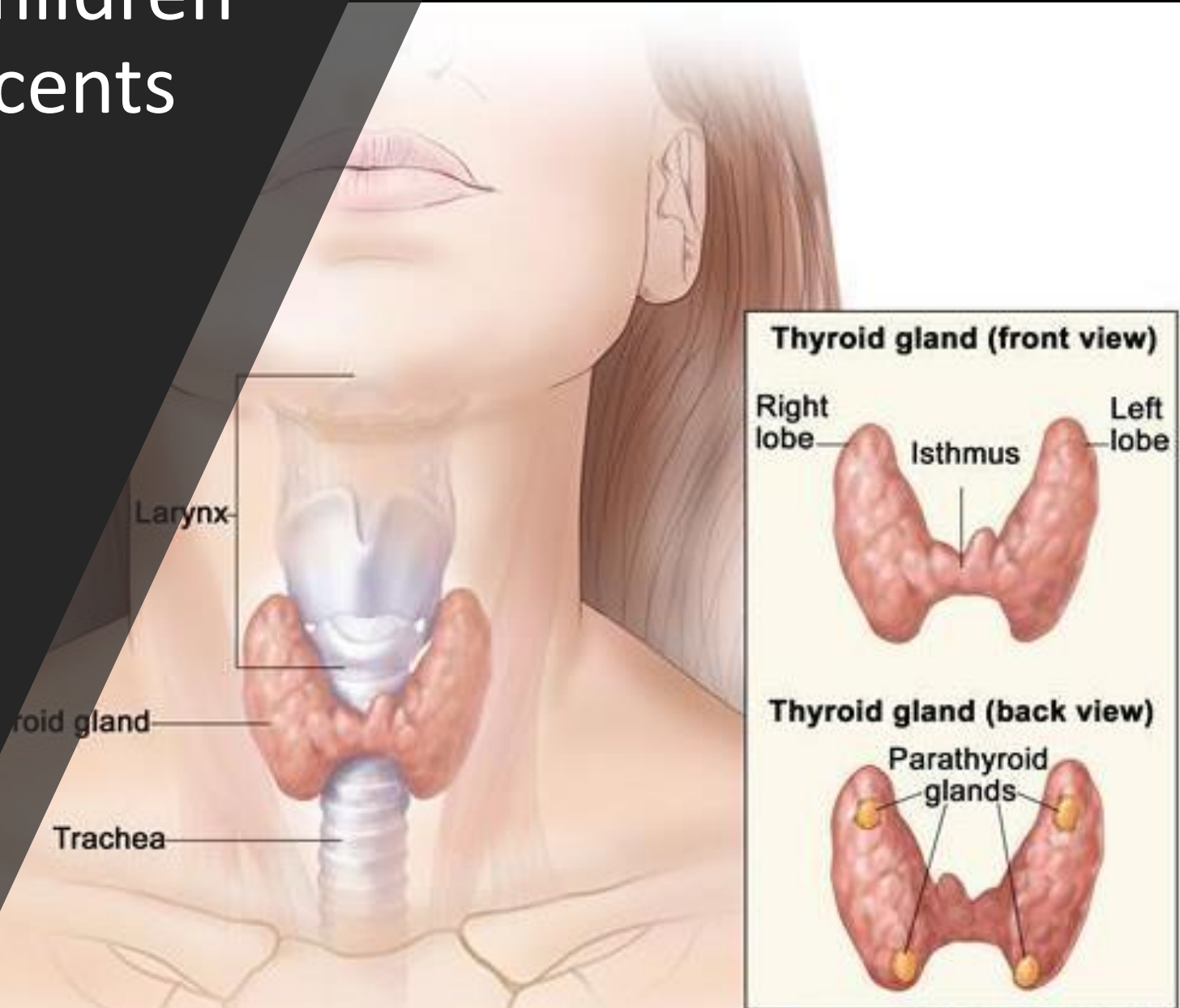


Thyroid Disorders in Children from Birth to Adolescents

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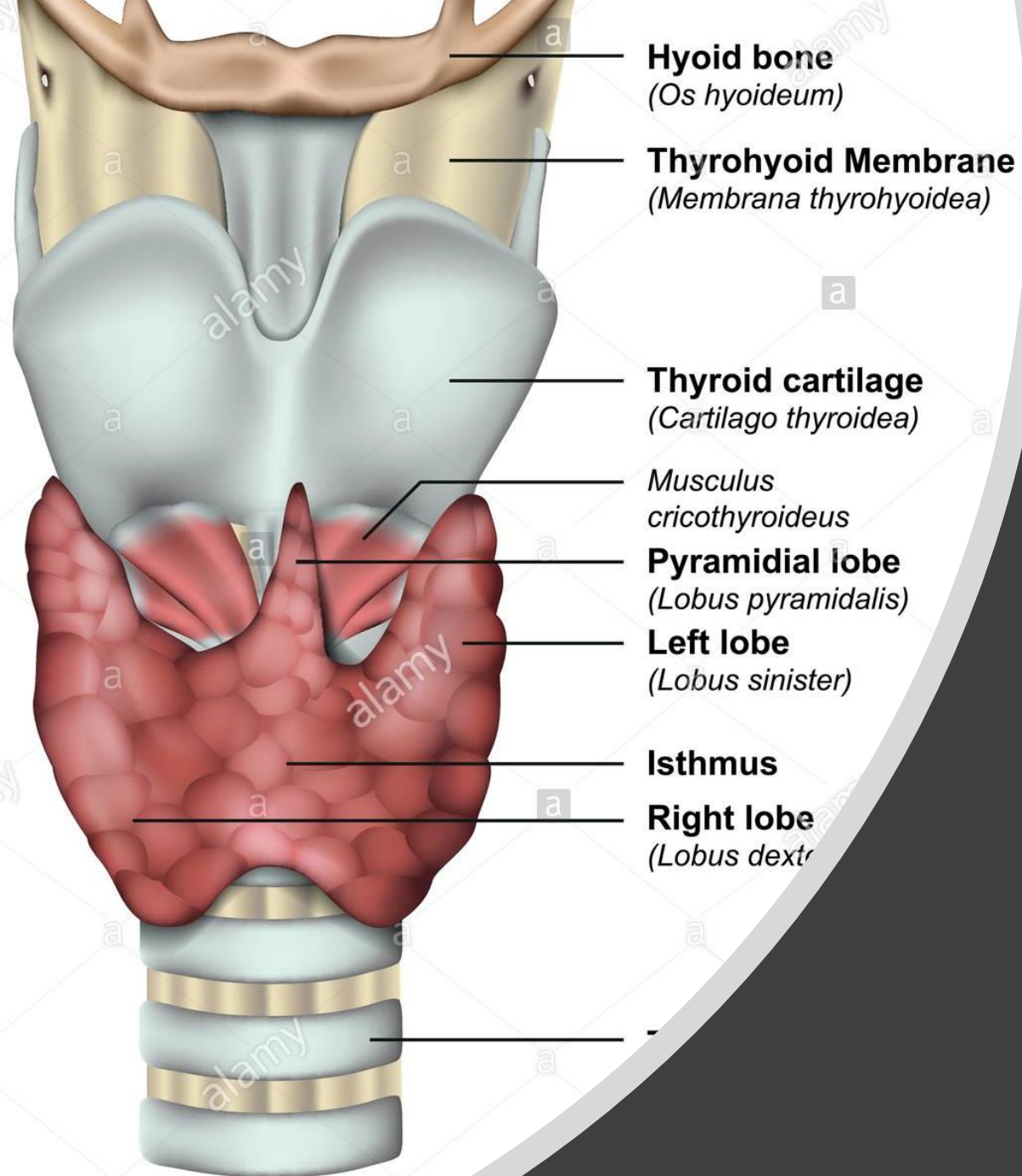
Objectives

- Introduction on thyroid gland regards, anatomy, physiology and thyroid hormone biosynthesis.
- Control and regulation of thyroid hormone synthesis.
- Physiological effects of thyroid hormones.
- Congenital hypothyroidism
 - Screening, causes & clinical presentations.
- Investigations & treatment of hypothyroidism.
- Thyrotoxicosis in children.
 - Investigation & treatment of Thyrotoxicosis.

Introduction

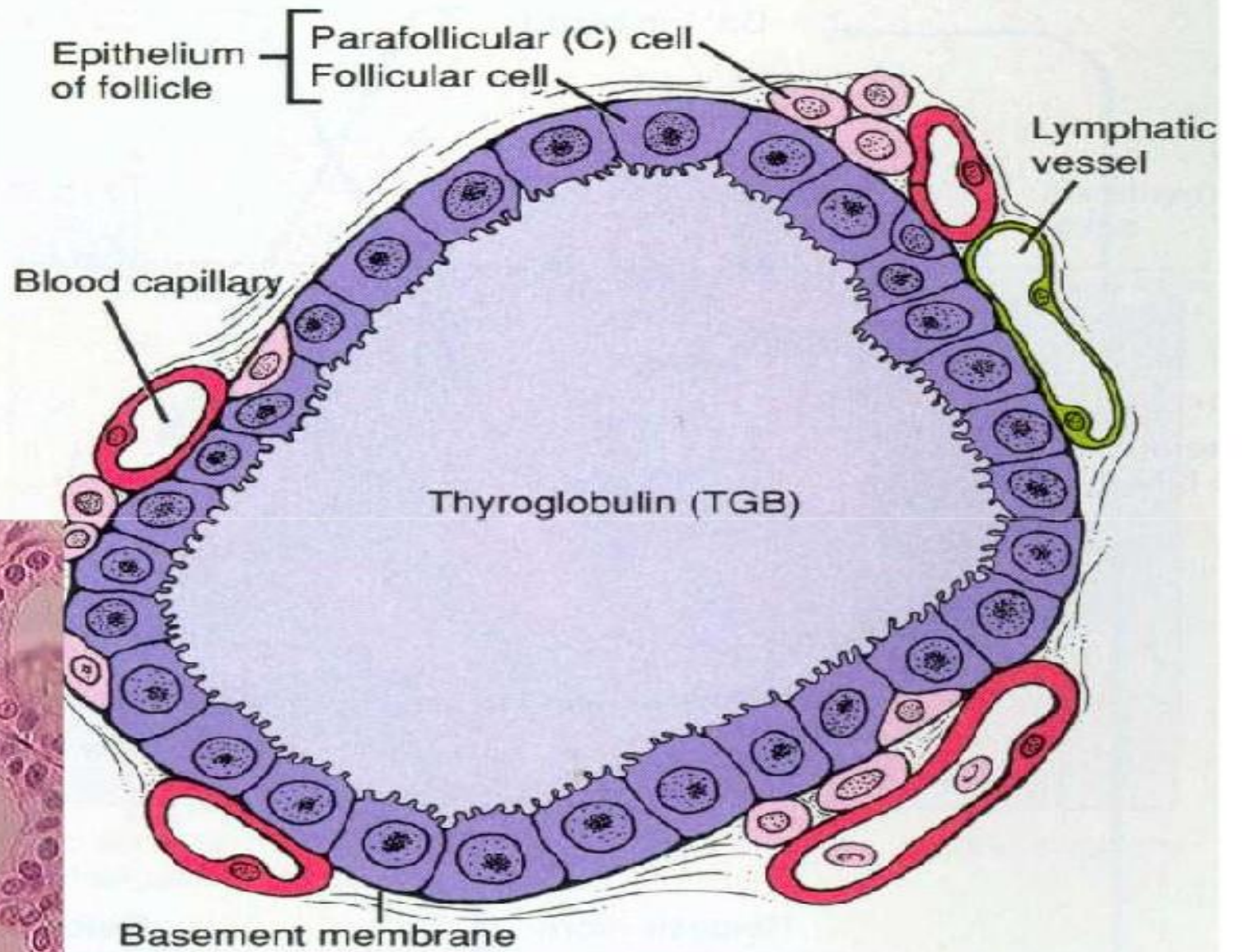
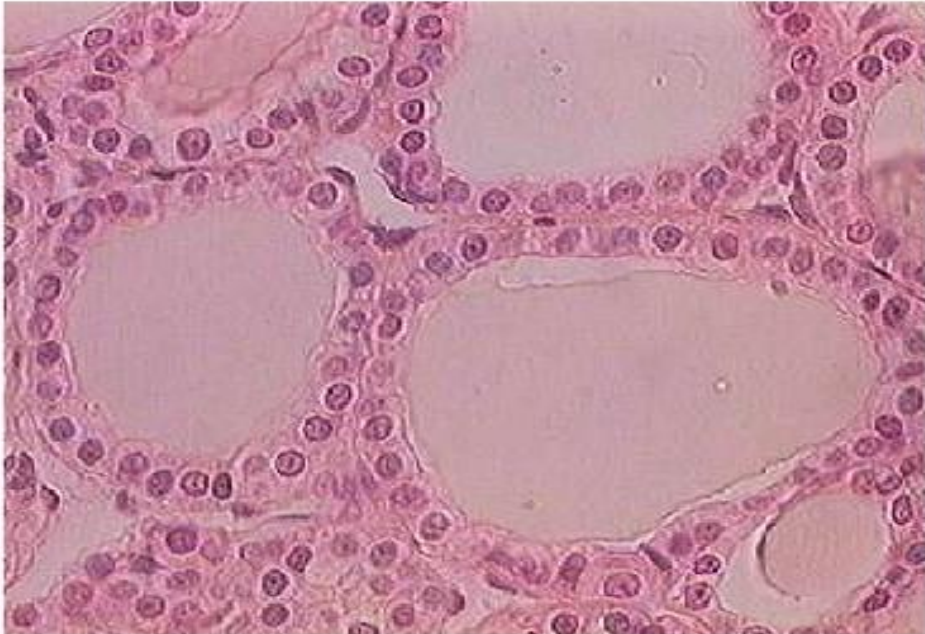
- Thyroid hormone is essential for somatic growth & neurological development in infancy & early childhood.
- Thyroid gland begins to develop at 4 weeks of gestation, while thyroid hormones are produced starting at 12 weeks gestation.
- Thyroxine is critical for the myelination of the central nervous system during the first 3 years after birth.
- Congenital hypothyroidism is the most preventable cause of potential intellectual disability.
- Thyroid hormones influence almost all aspects of normal child development and play a crucial role in growth, puberty, skeletal development & various tissues metabolism.

Anatomy



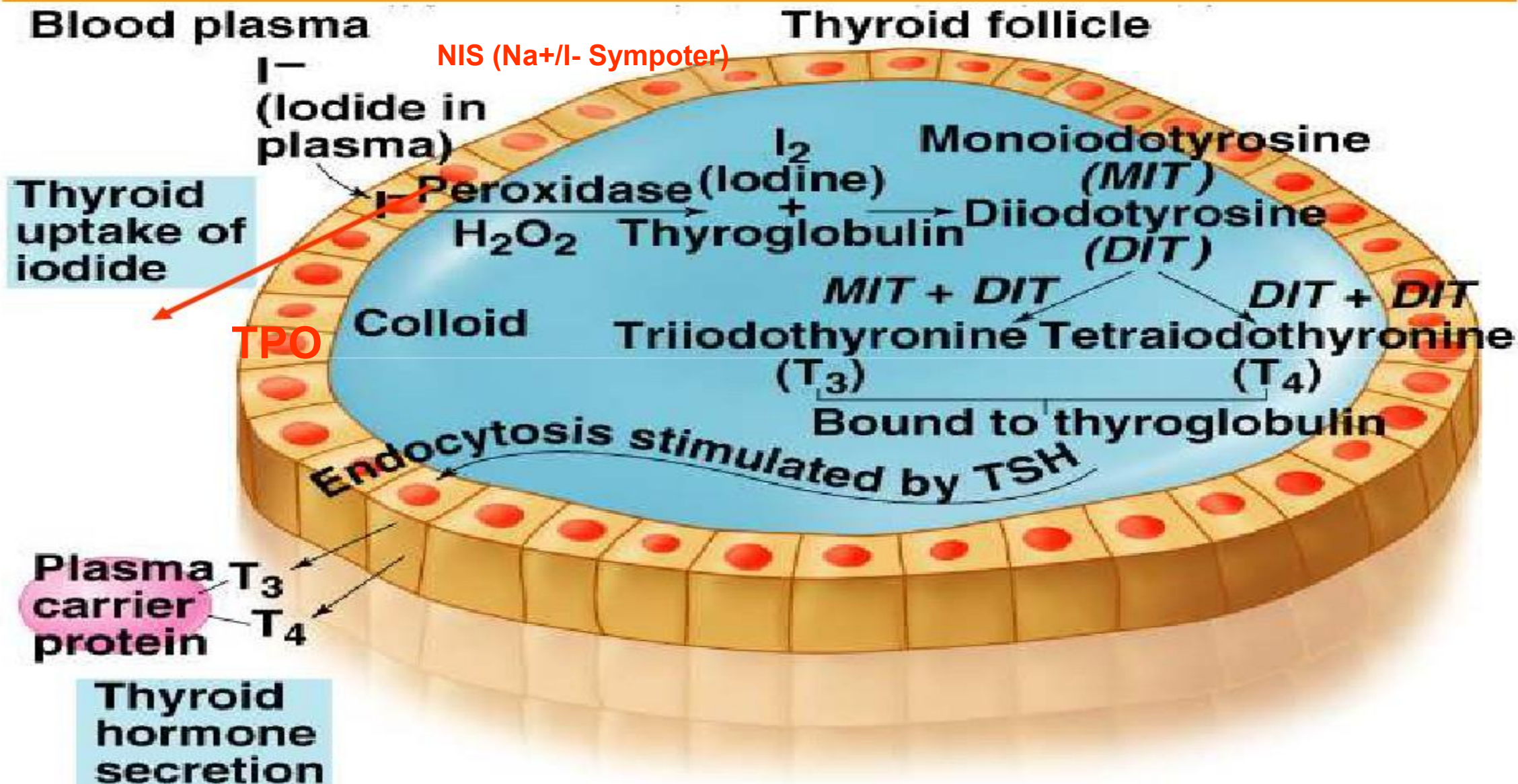
- The thyroid gland is formed from a midline outpouching of ectoderm of the primitive buccal cavity, which then migrates caudally.
- It consists of follicles made of colloid surrounded by follicular cells and basement membrane.
- Thyroid hormone is synthesized at a cellular level and stored in thyroglobulin, a glycoprotein that is the main constituent of the colloid.
- **Between the follicular cells are the parafollicular cells (C-cells), which are of neurogenic origin and secrete calcitonin.**

FUNCTIONAL
UNIT IS THE
FOLLICLE



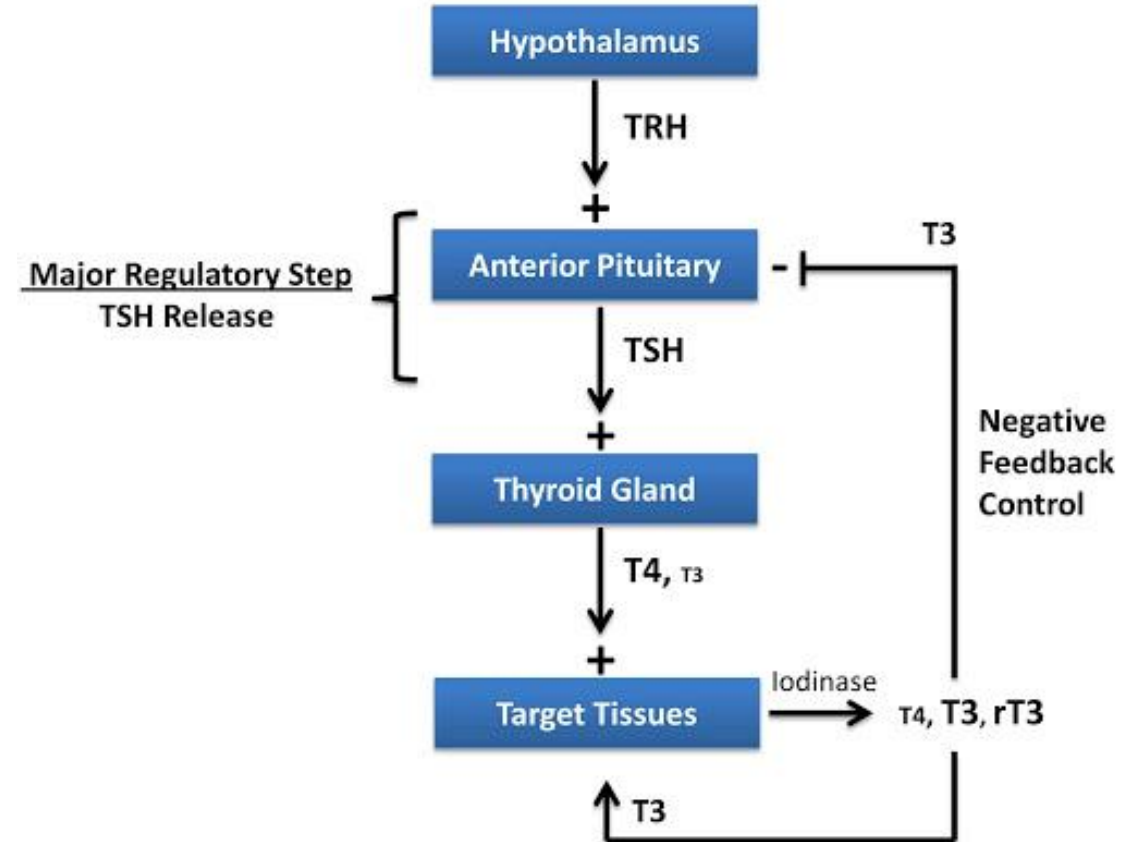
(b) Diagram of a single thyroid follicle

Thyroid Hormones synthesis



Control & Regulation

- TRH secreted from the hypothalamus stimulates TSH secretion from pituitary.
- Thyroid hormone release is regulated by TSH & iodine levels.
- TSH has many actions on thyroid hormone secretion:
 - Stimulates binding of iodide to protein.
 - Stimulates thyroid hormone release.
 - Stimulates pathways of intermediate metabolism.
 - Stimulates trapping of iodide.
 - Stimulates synthesis of thyroglobulin.
- Pharmacological doses of iodine block organification.



Physiological effects of thyroid hormones

- Fetal brain development which continues up age of three years.
- Skeletal maturation from birth until adolescence.
- Increase in basal metabolic rate.
- Inotropic & chronotropic effects on the heart.
- Increases sensitivity to catecholamines.
- Stimulates gut motility.
- Increase bone turnover.
- Stimulates gut motility.
- Increase in serum glucose & decrease in serum cholesterol.
- Conversion carotene to vitamin A.
- Play role in thermal regulation.



Congenital Hypothyroidism

Congenital hypothyroidism

- Is one of the most preventable causes of mental retardation in children.
- Incidence of 1/4000 live births.
- Most cases of thyroid dysgenesis are sporadic.
- **Primary persistent congenital hypothyroidism:**
 - Thyroid dysgenesis in 80 % of cases (agenesis, hypoplasia, ectopic gland).
 - Thyroid biosynthetic defects (Dyshormonogenesis) in 20% of cases.
- **Secondary congenital hypothyroidism:**
 - Congenital pituitary / hypothalamic abnormalities (idiopathic, Anencephaly, holoprosencephaly, S.O.D).

Screening for congenital hypothyroidism

- TSH is measured in Saudi Arabia from cord blood at birth, while in other countries heel prick samples are between 3-5 days of life.
- Screening program detects > 90% of cases of congenital hypothyroidism.
- Those secondary (pituitary/hypothalamic) are missed as TSH levels are low or normal.

Clinical manifestations of congenital hypothyroidism

- **Classical features include:**

- Macroglossia.
- hoarse cry.
- facial puffiness.
- umbilical hernia.
- hypotonia.
- mottling & cold extremities.
- lethargy.

- **Nonspecific features include:**

- prolonged unconjugated hyperbilirubinemia.
- gestation beyond 42 weeks.
- feeding difficulties.
- delayed passage of stool.
- hypothermia.
- respiratory distress in an infant weighing over 2.5 kgs.
- large anterior fontanelle and/or a persisting posterior fontanelle > 0.5 cm.

Clinical Manifestations



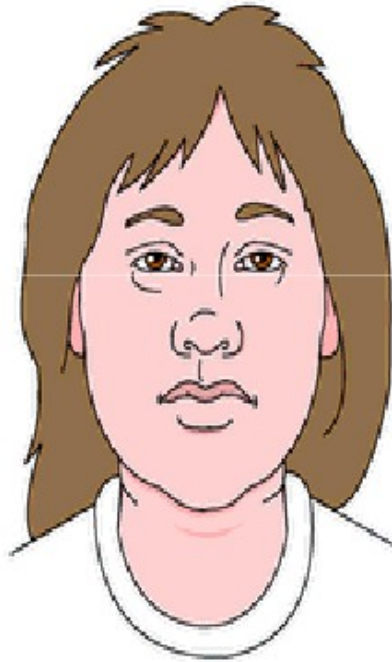
The ectopic lingual thyroid gland



Acquired Hypothyroidism

- More common in females and those with a family history of autoimmune thyroid disease.
- Caused by the circulation of antibodies against thyroglobulin (TG) and thyroid peroxidase (TPO) that were detectable in over 95% of patients with Hashimoto's thyroiditis.
- An increased prevalence has been noted in patients with other autoimmune diseases such as insulin-dependent diabetes.
- It may be part of an autoimmune polyglandular syndrome.
- Associated with some chromosomal abnormalities, such as Down syndrome, Turner syndrome, Klinefelter syndrome, and Noonan syndrome.

Clinical Presentations of Acquired Hypothyroidism



- Symptoms

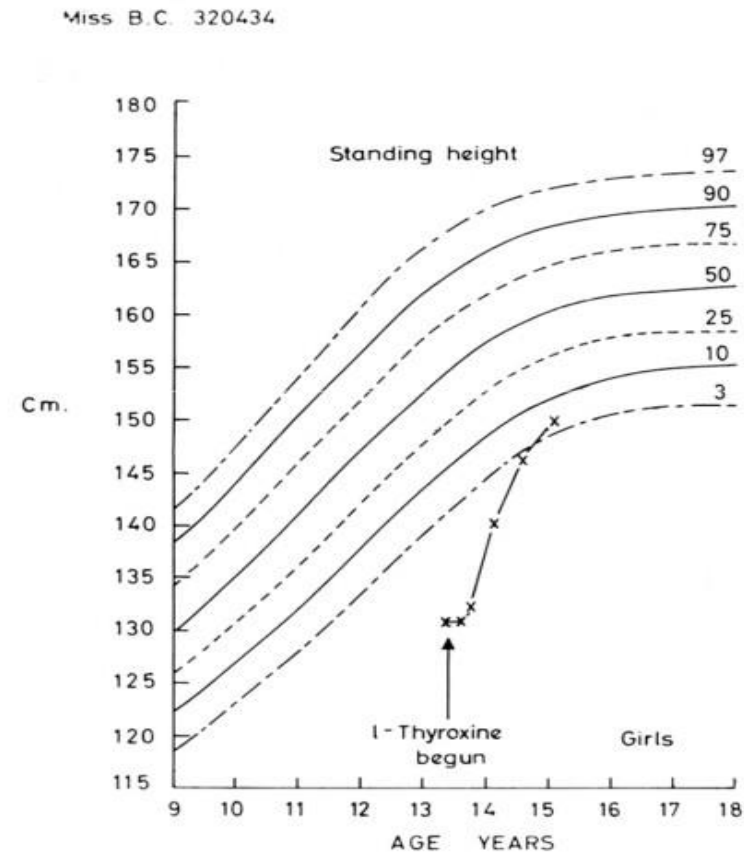
- General Slowing Down
- Lethargy/somnolence
- Depression
- Modest Weight Gain
- Cold Intolerance
- Hoarseness
- Dry skin
- Constipation (↓ peristaltic activity)
- General Aches/Pains
 - Arthralgias or myalgias (worsened by cold temps)
- Brittle Hair
- Menstrual irregularities
 - Excessive bleeding
 - Failure of ovulation



Untreated - 9 – year - of age child with congenital hypothyroidism



Hypothyroidism could present with short stature alone



Investigations

- The primary laboratory investigation for the assessment of hypothyroidism is thyroid profile including serum TSH, free T4, and occasionally free T3.
- Measurement of TSH, on the other hand, is not helpful in central hypothyroidism.
- Primary hypothyroidism is defined as High TSH, and low fT4, while subclinical hypothyroidism is defined by High TSH with normal fT4.
- In children fT3 is not a sensitive marker for hypothyroidism.
- In central hypothyroidism (hypothalamic /pituitary) free T4 is low and TSH is low as well.

Radiological investigations

- Ultrasonography represents a sensitive diagnostic tool to examine & locate the thyroid gland even in infancy.
- A radioactive iodine uptake scan may be useful to distinguish agenesis, hypogenesis & ectopia of the thyroid gland in cases with thyroid dysgenesis.
- Routine performance of thyroid scan in neonates with congenital hypothyroidism is no longer recommended.

Treatment

- Levothyroxine is the recommended treatment for children with primary or central hypothyroidism.
- The goals of treatment are to restore normal growth and development, including pubertal development.
- Levothyroxine doses, given by mouth, once daily on empty stomach as following:
 - Age 1 - 3 years: dose of 4 - 6 mcg/kg body weight.
 - Age 3 - 10 years: dose of 3 - 5 mcg/kg.
 - Age 10 - 16 years: dose of 2 - 4 mcg/kg.
- Alternatively, the replacement dose can be calculated on body surface area, in which case, the dose at any age is “100 mcg/m²/day”.
- The dose is then adjusted based on thyroid hormone measurements.

Thyrotoxicosis



Thyrotoxicosis in children

Causes of persistent thyrotoxicosis:

- Autoimmune thyroiditis (Graves disease).
 - 95% of young people with thyrotoxicosis have Graves disease.
- Diffuse toxic goiter.
- Multi-nodular toxic goiter.

Rare causes:

- TSH producing pituitary adenoma (TSHoma).
- Pituitary resistance to thyroid hormones
- Iatrogenic (ingestion of exogenous thyroid hormone or iodine).
- Activating mutations in the TSH receptor gene or GNAS1.

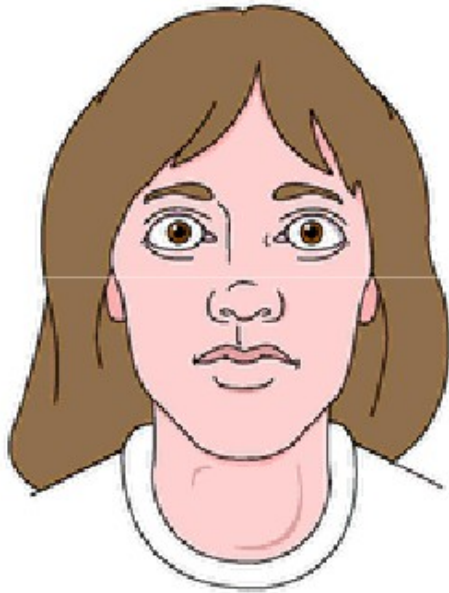
Thyrotoxicosis in children

- Occurs 1 in every 5000 children and adolescents.
- More than 95% of the cause is autoimmune Graves' disease.
- The underlying pathophysiology is brought into effect by circulating TSH receptor antibodies that mimic the action of TSH by binding to the TSH receptor and stimulating the thyroid gland to produce and release supraphysiological levels of T3 and T4.
- The ophthalmological manifestations of Grave's disease are a result of antibodies against a TSHR-like protein in retroorbital connective tissue.
- Graves' disease is much less common in childhood than in adulthood.
- Incidence rises sharply during puberty so about 80 % of Pediatric cases occur after 11 years of age.
- Strong female predominance develops, at a ratio of about 5:1.

Graves' disease

- Autoimmune disease caused by stimulatory TSH receptor antibodies.
- Accounts for 95% of cases of hyperthyroidism in children.
- A family history of autoimmune thyroid disease is present in 60% of patients.
- Patients with Graves' disease have an increased incidence of HLA haplotypes A1, B8, and DR3.
- Antibodies to the thyroid peroxidase (TPO) and thyroglobulin antibodies can also be detected in Graves' disease.
- associated with other autoimmune diseases.
- There is an increased risk of Graves' disease in children with Down syndrome.

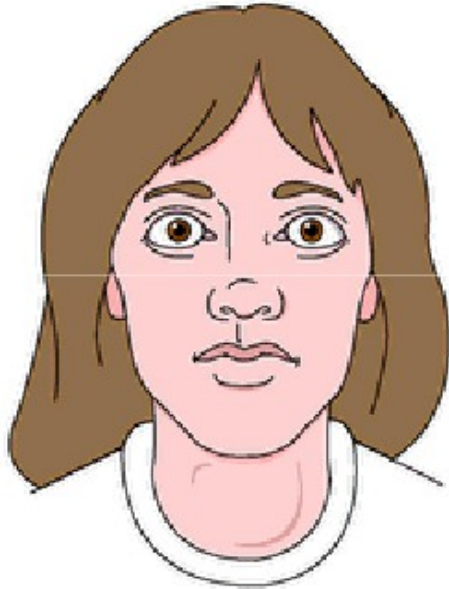
Clinical manifestations of Hyperthyroidism



Symptoms:

- Jittery, shaky, nervous.
- Difficulty concentrating.
- Emotional lability.
- Insomnia.
- Palpitations, feeling hot.
- Weight loss.
- Diarrhea.
- Fatigue.
- Menses : lighter flow, shorter duration

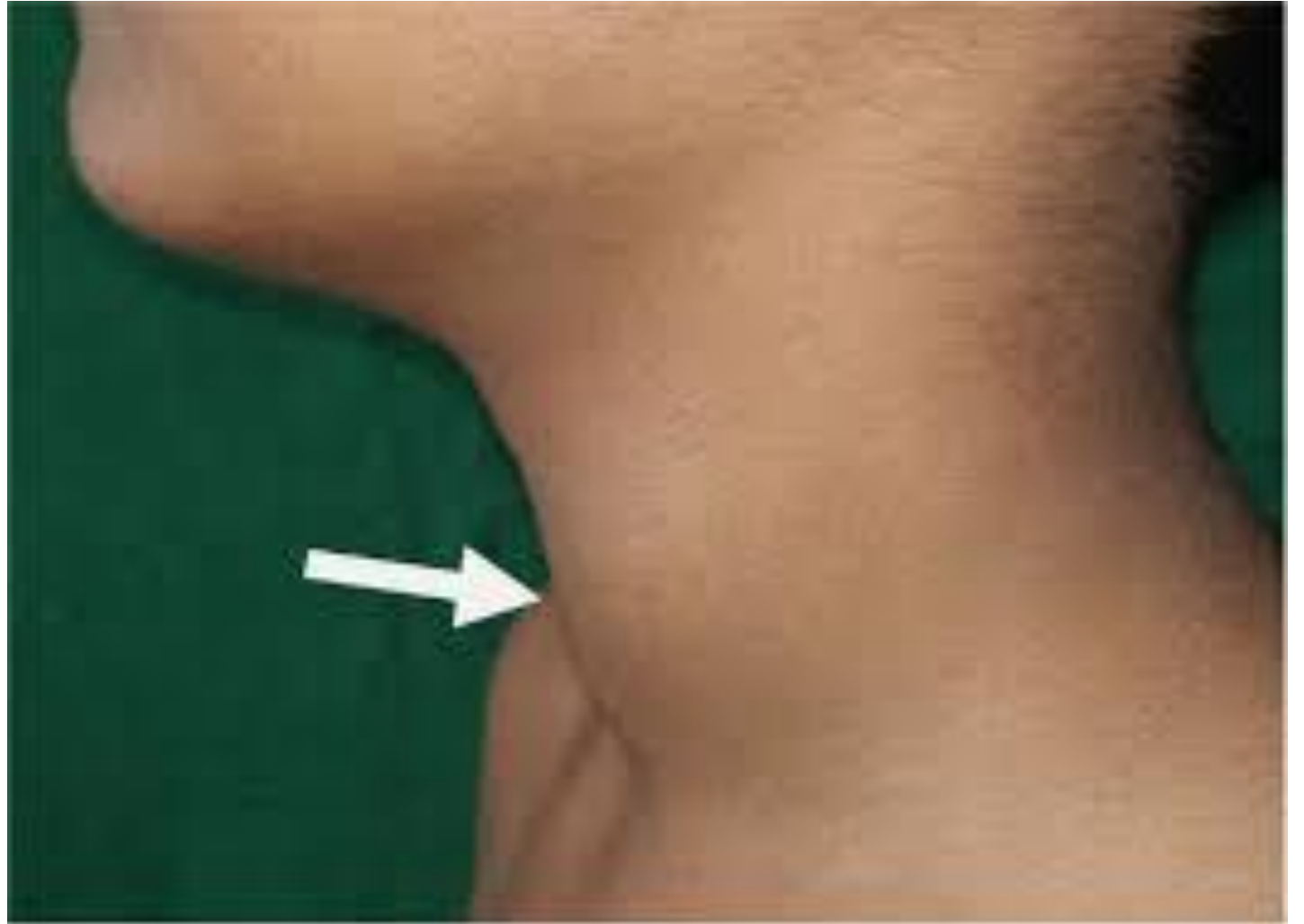
Clinical manifestations of Hyperthyroidism



Examination

- Eye findings (20%).
- Goiter.
- Thyroid bruit or thrill.
- Sinus tachycardia & atrial fibrillation.
- Flow murmur.
- Systolic hypertension.
- Hyperreflexia.
- Tremor.
- Proximal muscle weakness.
- Clubbing.
- Onycholysis
 - separation of nail from the nailbed
- Dermopathy.

Goiter in a children could be seen in hypo/ hyper/ or euthyroidism



Exophthalmos and lid retraction in a child with thyrotoxicosis



Clubbing in Thyrotoxicosis



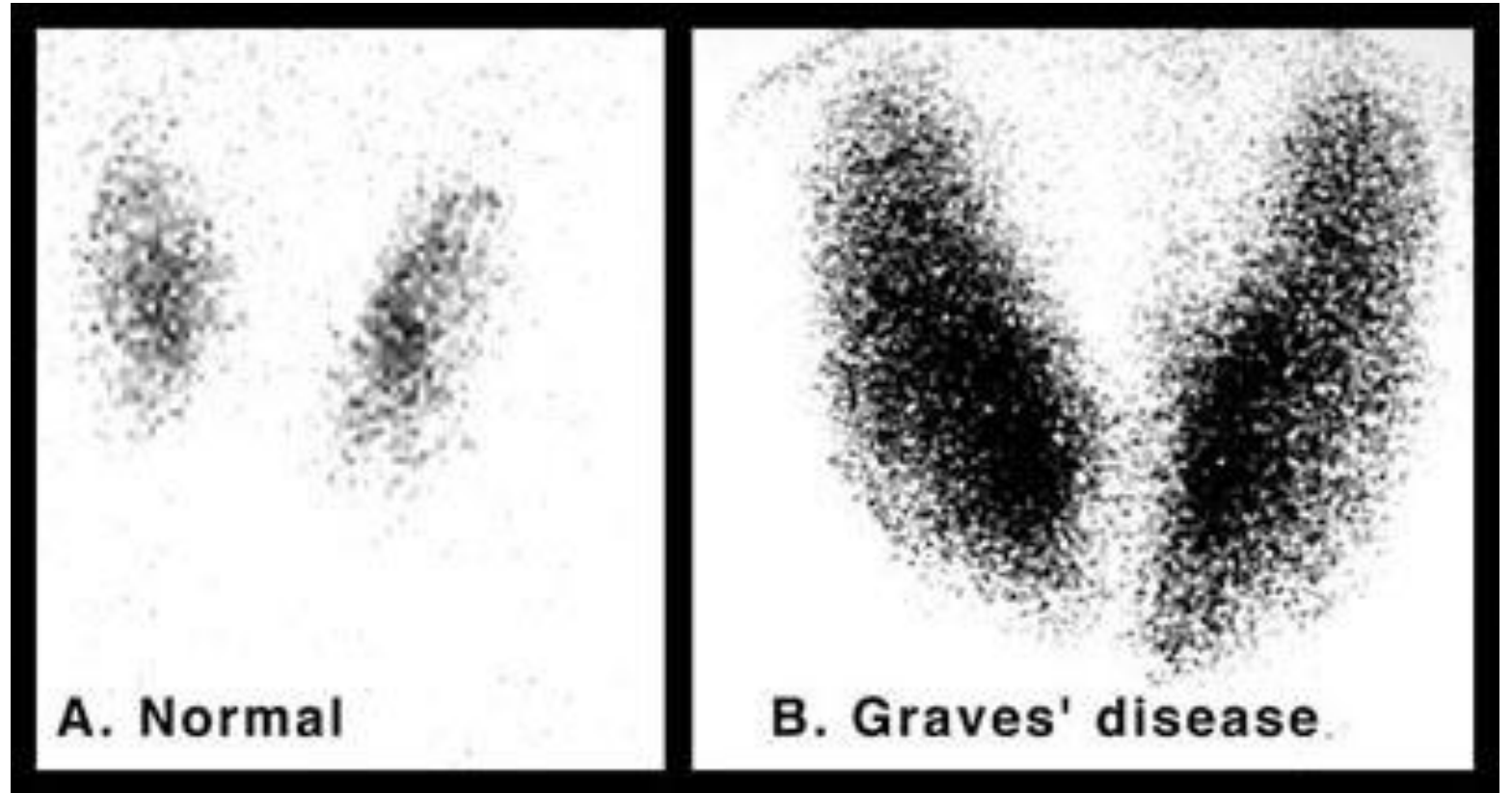
Pretibial Myxedema in Thyrotoxicosis



Investigations of thyrotoxicosis

- TSH level usually low $< 0.05 \mu\text{u/ml}$
- High FT4 & FT3
- In 5% high FT3 with normal T4 (T3 Thyrotoxicosis)
- Thyroid receptor (TRAB) are usually elevated at diagnosis.
- Antibodies against thyroglobulin, peroxidase or both are present in the majority of patients.

Radioiodine-131 scan showing normal uptake (A) and highly increased uptake (B) of contrast by the thyroid gland.



Treatment of Thyrotoxicosis in Children

Anti-thyroid medications:

- Antithyroid drug therapy with (carbimazole or methimazole and propylthiouracil) is associated with side effects:
 - Rash, granulocytopenia, arthritis, and hepatitis.
- Long-term remission rate as low as 30%–40% even after prolonged therapy.
- Propranolol (1 mg/kg body weight) may help relieve symptoms from autonomic dysfunction and block the conversion of T4 to the biologically more active T3.
- In neonatal thyrotoxicosis, thyroid hormone synthesis may be acutely blocked by iodide (Lugol's solution).

Radio-active iodine -131 therapy

- Radio-active iodine -131 therapy is associated with cure rates as high as 90%.
- Represents the least expensive treatment option for Graves' disease.
- However, the long-term safety of iodine-131 in children and adolescents has not been evaluated extensively.
- Radioiodine therapy should be avoided in children less than 5 years of age because the risk of thyroid cancer after external radiation is highest in children less than 5 years of age and progressively declines with advancing age.

Subtotal thyroidectomy

- Subtotal thyroidectomy has favorable cure rates (90%) and reverses the hyperthyroid state rapidly but entails a complex surgical procedure that can result in:
 - Permanent hypothyroidism.
 - Hypoparathyroidism.
 - Dysphonia due to damage to the recurrent laryngeal nerves.
 - Bleeding.

