Uelin Mair and his wife. Broadsheet
wood engraving c. 1521. Gotha, Landesmuseum.







Emergence of Hypothyroidism as a Defined Clinical Syndrome

- Victor Horsley -- association of thyroid removal and clinical hypothyroidism
- The term, “myxedema” designated by William Ord
- Reverdin and Kocher demonstrated that thyroid gland removal was associated with the myxedematous state



Emergence of Hypothyroidism as a Defined Clinical Syndrome, continued

- “Report on Myxedema” promulgated by the Clinical Society of London (May 25, 1888)
- Early “hormone replacement experiments” of Charles-Edouard Brown-Sequard
- Crude extract of sheep thyroid injected into a myxedematous patient



Clinical Society's Report on Myxœdema, Plate I.



Fig. 1.



Fig. 2.



Fig. 3.

From Photographs.

Danielsson & Co, lith.



FIG. 14.—M. H., ADVANCED MYXEDEMA AT COMMENCEMENT OF TREATMENT, WHEN THE DISEASE HAD LASTED FOR TWELVE YEARS.



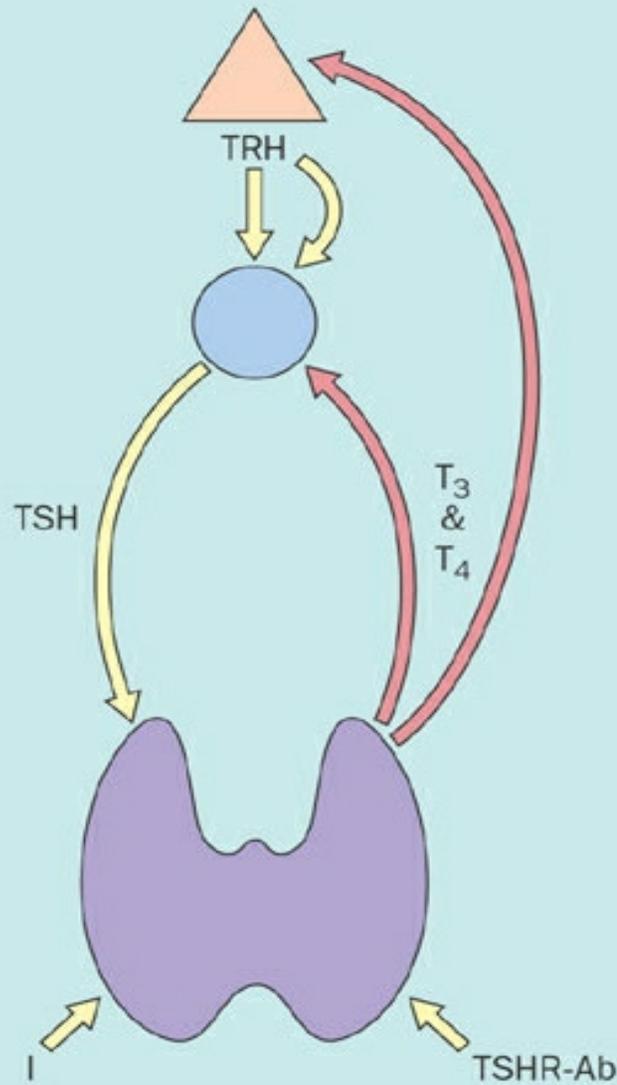
FIG. 15.—M. H., AFTER TREATMENT FOR SEVEN MONTHS



Pathophysiologic Principles

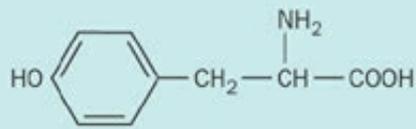
- Relationship between TRH and TSH, and the role of the T3 concentration
- Mechanisms of action of TSH
- Release of thyroid hormone
- Conversion of T4 to T3
- T3 initiation of transcriptional processes

Positive and negative feedback loops acting on the hypothalamic-pituitary-thyroid axis

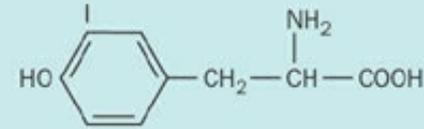




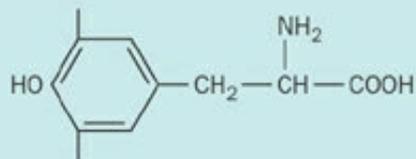
Thyroid hormones and related compounds



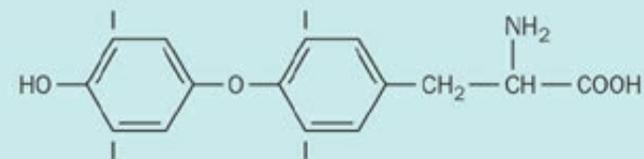
Tyrosine



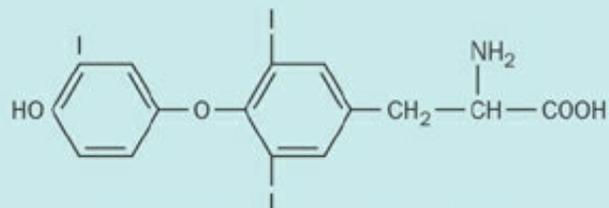
3-iodotyrosine (MIT)



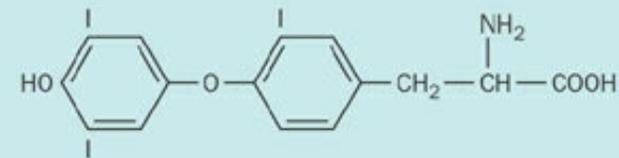
3,5-diiodotyrosine (DIT)



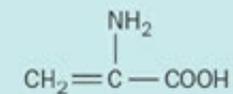
Thyroxine (T₄)



3,5,3'-triiodothyronine (T₃)



3,3',5'-triiodothyronine (reverse T₃)



Dehydroalanine (DHA)



Cutaneous Features of Hypothyroidism

- Boggy, but non-pitting edema
- Cold pallor
- Hypercarotenemia and “yellowish tint”
- Hyperpigmentation if associated with Addison’s Disease
- Hyperkeratosis
- Dry and brittle hair
- Absent lateral eyebrow hair





Gastrointestinal Features of Hypothyroidism

- Decreased peristaltic activity
- Rarely is there overt obesity
- Ascites seen only with other effusions
- Association with achlorhydria and impaired intrinsic factor production
- Abnormal hepatic chemistries
- Decreased taste
- Association with Celiac Disease



Neurologic Features of Hypothyroidism

- Lethargy, mental sluggishness, intellectual impairment and dementia
- Psychiatric manifestations
- Abnormal EEG; elevated CSF protein
- Hearing loss and impaired night vision
- DTR delay; carpal and tarsal tunnel syndromes



Muscular Features of Hypothyroidism

- Muscular cramps, aching, and stiffness
- Pseudohypertrophy
- Decreased urinary creatinine and increased creatine tolerance
- Increased prevalence of hyperuricemia and gout



Skeletal Features of Hypothyroidism

- Rheumatic symptoms
- Joint effusions
- Impaired bone growth and maturation
- Decreased bone turnover



Cardiovascular Features of Hypothyroidism

- Decreased myocardial inotropic and chronotropic contractility
- Hypertension
- Tendency to a large flabby heart suggestive of congestive heart failure, but with normal response to exercise and the Valsalva maneuver
- Hypercholesterolemia secondary to decreased cholesterol metabolism



Cardiovascular Features of Hypothyroidism, continued

- Abnormal serum enzymes
- EKG changes
- Abnormal systolic time intervals
- Pericardial effusion



Pulmonary Features of Hypothyroidism

- Pleural effusion
- Decreased diffusing capacity and voluntary ventilation capacity
- Central and obstructive sleep apnea
- Hypoventilation secondary to respiratory muscle weakness and reduced pulmonary responses to hypercapnia and hypoxia



Hematopoietic Features of Hypothyroidism

- Normocytic, normochromic anemia
- Macrocytic anemia
- Hypochromic, microcytic anemia
- Decreased factors VIII and IX
- Decreased platelet adhesion



Renal Features of Hypothyroidism

- Decreased glomerular filtration rate and renal blood flow
- Tendency to hyponatremia



Endocrinologic Features of Hypothyroidism

- Increased pituitary size
- Increased serum prolactin
- Decreased adrenocortical metabolites
- Decreased pituitary sensitivity to hypoglycemia
- Decreased cAMP response to catecholamines



Reproductive System Features of Hypothyroidism

- Menstrual irregularities in women – both oligo-amenorrhea or hypermenorrhea-menorrhagia can occur with resultant decreased fertility
- Hypogonadism in men – decreased libido and erectile dysfunction
- Decreased sex hormone binding globulin

Etiologies of Primary Hypothyroidism: Congenital Hypothyroidism



- Structural defects are the most common, but hormone synthetic and action defects can also occur
- Incidence and clinical effects
- Role of postpartum screening

Etiologies of Primary Hypothyroidism: Iodine Deficiency



- Normal urinary iodine excretion and deficiencies
- Geographic pervasiveness of iodine deficiency
- Significance of Jod-Basedow

Etiologies of Primary Hypothyroidism: Post-ablative Hypothyroidism



- Following complete surgical extirpation
- Following subtotal thyroidectomy
- Following radioactive iodine therapy
- Following neck irradiation

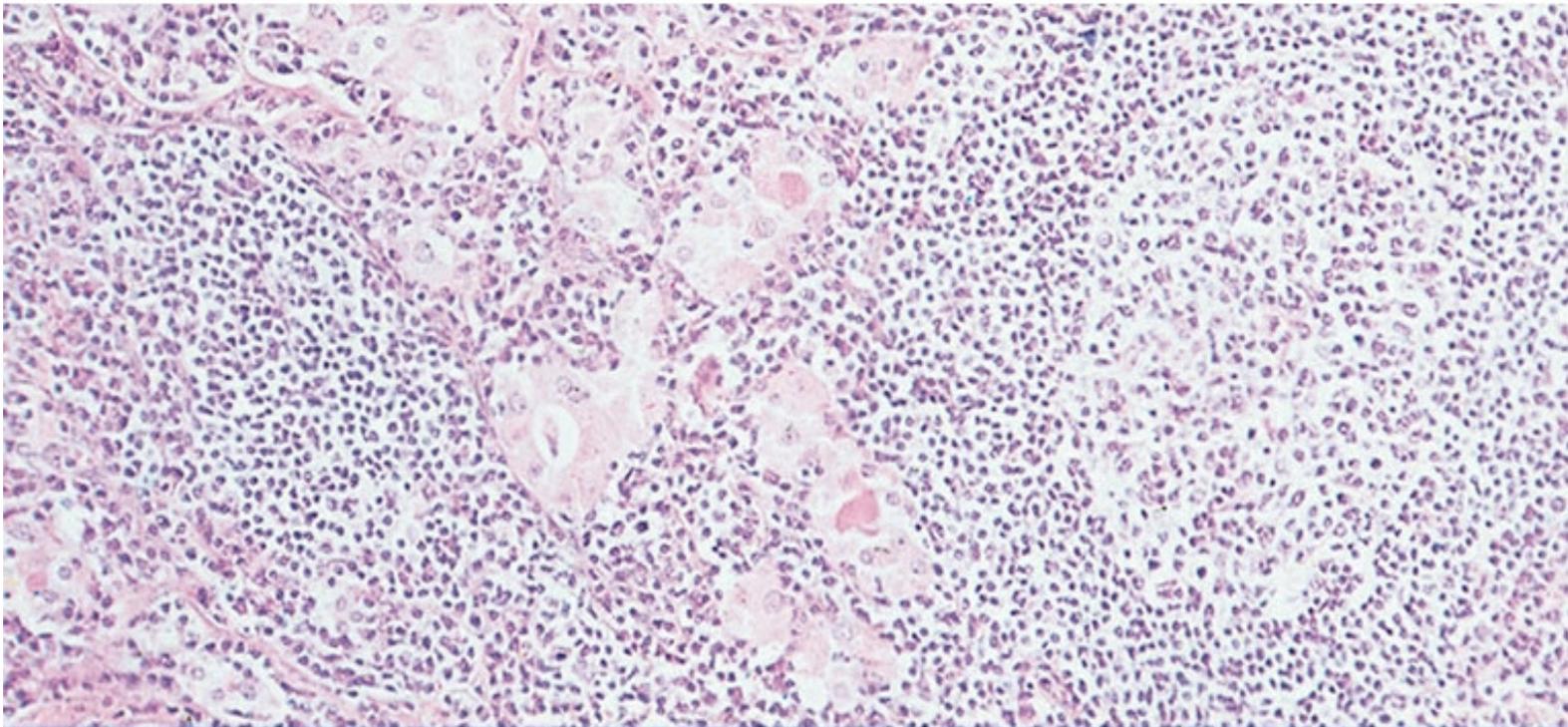
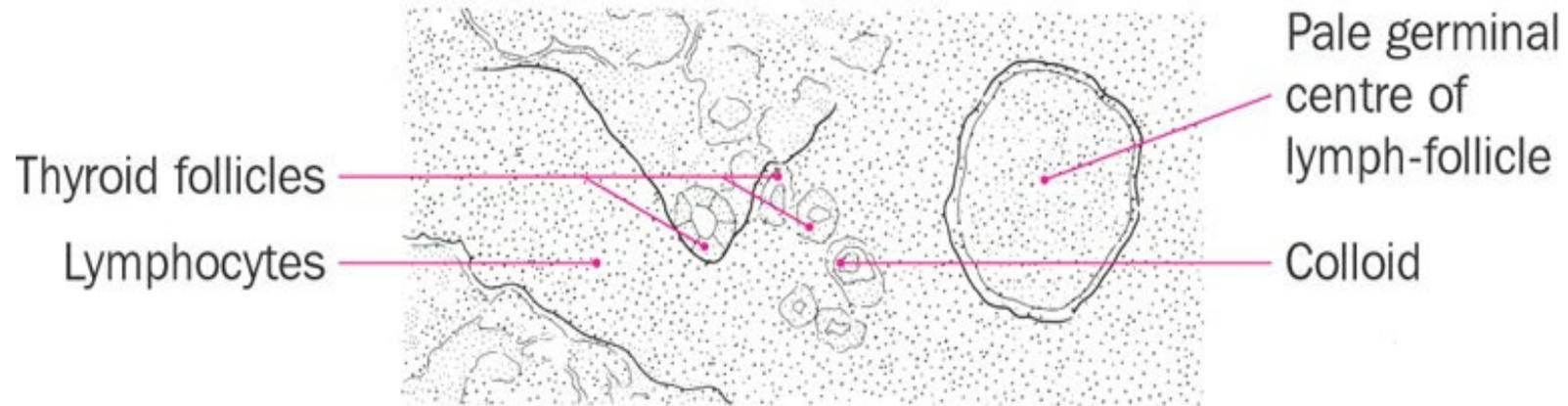


Etiologies of Primary Hypothyroidism: Chronic Autoimmune Thyroid Disease

- The most common cause of hypothyroidism
- Anti-thyroglobulin and anti-thyroperoxidase antibodies
- Role of antigen specific T cells
- Significant prevalence of disease processes
- Associated with other target organ auto-antibodies
- Contribution of Dr. Hakaru Hashimoto

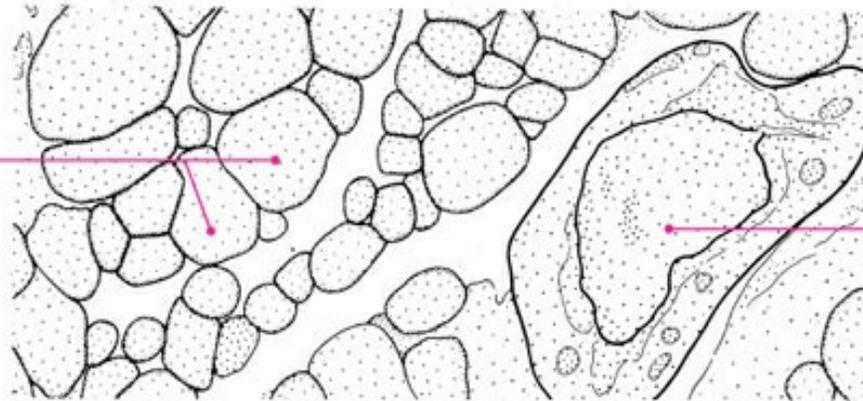


Hakaru Hashimoto

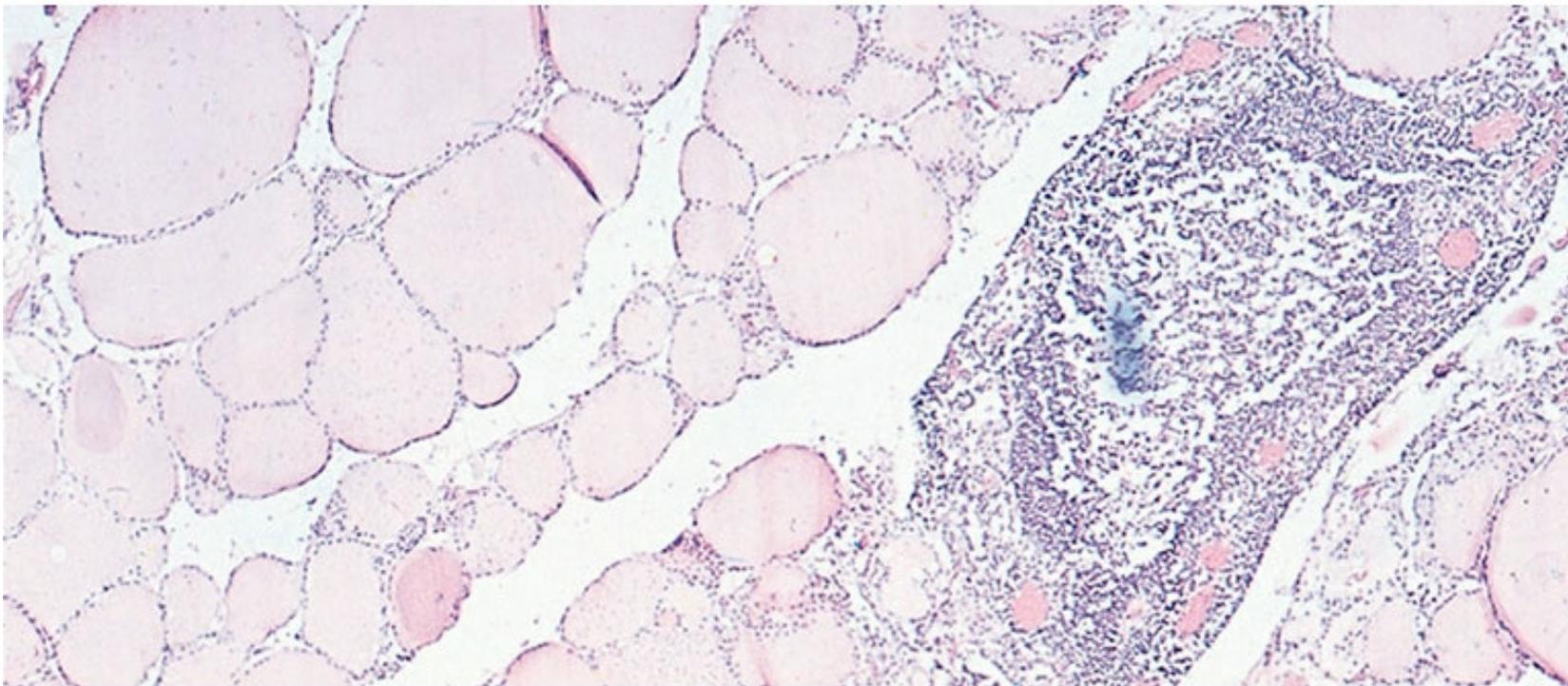




Normal follicles



Focal lymphoid
thyroiditis





Etiologies of Primary Hypothyroidism: Transient Hypothyroidism

- Classically seen in inflammatory thyroid diseases
- Syndrome of de Quervain's thyroiditis
- Development of hypothyroidism in painless inflammatory thyroid conditions
- Discriminating role of the radioactive iodine uptake test

Etiologies of Primary Hypothyroidism: Role of Iodine



- The Wolff-Chaikoff Effect
- Increased vulnerability in the setting of pre-existing thyroid disease
- Fetal syndromes

Etiologies of Primary Hypothyroidism: Miscellaneous Etiologies



- Associated with foods of the Cruciferae family
- Effect of lithium
- Role of other goitrogens
- TSH and Thyroid Hormone Resistance Syndromes
- In the proper setting, always consider secondary hypothyroidism

Etiologies of Primary Hypothyroidism: Subclinical Hypothyroidism



- Primary a “laboratory diagnosis”
- Most commonly associated with autoimmune thyroiditis
- High TSH, high antibody titer, and increased age are associated with greater progression to overt hypothyroidism
- Higher incidence in areas of iodine sufficiency



The Diagnosis of Hypothyroidism

- Role of pre-emptive screening
- Decreased FT4 and increased TSH as the mainstay of diagnosis
- Limited role of serum T3 evaluation



The Diagnosis of Hypothyroidism: Role of Ancillary Tests

- Ancillary tests may lead to confirmatory testing, or they may be corroborative of results of such studies
- Limited role of tests that measure the peripheral effect of thyroid hormone
- Adjunctive role of the radioactive iodine uptake



Subclinical Hypothyroidism – Overview

- By definition, hypothyroid function test results in the absence of a clearly defined hypothyroid clinical state
- Patient may come to medical attention because of symptomatology they, or their physician, feels may be hypothyroid related
- Perhaps affecting 10% of the population, with a greater incidence in white, older individuals, and women
- Most commonly seen with serologic evidence of autoimmune thyroid disease
- In Primary hypothyroidism, the serum TSH is the gold standard

Subclinical Hypothyroidism – Principles of Management



- Is not the ultimate goal of Medicine to diagnose and treat disease as proximate as possible to its inception?
- Do we not already diagnose other endocrinologic disease states before the clinical threshold is broached? (e.g. hyperparathyroidism, functioning adrenal incidentalomas, diabetes mellitus)
- Does not subclinical hypothyroidism inexorably progress to overt hypothyroidism? Yes, but the clinical diabetic state may reverse -- albeit with lifestyle changes.

Subclinical Hypothyroidism – Are There Clinical Consequences of the Untreated State?



- The data still remains controversial, but there may be an increased risk of cardiovascular disease and mortality, congestive heart failure, and deep vein thrombosis.
- The risk appears to correlate with TSH levels as does hypercholesterolemia and other surrogates of cardiovascular risk

Subclinical Hypothyroidism – Are There Clinical Consequences of the Untreated State? (Continued)



- Associated with an increased risk in pregnancy for miscarriage, low birth weight babies, and developmental dysfunction
- A correlation with both ultrasonic findings of non-alcoholic fatty liver disease (NAFLD), elevation of hepatic enzymes, and common duct biliary stones
- There are reports showing both a correlation and no correlation with neuropsychiatric disease
- May be associated with defects in memory and executive function, and with an increased risk of Alzheimer's disease

Subclinical Hypothyroidism – Who Should be Treated



- Patients with high titers of antithyroid antibodies are likely to become clinically hypothyroid and would likely benefit from thyroid hormone replacement therapy
- Pregnant women and women considering pregnancy should be treated – further, the TSH range in pregnancy is less than 2.5 for the first trimester (effect of HCG) and less than 3 in the second and third trimesters.

Subclinical Hypothyroidism – Why All the Fuss?



- We would never think of allowing someone already on thyroid hormone replacement therapy to have values outside the normal range, so why are we reticent to treat patients who initially present with values outside that range?
- Would we allow this to be a standard of care for diabetes mellitus, or other endocrine deficiency states?
- However, the upper limit of normal may be slightly higher in the elderly population, and that must be taken into consideration

Subclinical Hypothyroidism – Why All the Fuss? (Continued)



- Suppressed TSH levels are associated with an increased risk of atrial fibrillation and loss of bone density.
- But do we not monitor all of our patients on thyroid hormone replacement therapy?
- Yes, but 41% of patients over the age of 65 and on thyroid hormone replacement therapy have decreased TSH levels.
- Cost must always be a factor in drug prescribing. Generic L-thyroxine is among the most inexpensive of medications.

Subclinical Hypothyroidism – Why All the Fuss? (Continued)



- The modest goiter that may be associated with subclinical hypothyroidism may shrink, but this is an inconsequential issue.
- Treatment would certainly ward off “creeping hypothyroidism”
- If we start with the lowest possible doses of L-thyroxine replacement therapy (25 to 50 mcg/day), this will avoid overtreatment.
- In younger patients with an intact pituitary thyroid axis, the treatment dose could approach the full replacement dose of 1.6 mcg/Kg/day.

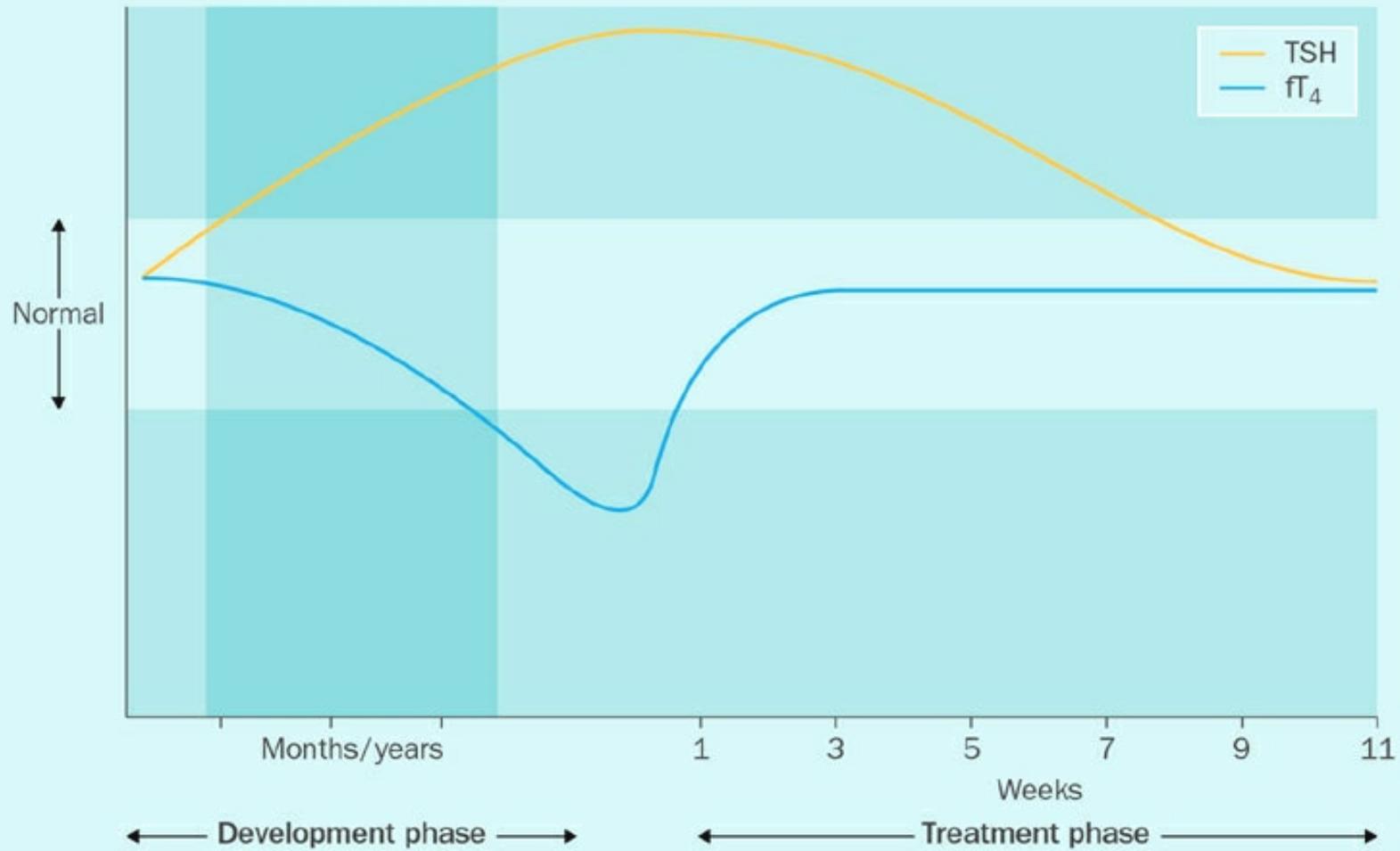
Treatment of Primary Hypothyroidism: Principles and Practices



- Role of L-thyroxine as recommended replacement therapy
- Changing dose requirements over time
- Role of the TSH assay as the gold standard
- T3 replacement medication does not appear to be necessary



Change in thyroid-stimulating hormone and free thyroxine levels over time during the development of hypothyroidism and after initiation of thyroxine replacement



Treatment of Primary Hypothyroidism: Principles and Practices, continued



- No role for desiccated thyroid
- Role of co-morbid conditions in determining hormone replacement dose and frequency of change
- Myxedema coma requires aggressive treatment
- Hierarchy of clinical improvement

Treatment of Primary Hypothyroidism: Principles and Practices, continued



- Hormone requirements decrease with age
- Pregnancy increases hormone requirements
- Drugs may affect thyroid hormone levels



Conclusion

- There is no disease entity that more classically bridges clinical observation with understanding of pathophysiologic principles
- While diagnosis can be made with exquisite exactness, such diagnosis and its resultant therapy must always be placed within the bounds of clinical observation and response





**AL GRANDUCA
PIETRO LEOPOLDO I
QUARANTA ANNI
DOPO
LA SUA MORTE**

