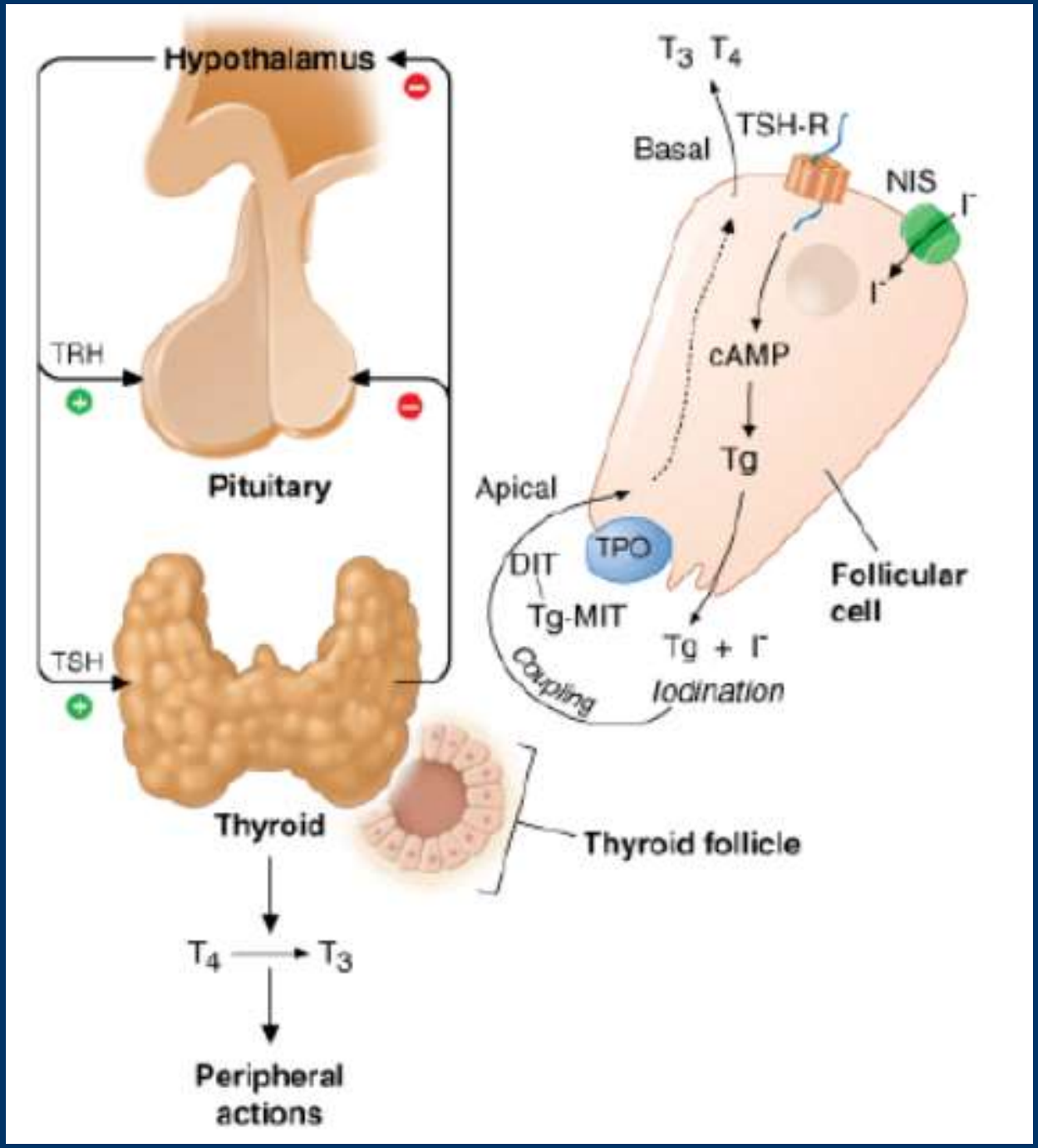
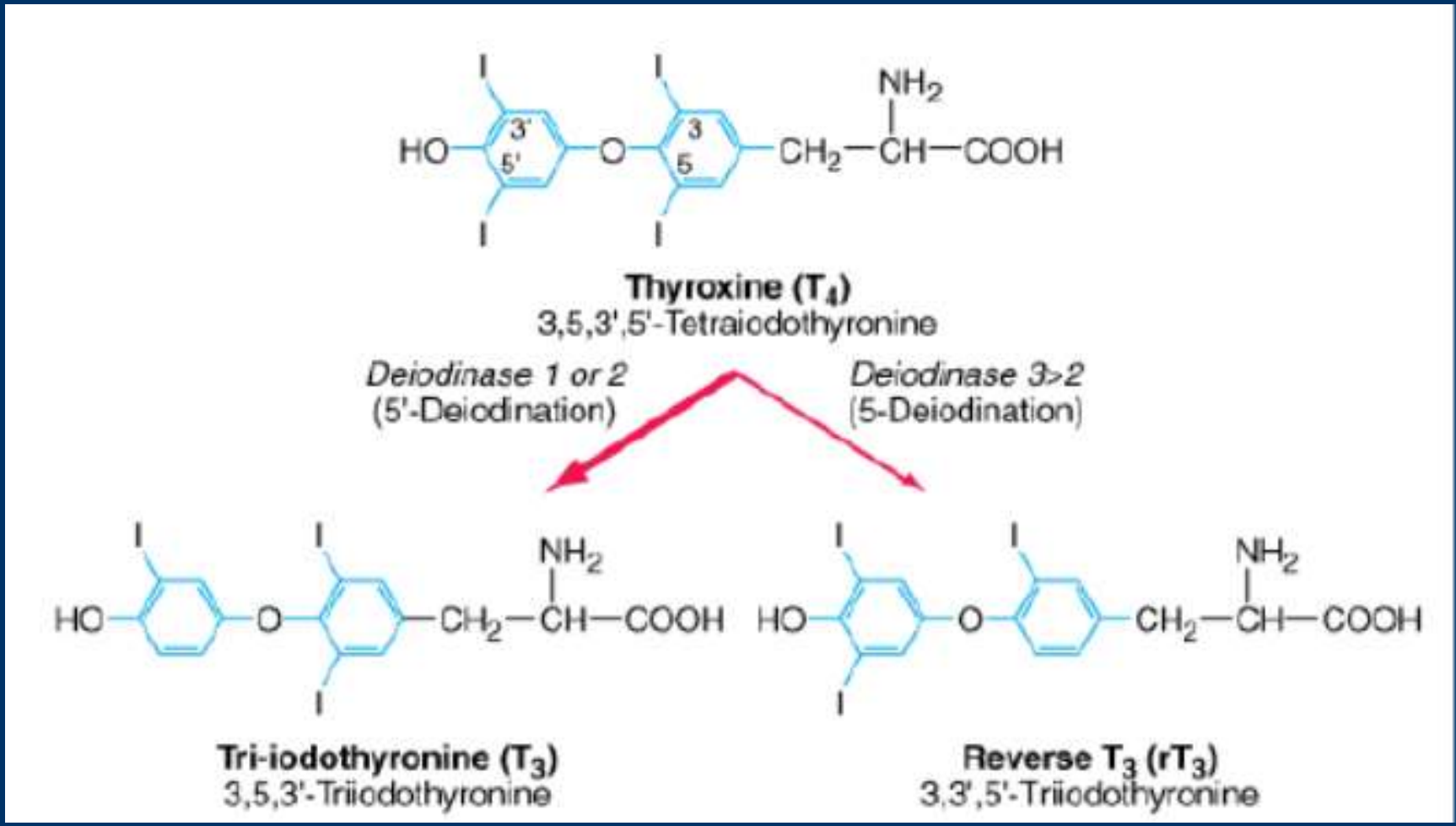

In the name of God


Hypothalamus
TRH
Pituitary
TSH
Thyroid
T_4 → T_3
Peripheral actions
T_3 T_4
Basal
TSH-R
NIS
I^-
I^-
cAMP
Tg
Apical
TPO
DIT
Tg-MIT
Follicular cell
Tg + I^-
Iodination
Coupling
Thyroid follicle


Thyroxine (T_4)
3,5,3',5'-Tetraiodothyronine
Deiodinase 1 or 2
(5'-Deiodination)
Deiodinase 3>2
(5-Deiodination)
Tri-iodothyronine (T_3)
3,5,3'-Triiodothyronine
Reverse T_3 (rT_3)
3,3',5'-Triiodothyronine

Introduction

Many structural or functional abnormalities can impair thyroid hormones production.

Classified as :

1- Primary (95%)

2-Central (5%)

Prevalence

Neonatal screen:

Congenital hypothyroidism **1/4000 newborn**
1/1000 (Iran)

Acquired hypothyroidism:

Adult women 2%
Adult men 0/2%

Old age hypothyroidism: *

Female %9.3
Male %1.3

*2779 people in UK with a medium age of 58 years
Whickham survey 1995

Effects of Thyroid Hormone

- Fetal brain and skeletal maturation
- Increase in basal metabolic rate
- Inotropic and chronotropic effects on heart
- Increases sensitivity to catecholamines
- Stimulates gut motility
- Increase bone turnover
- Increase serum glucose, decrease serum cholesterol

Pathogenesis

T3 is biological active hormone

Decrease :

↓ B.M.R - calorigenesis

Respiratory function:

↓O2 -↓Co2 - macroglossia - sleep apnea

airway edema - muscle weakness

C.V. system:

↓C.O.P -↓P.R - D.HTN - Blocks

Renal:

↓ R.B.F - G.F.R - Na resorption - bladder atony

C.H.O metabolism:

↑ **Insulin sensitivity**

↓ **Appetite**

↓ **Gluconeogenesis** → **hypoglycemia**

↓ **Glycogenolysis**

Hematology:

Blood volume (20%)

Erythropoetin - H.ct (30%)

Vit.B.12

W.B.C - Pmn

Congenital Hypothyroidism

- Rare
- Absent thyroid tissue or hereditary defects in TH synthesis
- Mental retardation due to lack of T_4
- Symptoms
  - difficulty eating, hoarse cry, abdominal protrusion, excessive sleeping, slow pulse, cold skin
  - impaired growth, cretinism

Two Forms of Cretinism: Neurologic

- Neurologic form - neuromotor defects, deaf-mutism, problems with gait and coordination

Courtesy of WHO

Deaf-mutism

Male from Ecuador, 40 years old, unable to stand or walk

TABLE 2
Aetiology of congenital hypothyroidism.

Permanent

- Thyroid dysgenesis
- Thyroid agenesis
- TSH – defective synthesis (central hypothyroidism)
  - hypo-responsiveness
- Stimulating G protein deficiency
- Iodide transport defect
- Iodide organification defect
- Thyroglobulin synthesis defect
- Iodotyrosine deiodinase deficiency
- Other gene defects

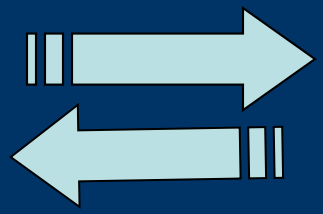
Transient

- Maternal antithyroid drug ingestion
- Excess maternal iodide ingestion (e.g. amniofetography)
- TSH receptor blocking antibodies
- Extreme prematurity
- Transient hyperthyrotrophinaemia

Chronic Autoimmune Thyroiditis
Hashimoto disease

Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is the most common cause of hypothyroidism in iodine-sufficient areas of the world. It is characterized clinically by gradual thyroid failure, goiter, or both, due to autoimmune-mediated destruction of the thyroid gland. Nearly all patients have high serum concentrations of antibodies against one or more thyroid antigens, lymphocytic infiltration of the thyroid, which includes thyroid-specific B and T cells, and apoptosis of thyroid follicular cells.

Spectrum of thyroid autoimmunity

Grave's Disease  **Hashimoto Disease**

Postpartum thyroiditis

Silent thyroiditis

Drug induced thyroiditis

Possible precipitating factors

- **Genetic (*HLA DR2,3,4*)**
- **Infection (*congenital rubella*)**
- **Stress**
- **Humoral factors (sex steroids , pregnancy)**

Pathogenesis

- Thyroid auoantigenes
- Role of B cells
- The primary role of T cells
- Potential mechanism of thyroid injury

Molecular mimicry
Bystander activation
Thyroid cell expression of HLA Ag
Thyroid cell apoptosis

- The disease clusters in families, sometimes alone and sometimes in combination with Graves' disease

- It is more common in women.

- The concordance rate in monozygotic twins is 30 to 60 percent

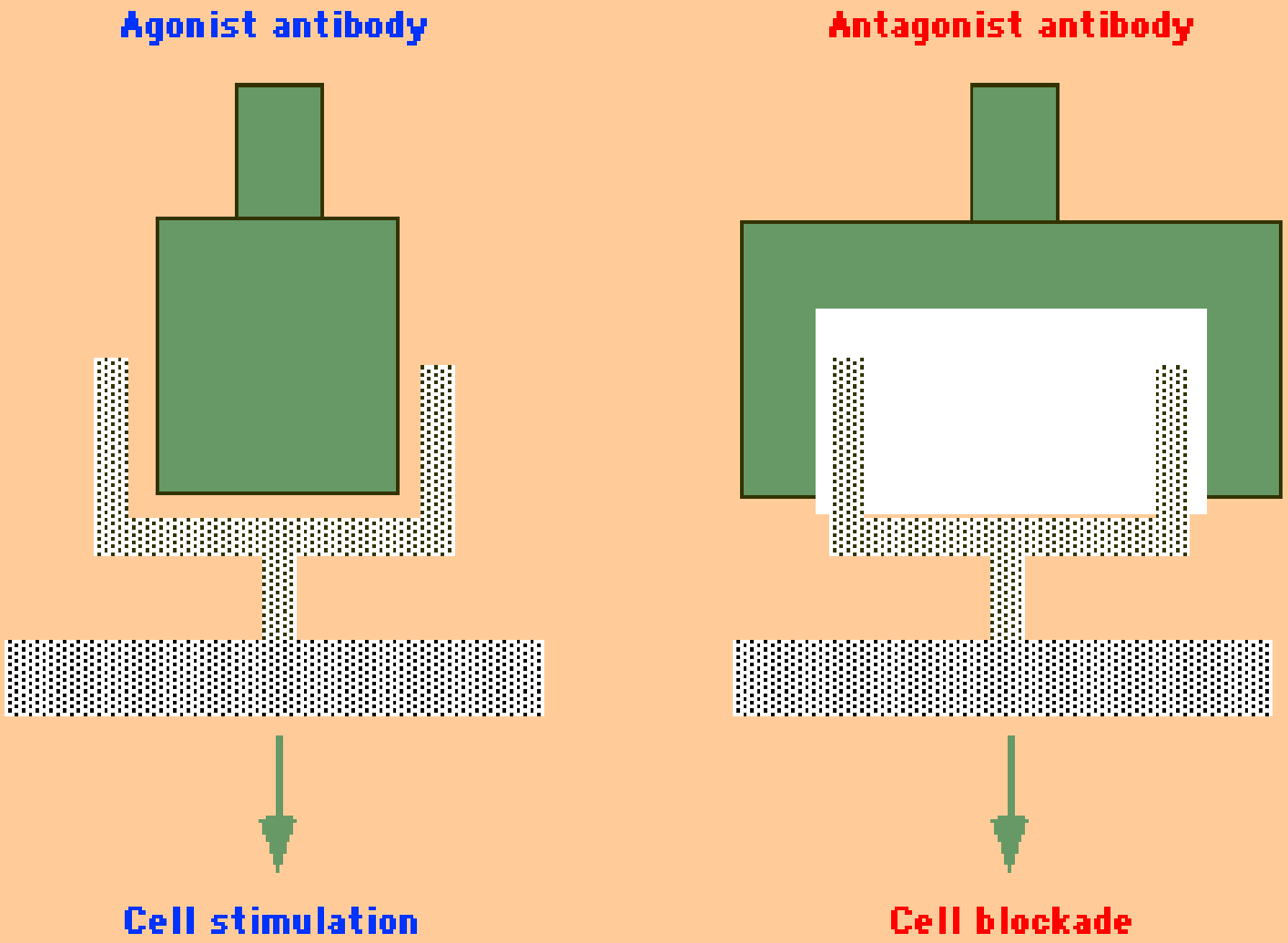
- It occurs with increased frequency in patients with Down's syndrome and Turner's syndrome.

- There is an association, albeit relatively weak, with certain HLA alleles.

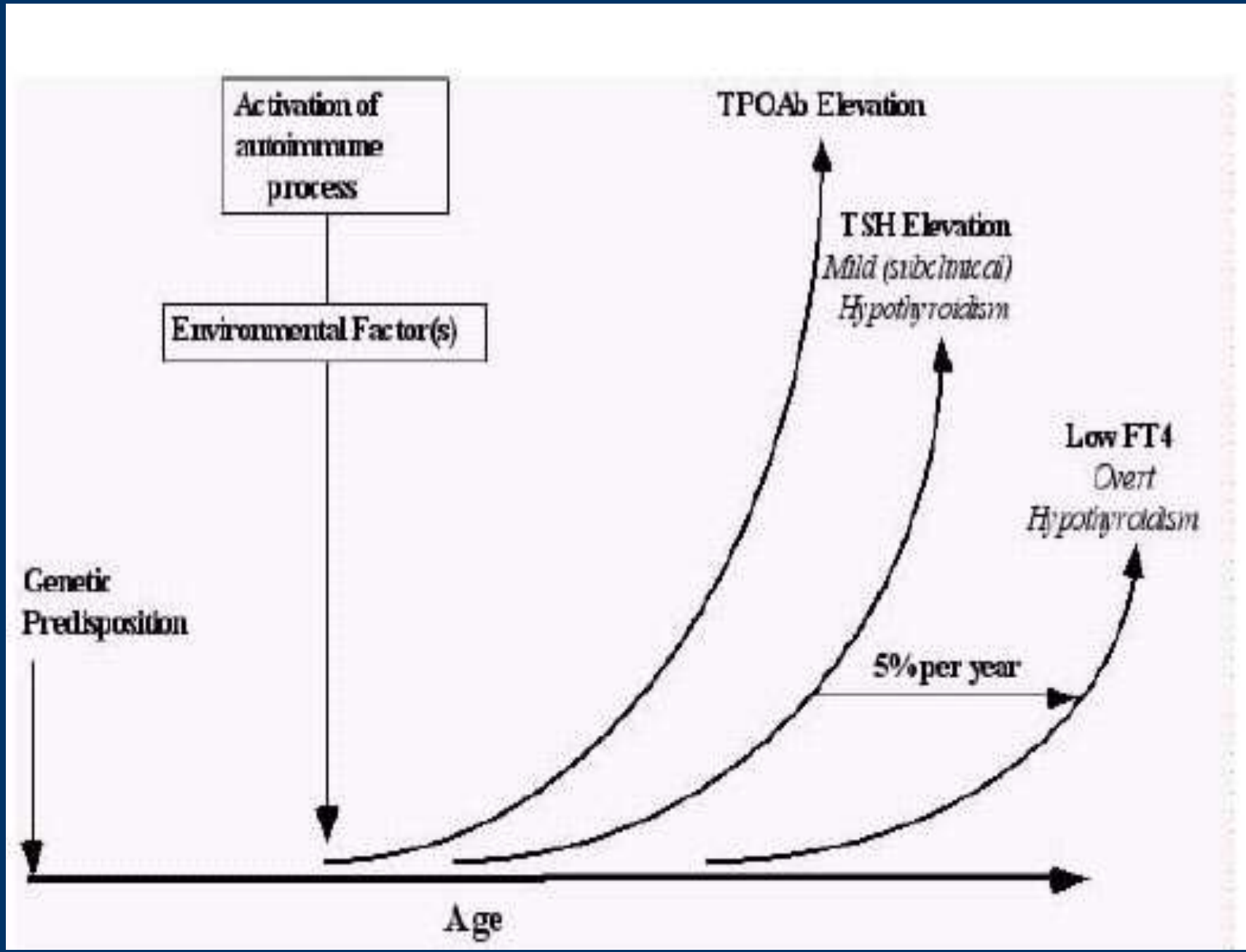
Estimated Prevalence of Antithyroid Antibodies (in percent)

Group	Anti-TSHR Ab	Anti-Tg Ab	Anti-TPO Ab
General population	0	5-20	8-27
Graves' disease	80-95	50-70	50-80
Autoimmune thyroiditis	10-20	80-90	90-100
Relatives of patients with autoimmune thyroiditis	0	30-50	30-50
Type 1 diabetes	0	30-40	30-40
Pregnant women	0	about 14	about 14

Anti-TSHR Ab = Antithyrotropin receptor antibodies
Anti-Tg Ab = Antithyroglobulin antibodies
Anti-TPO Ab = Antithyroid peroxidase antibodies

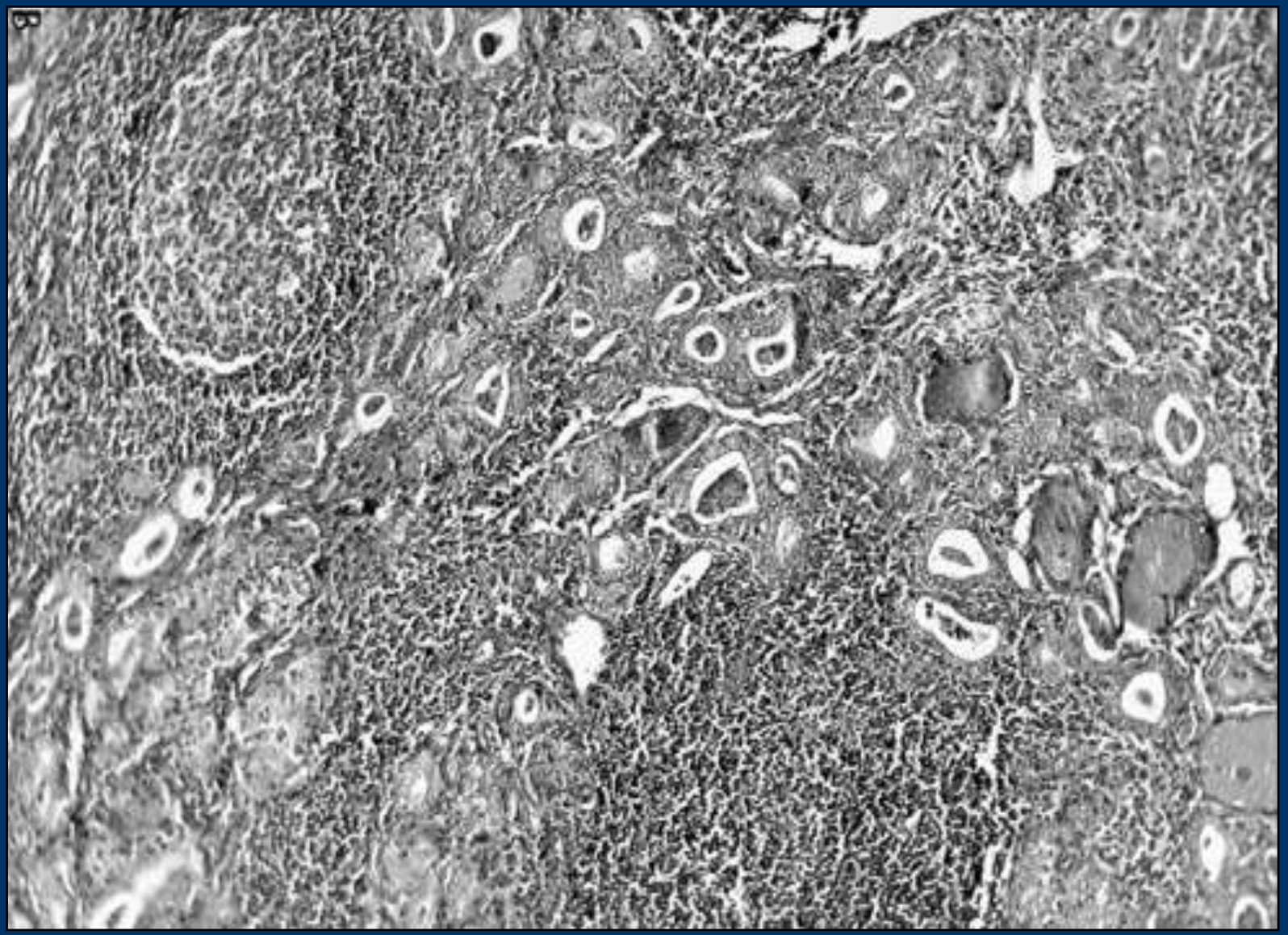


TSH receptor antibodies Antibodies to the TSH receptor may be stimulatory (eg, in patients with Graves' disease) and cause hyperthyroidism, or inhibitory (eg, in chronic autoimmune thyroiditis) and cause hypothyroidism.


Activation of autoimmune process
Environmental Factor(s)
Genetic Predisposition
TPOAb Elevation
TSH Elevation
Mild (subclinical) Hypothyroidism
Low FT4
Overt Hypothyroidism
5% per year
Age

PATHOLOGY

The characteristic histopathological abnormalities are profuse lymphocytic infiltration, lymphoid germinal centers, and destruction of thyroid follicular cells .
fibrosis and areas of follicular-cell hyperplasia, presumably induced by TSH, are also seen in patients with severe disease. The intrathyroidal lymphocytes are both T and B lymphocytes.



Lymphocytic infiltration

Organ-Specific Autoimmune Diseases	
chronic hepatitis	hypoparathyroidism (some forms)
Hashimoto's disease	
myxoedema	diabetes mellitus (some forms)
lymphocytic thyroiditis	vitiligo
Graves' disease	
pernicious anaemia	premature ovarian failure
Addison's disease	allergic alveolitis

Fig. 15.5 Table of the organ-specific autoimmune diseases. All of these disorders are characterised by the presence of circulating antibodies and lymphocytic infiltration of the gland or tissue.

Clinical presentation

Infantile hypothyroidism

- **Cretenism :**
- ***Sever retardation of mental & growth.***
- **Feeding problem.**
- **Failure to thrive.**
- **Prolong jaundice.**
- **Constipation.**
- **Coarse face. Hoarse voice.**
- **Coarse cry & somnolence.**
- **Protuberance of abdomen.**
- **Dry skin & hair.**
- **Growth & development retardation. (dwarfism).**
- **Delay eruption of teeth & fontanel's closure.**

Juvenile hypothyroidism

- Sever & disproportionate short stature.
- Delay puberty.
- Delay eruption of permanent teeth.
- Precocious puberty.
- Poor intellectual performance.
- Coarse appearance.

Adult clinical presentation

Symptoms

- Tiredness, weakness
- Dry skin
- Feeling cold
- Hair loss
- Difficulty concentrating and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea
- Hoarse voice
- Menorrhagia (later oligomenorrhea or amenorrhea)
- Paresthesia
- Impaired hearing

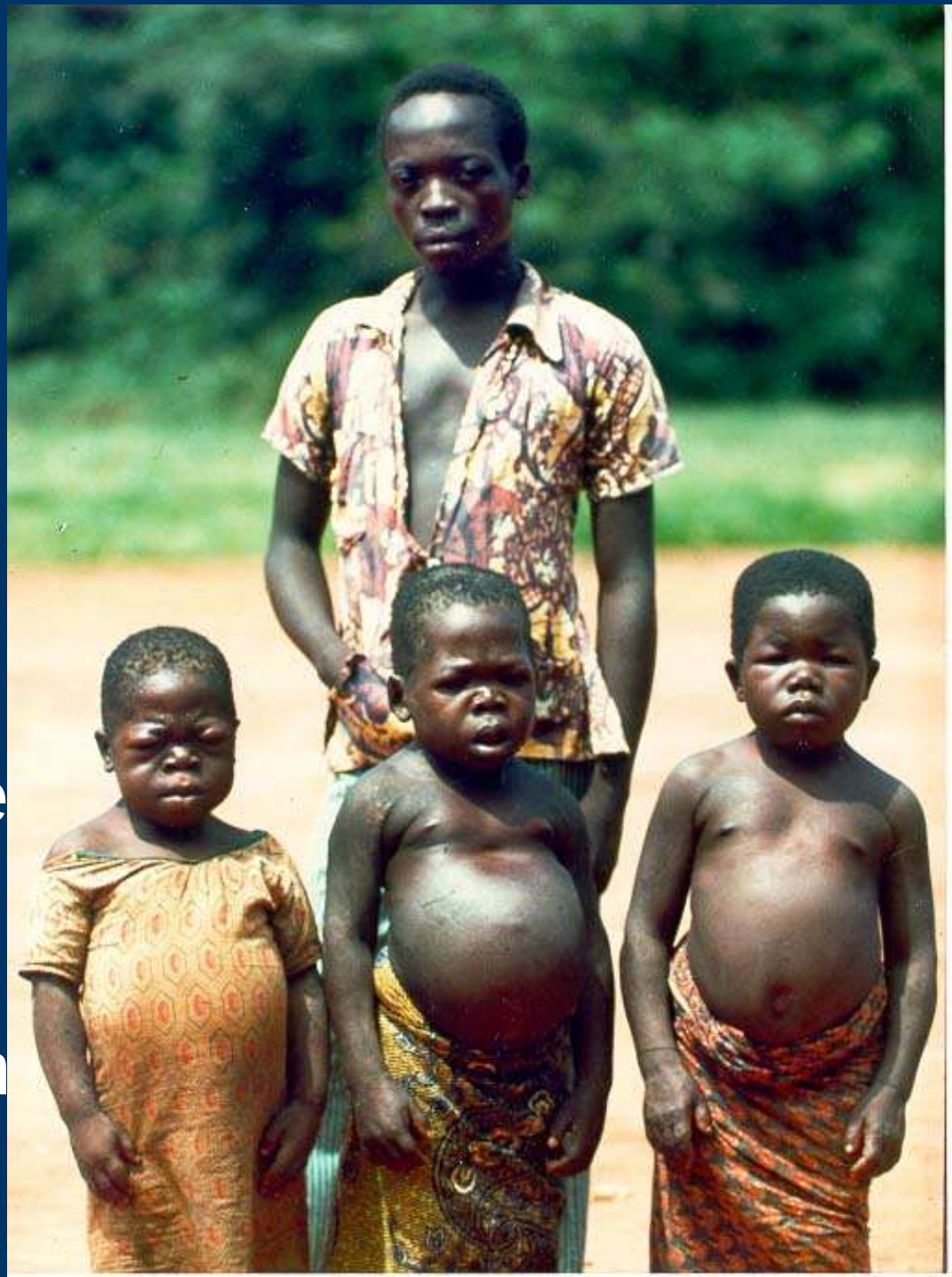
Signs

- Dry coarse skin; cool peripheral extremities
- Puffy face, hands, and feet (myxedema)
- Diffuse alopecia
- Bradycardia
- Peripheral edema
- Delayed tendon reflex relaxation
- Carpal tunnel syndrome
- Serous cavity effusions

Major Symptoms and Signs of Hypothyroidism

Mechanism	Symptoms	Signs
Slowing of metabolic processes	Fatigue and weakness	Slow movement and slow speech
	Cold intolerance	Delayed relaxation of tendon reflexes
	Dyspnea on exertion	Bradycardia
	Weight gain	Carotenemia
	Cognitive dysfunction	
	Mental retardation (infant)	
	Constipation	
	Growth failure	
Accumulation of matrix substances	Dry skin	Coarse skin
	Hoarseness	Puffy facies and loss of eyebrows
	Edema	Periorbital edema
		Enlargement of the tongue
Other	Decreased hearing	Diastolic hypertension
	Myalgia and paresthesia	Pleural and pericardial effusions
	Depression	Ascites
	Menorrhagia	Galactorrhea
	Arthralgia	
	Pubertal delay	

Adult male with 3 women of same age (17-20 years) from Congo with myxedamatous form



Other thyroid pathologies

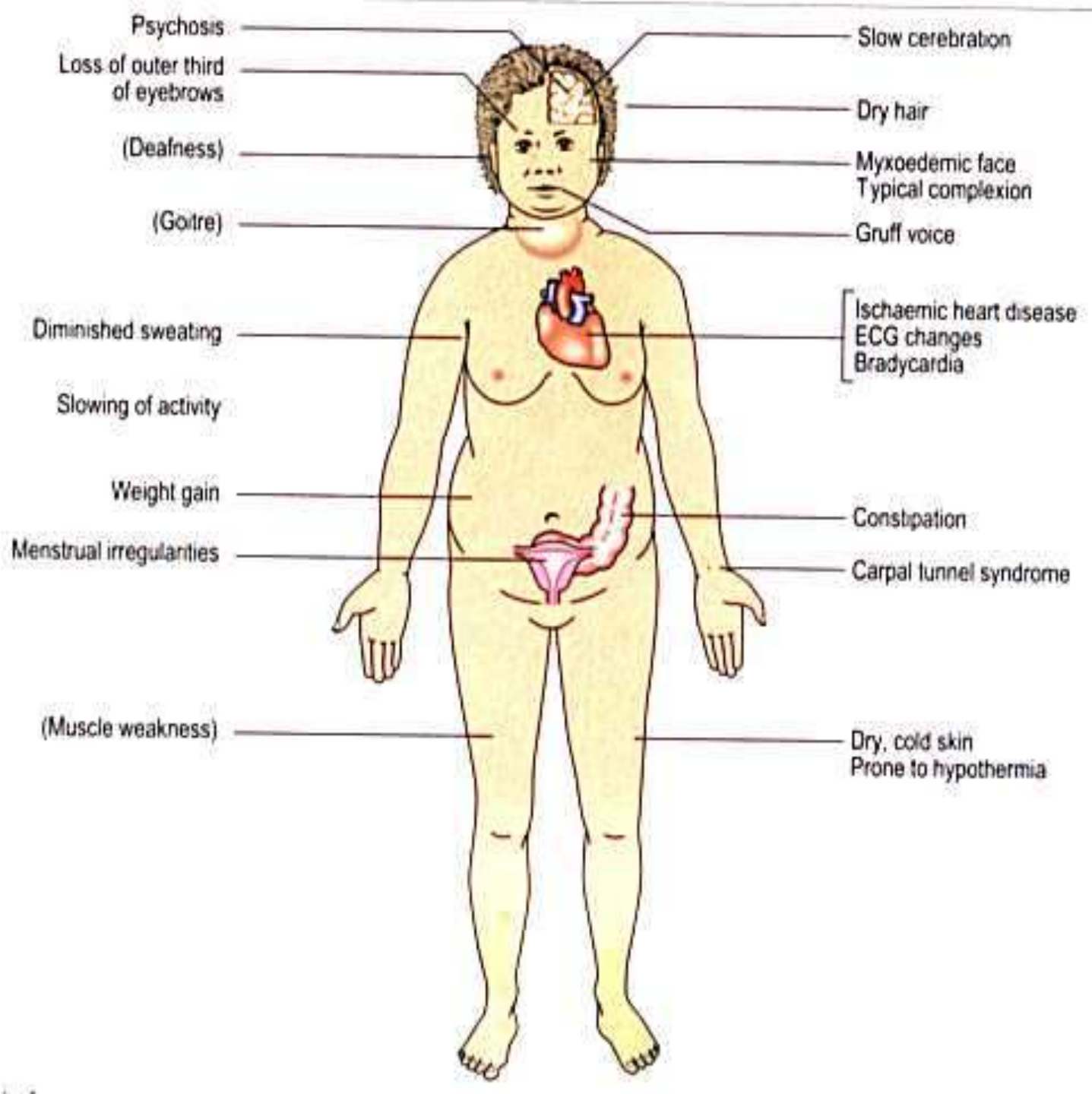
Goitre

Nanisme

Hypo-thyroidism

Myxedema

Features:

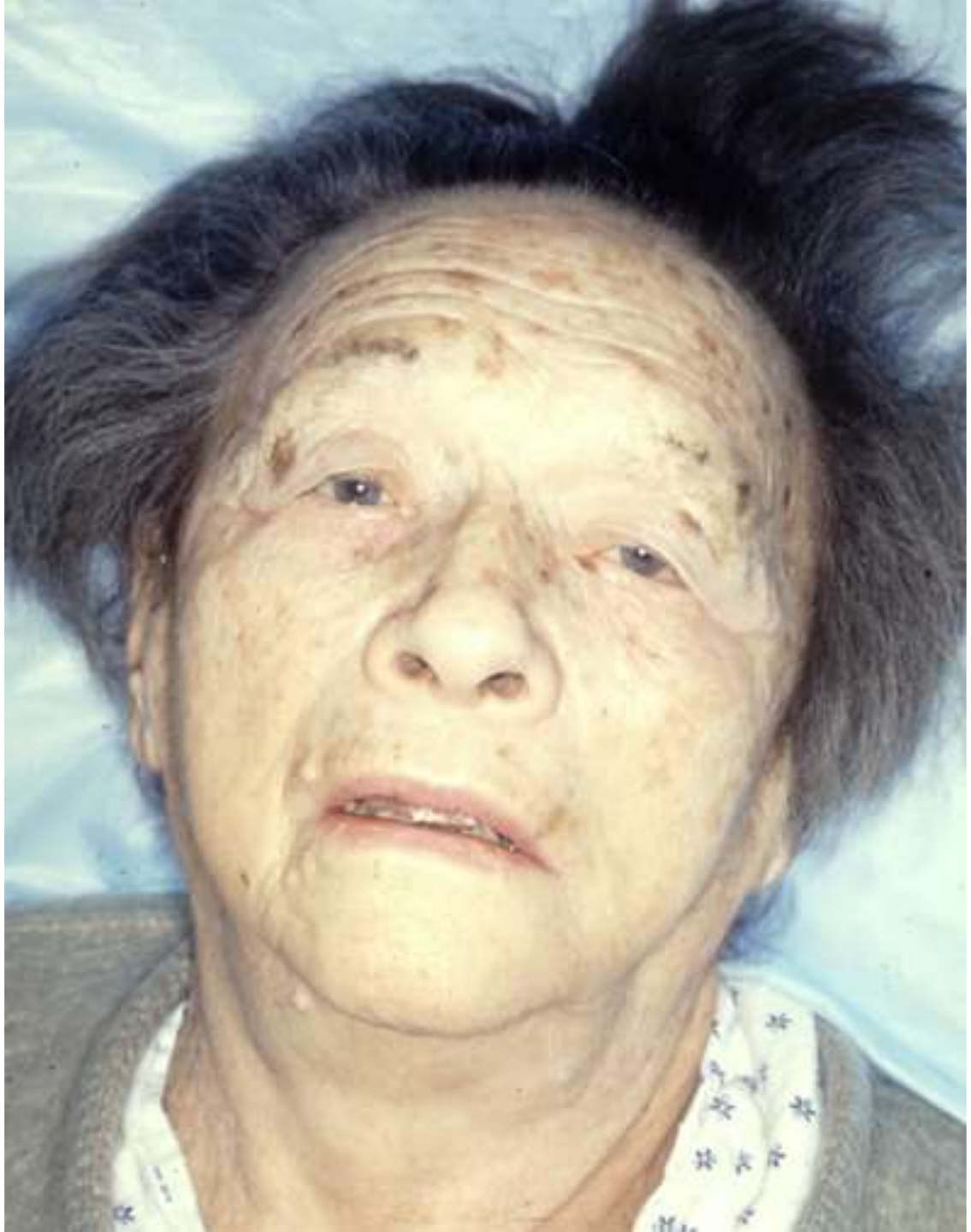


Hypothyroidism & Signs & Symptoms:

- Shrunken fibrotic thyroid gland by palpation
- Cool peripheries
- Dull facial expression
- Hoarse voice with slow speech
- Intolerance to cold
- Hair and skin is coarse and dry
- Bradycardia
- Weight gain
- Carpal tunnel syndrome
- Drooping eyelids

Hypothyroid Face

Notice apathetic facies, bilateral ptosis, & absent eyebrows

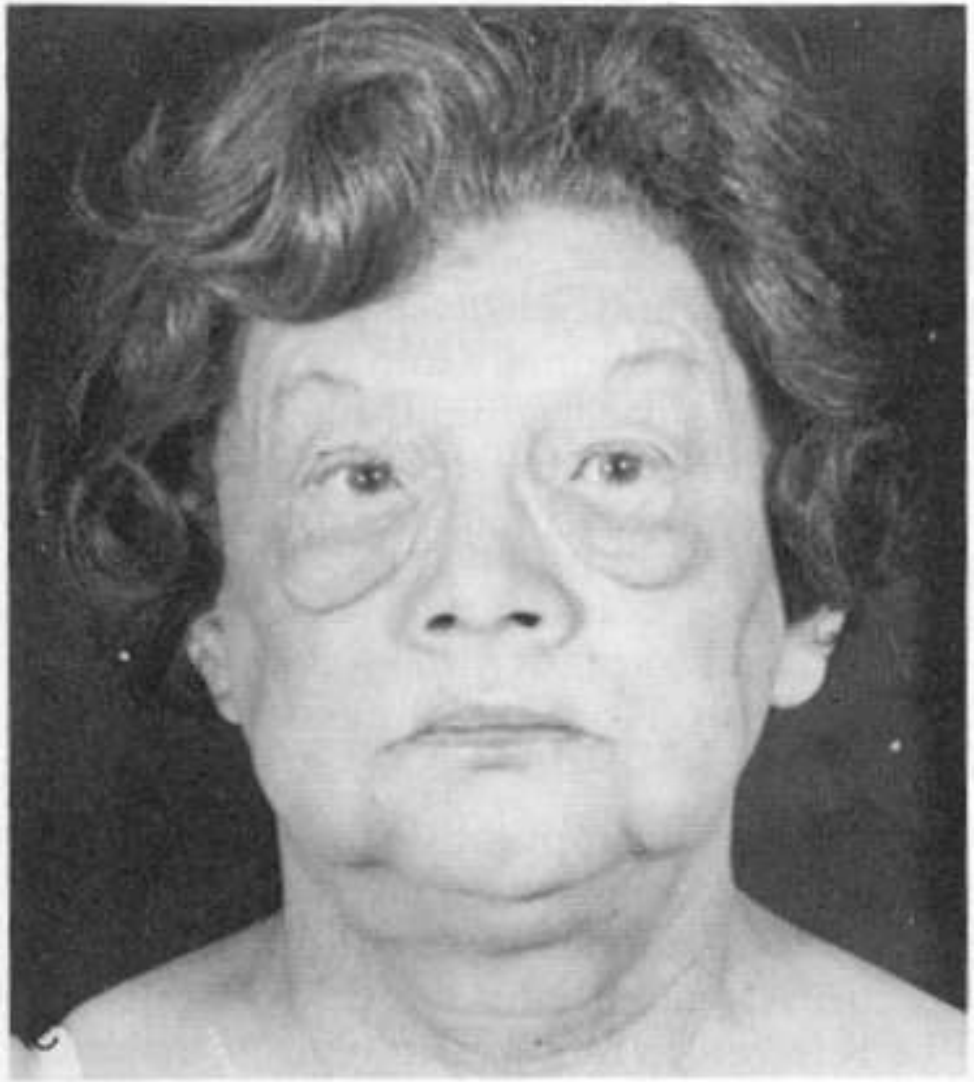


Faces of Clinical Hypothyroidism

Hypothyroidism & Signs & Symptoms:

- Lethargy
- Puffy face
- Muscle fatigue
- Loss of eyebrows in outer third
- Depression

- Headaches
- Menstrual disturbance
- Growth retardation in children, delayed teething and slow mental development

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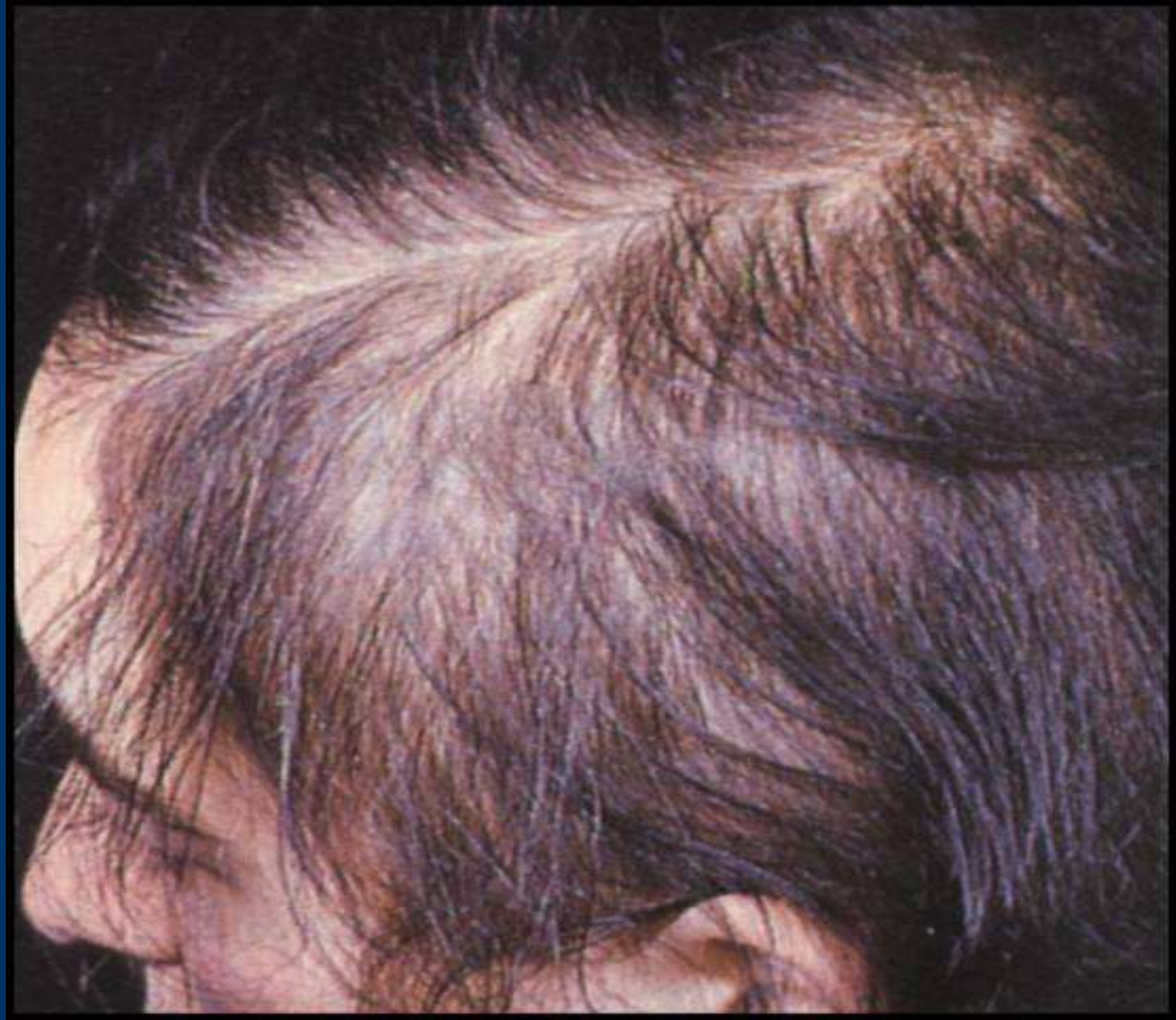


(A)The classic torpid facies of severe myxedema in aman.
(B) The facies in pituitary myxedema, covered by fine wrinkles.

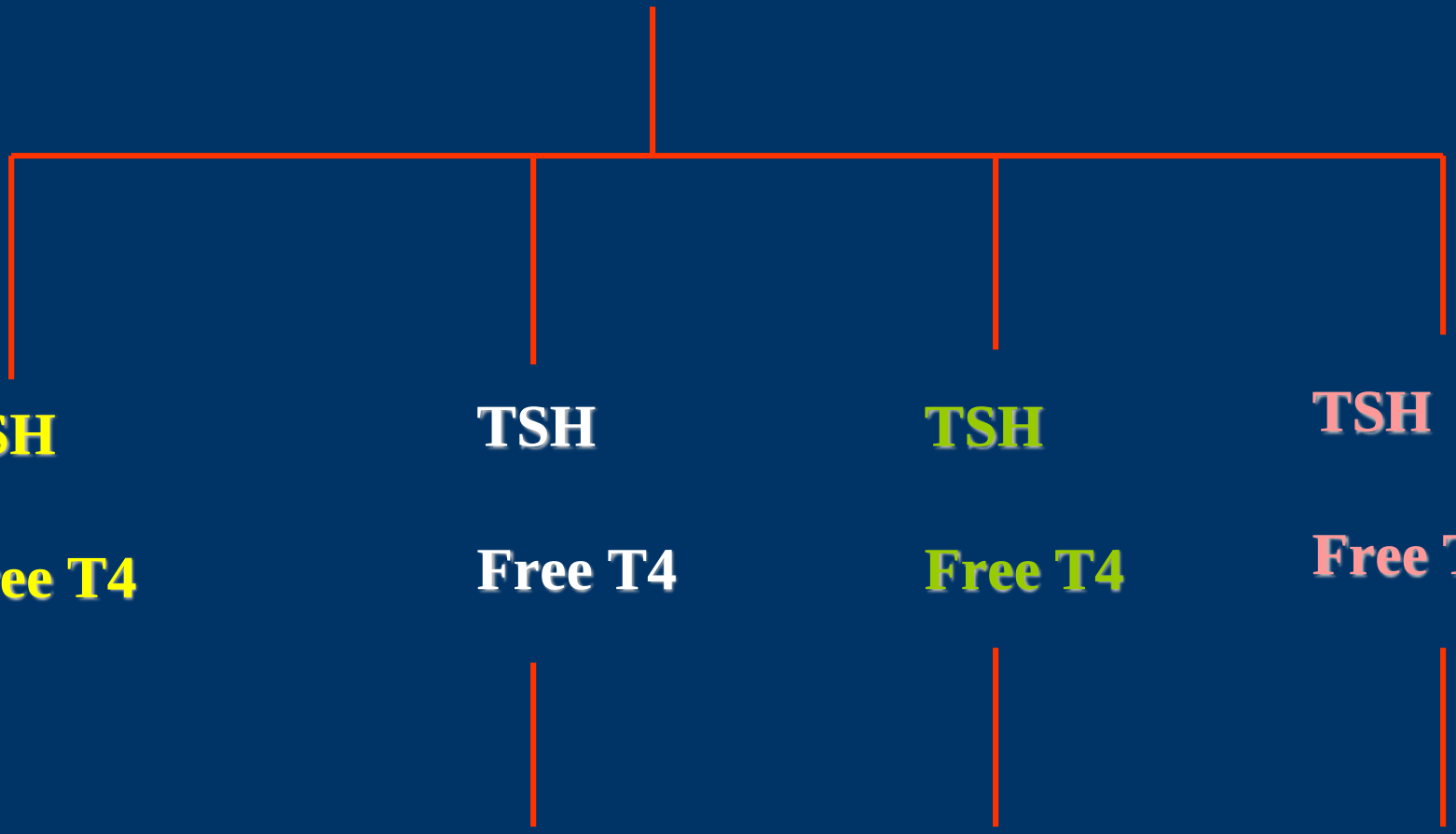
Cretinism Cont…

www.emedicine.com/ped/topic501.htm


A
B
Before treatment
After treatment

Diagnosis

TSH and Free T4



Indications to test for hypothyroidism†

Clinical symptoms and signs

Fatigue
Cold intolerance
Constipation
Impaired memory
Slowed mental processing
Depression
Nerve entrapment syndromes
Ataxia
Muscle weakness
Muscle cramps
Menstrual disturbance
Infertility
Bradycardia
Diastolic hypertension
Hoarseness
Goitre
Periorbital oedema
Weight gain
Galactorrhoea

Laboratory test abnormalities

Hypercholesterolaemia
Hyponatraemia
Hyperprolactinaemia
Hyperhomocysteinaemia
Anemia
Creatine phosphokinase elevation

Central Hypothyroidism

- **Imaging (R/O SOL)**
- **Functional status of the other axis**

Treatment

Thyroid hormone preparations

- Synthetic L-T4
- Synthetic L-T3
- Combined T4 & T3
- Desiccated thyroid

Average Replacement Dose of T4

- I.6 to 1.8µ/kg ideal body Wight/day
- 75-125µg/day in women and 125-200µg/day in men
- Older patients(>60years) require 20% to 30% less T4 per kg ideal body weight than do younger patients

Future perspectives

T4 + T3 Better than T4 Alone ?

Special treatment situation

- Elderly patients
- Underlying CAD
- Pregnancy
- Concomitant drug administration
- Surgical patients

Risk of a suppressed TSH

- **Effects on Bone Mass**
- **Cardiac Effects**

Cardiac effects

- Increased heart rate
- Atrial fibrillation , 3-fold greater risk of Af over the next decade in thyrotoxic 60-year-olds
- Increase in myocardial contractility

Bone effects

- Overt thyrotoxicosis is associated with increased bone turn over and negative calcium balance
- Significant bone loss in postmenopausal (but not in premenopausal) women at the lumbar
- The detrimental effect appeared more marked on cortical than on trabecular
- There is little evidence from retrospective studies of an actual increase in Fx incidence

Transient hypothyroidism

- Postpartum thyroiditis
- Subacute thyroiditis
- After withdrawal of thyroid hormone Therapy in euthyroid patients
- Following I131 treatment for Graves'disease
- Removal of toxic adenoma or subtotal thyroidectomy for Graves'disease

Sub clinical hypothyroidism

Preclinical hypothyroidism

Introduction

High serum TSH + normal T4 & T3 and few or no signs and symptoms. Such patients are often identified through routine screening or in the course of an evaluation of common nonspecific symptoms or hypercholesterolemia.

Prevalence

There is an age dependent increase in TSH level.

Women older than 65 >10%

Men older than 65 > 4%

Etiology

Causes are the same as overt hypothyroidism.

- **Most patients have chronic autoimmune thyroiditis & high anti- TPO titer.**
- **Post ablation of Graves disease.**
- **External radiation.**
- **T1DM**
- **Drugs:**

  Lithium
  Amiodarone
  INF
  Smoking …

Differentional Diagnosis

Other causes of elevated levels of serum TSH and normal levels of serum free T4 include :

1- Intermittent noncompliance with thyroxine therapy.

2-Recovery from severe nonthyroidal illness.

3- Chronic renal failure.

4- primary adrenal failure.

5- HighTSH levels as an artifact due to circulating heterophilic antibodies against thyrotropin.

Natural history

Subclinical hypothyroidism

Overt hypothyroidism

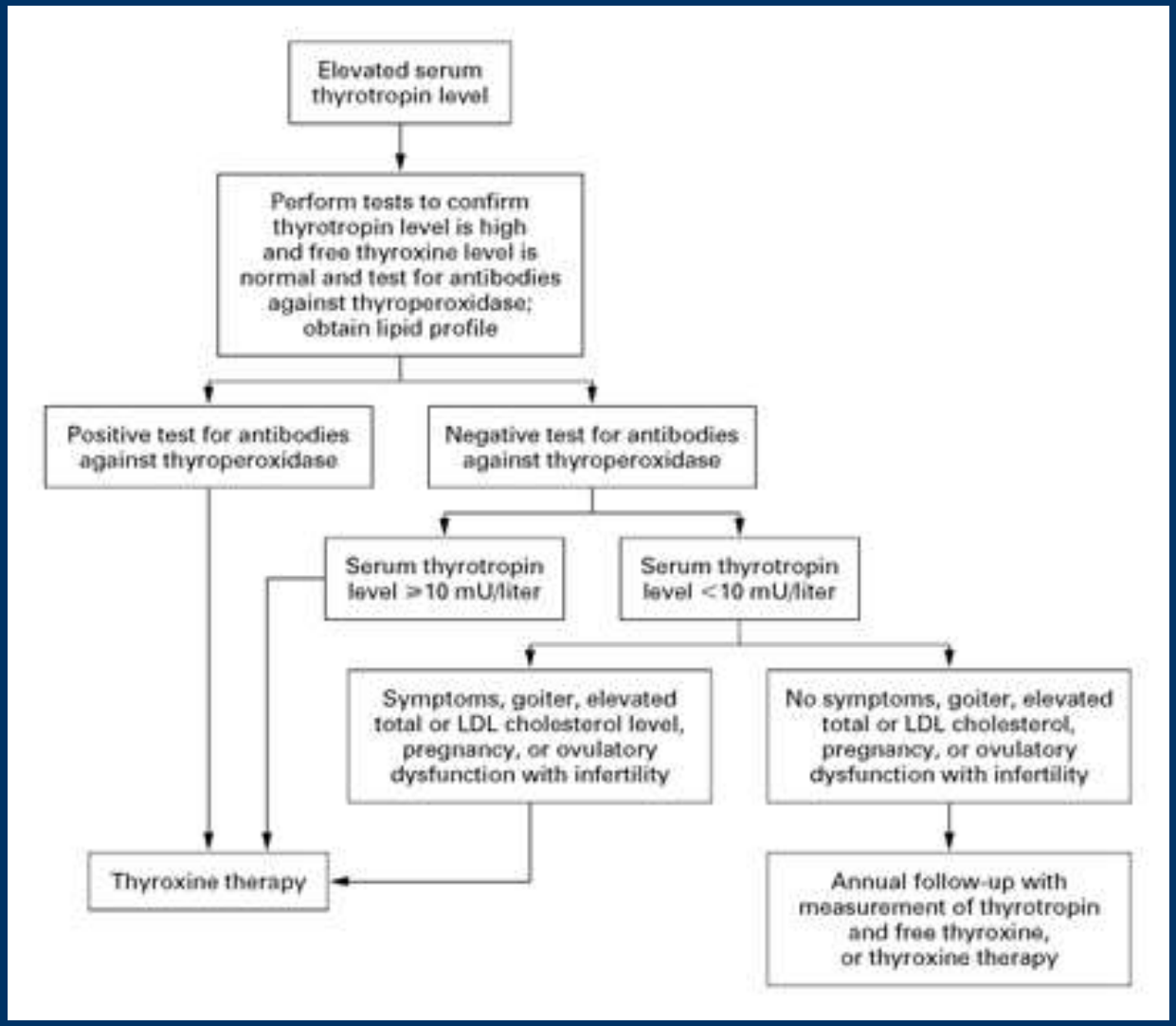
Treatment

Subclinical hypothyroidism is common especially among older women.

Who must be treated?

- **TSH > 10**
- **Goiter**
- **Positive titer of anti- TPO**
- **Hyperlipidemia**
- **Menstrual disturbance , infertility.**
- **Pregnancy**

The others must be followed annually.



Approach to subclinical hypothyroidism

Conclusions and Recommendations

Thyroxine Therapy

- An initial dose of thyroxin of 0.05 to 0.075 mg per day is usually sufficient to normalize the serum thyrotropin level.
- Patients with coronary artery disease should receive lower initial doses (e.g., 0.0125 to 0.025 mg daily).
- Serum TSH levels should be measured four to six weeks after therapy is begun, after any change in the dose, and then annually once the levels become stable.
- Thyroxin requirements may increase over time if there is progressive thyroid failure.


Thank you
Any question?