

# HYPOTHYROIDISM



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# Epidemiology

Hypothyroidism (clinical and subclinical) affects 0,2-10% of the population, most commonly women in 40-60 years of age (5-10%), 10 times less often men

Yearly incidence: 0,4 % for women and < 0.1% for men

Prevalence of subclinical hypothyroidism is 6-10%, for women up to 15% and for men 3%.

Incidence of hypothyroidism in newborns is 1 in 3000-4000 births

# Etiology

The most common cause of hypothyroidism is thyroid disease – **primary hypothyroidism**

Rarely is caused by pituitary disease - **secondary hypothyroidism**,

Extremely rare is caused by hypothalamic disorders- **tertiary hypothyroidism**

Primary hypothyroidism is the most frequently of all, 95%.

Iodine deficiency is the most common cause of hypothyroidism in the world, autoimmune thyroid disorders afterwards then surgery. Other causes are congenital deficiency of thyroid tissue or thyroid hormone synthesis disorders, radioiodine ablation, neck irradiation, non-immune inflammation and certain medications.

# CAUSES OF HYPOTHYROIDISM

(sufficient iodine intake)

1. **Congenital**
2. **Spontaneous-** chronic autoimmune disorders
  - a) *Atrophic autoimmune thyroiditis*
  - b) *Hashimoto's thyroiditis*
3. **Iatrogenic** (destructive hyperthyroidism treatment, goitrogens, drugs)

# HYPOTHYROIDISM (DEFINITIONS)

## **I According to the time of occurrence**

- Congenital
- Acquired

## **II According to the level of endocrine disorder (etiology)**

- Primary
- Secondary and tertial (central)

## **III According to the level of disease (clinical presentation)**

- Clinical
- Subclinical

**Myxedema**  
**Cretenism**

# 1. ACCORDING TO THE TIME OF OCCURRENCE

## 1. CONGENITAL:

Thyroid insufficiency develops in utero, and it is manifested on the time of the birth

# with goitre

# without goitre

## 2. ACQUIRED: in previously healthy people



# CONGENITAL HYPOTHYROIDISM INCIDENCE

## 1. WHITE RACE

- Europe 1:3000 up to 1:7300
- America 1:3600 up to 1:5700

## 2. YELLOW RACE

- Japan 1:5700

## 3. BLACK RACE

1:20000

## 4. INDIANS

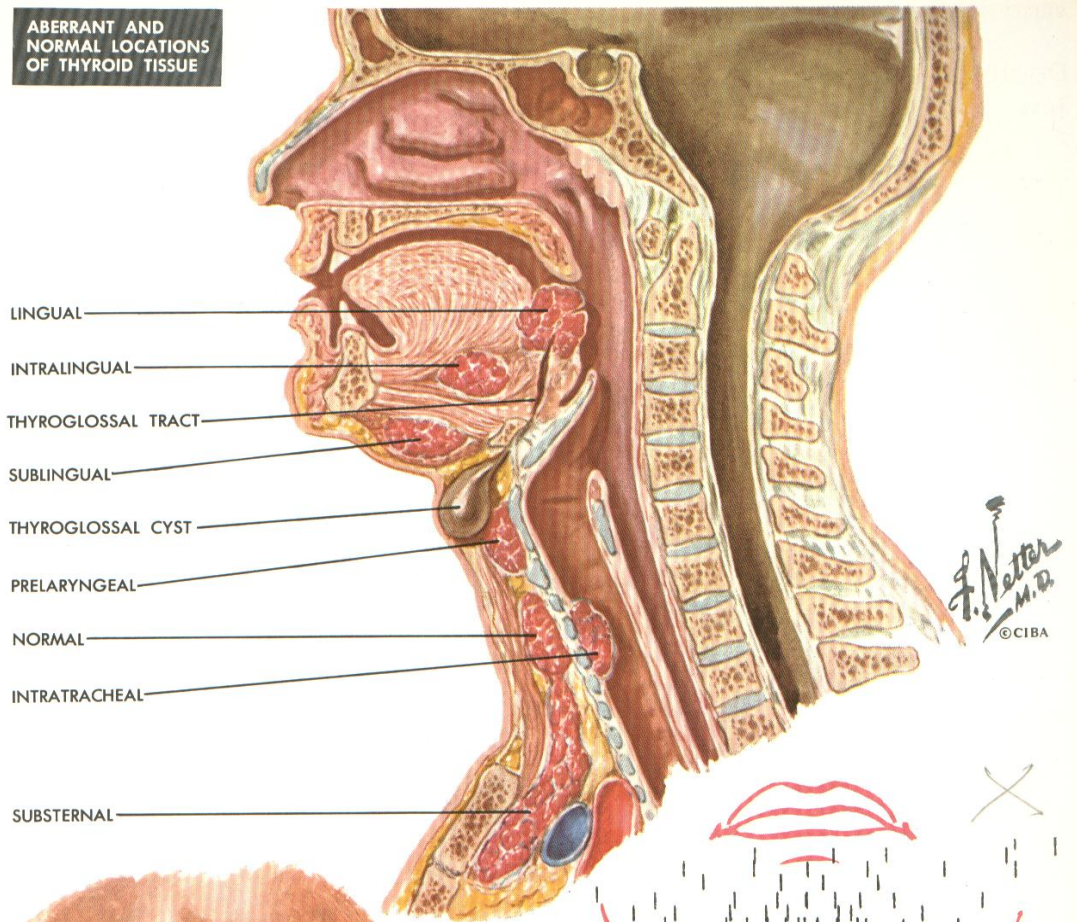
1:700

- **CROATIA 1:4127**

- **1 : 3500-4000 newborns**

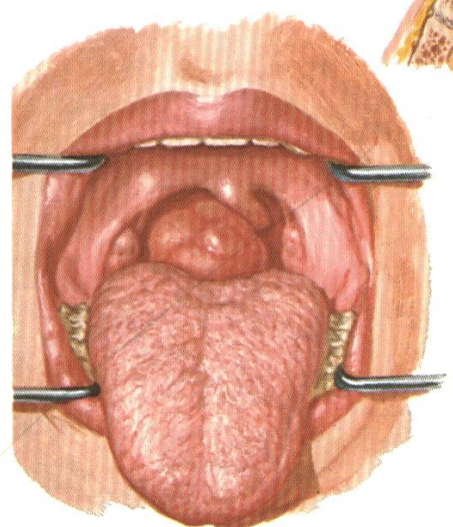


ABERRANT AND  
NORMAL LOCATIONS  
OF THYROID TISSUE

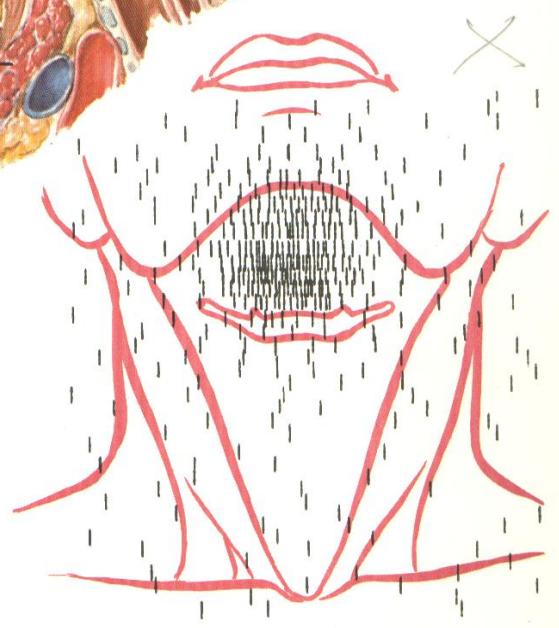


*F. Netter*  
M.D.  
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# Lingual thyroid gland



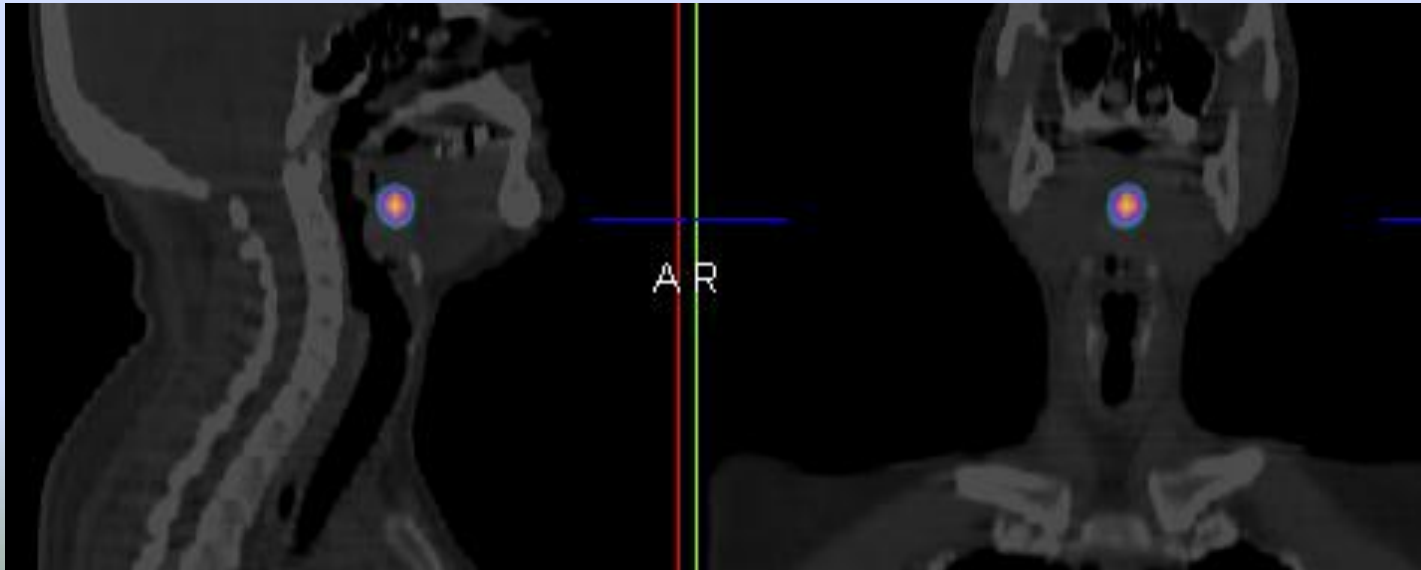
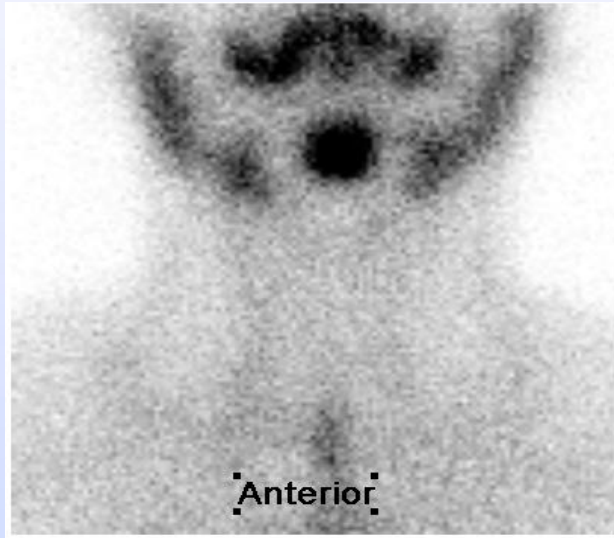
LINGUAL THYROID



SCINTIGRAM, LINGUAL THYROID



# Lingual thyroid gland



## **2. ACCORDING TO THE PATHOGENESIS** (due to the level of endocrine disorder)

- 1) primary (thyroid gland level)**
- 2) secondary (pituitary gland level)**
- 3) tertiary (hypothalamic level)**
- 4) periphery (receptors or postreceptor defect)**

# Primary hypothyroidism (thyroprivic)

- primary idiopathic hypothyroidism
- postablative
- congenital hypothyroidism due to thyroid aplasia/dysplasia
- atrophic thyroiditis
- hypothyroidism with goitre:
  - Hashimoto's thyroiditis
  - endemic iodine deficiency
  - antithyroid substances
  - iodide-induced goitre with hypothyroidism
  - hereditary defects of thyroid hormone synthesis

# Secondary and tertiary hypothyroidism (trophoprivic)

**Trophoprivic hypothyroidism**- disorder of the hypothalamic- pituitary axis

- Sheehan syndrome
- infiltrative process in hypothalamic or pituitary area
  
- Usually there is a lack of the other pituitary hormones
- low T3 and T4
- TSH low
- TRH-test to differentiate between hypothalamic or pituitary etiology

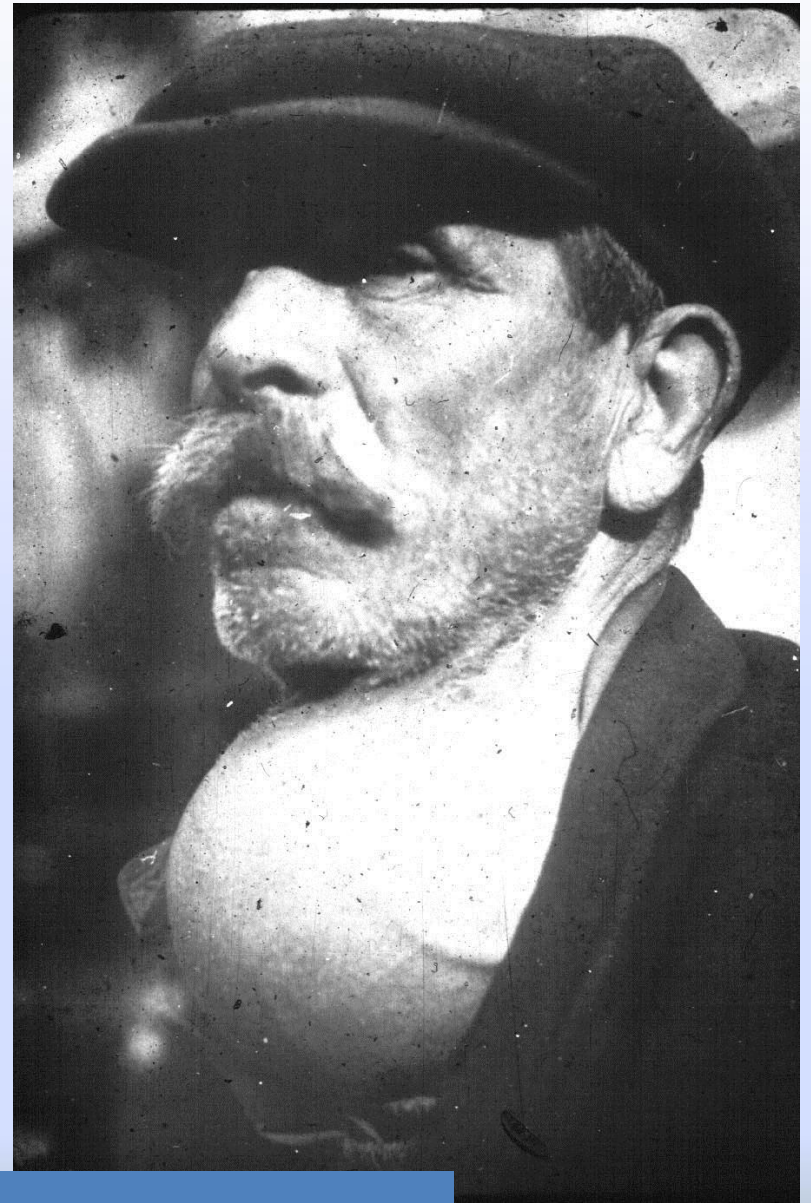
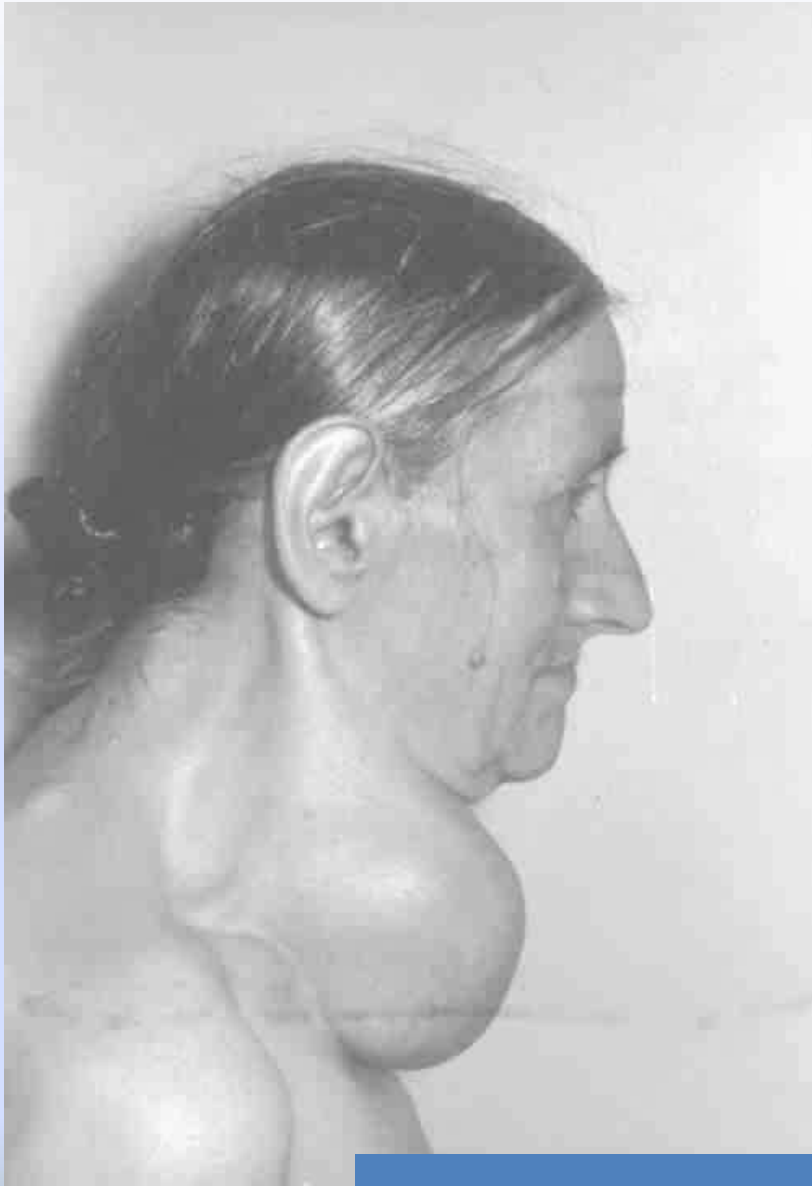
# Clinical hypothyroidism

Spontaneous:	43%
After I-131 treatment:	22%
Postoperative:	9%
Thyroiditis:	8%
Thyroid cancer:	8%
Hypopituitarism :	4%
Medications:	1%

# ENDEMIC GOITER

- Goiter in more than **5%** of population or in more than 5% of the school age children (6-12 years)
- **Insufficient iodine intake**- the most common cause of endemic goiter
- Less common cause of endemic goiter in some areas are natural goitrogens in the daily diet





**Endemic goiter**

# Endemic cretinism

- In infants as a result of an intrauterine thyroid insufficiency, the most severe of all endemic goiters
- Mental retardation, stunted growth (dwarfism)
  - A hoarse-sounding cry
  - Somnolence
  - Feeding difficulties
  - Opstipation
  - Dry skin
  - Slow growth of hair and nails
  - Epiphyseal dysgenesis



Endemic  
cretinism

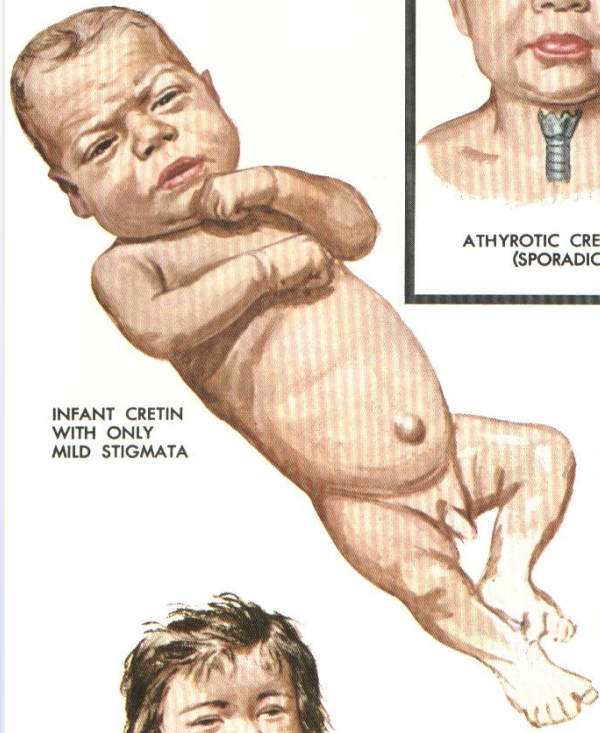




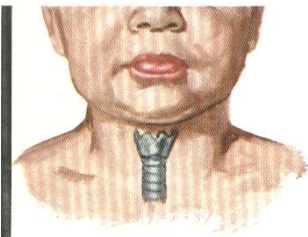
# MYXOEDEMATOUS CRETENISM



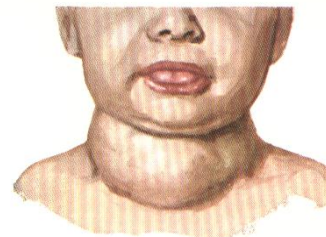
A man and 3 females (age range, 17-20 y) with myxedematous cretinism from the Republic of the Congo in Africa, a region with severe iodine deficiency



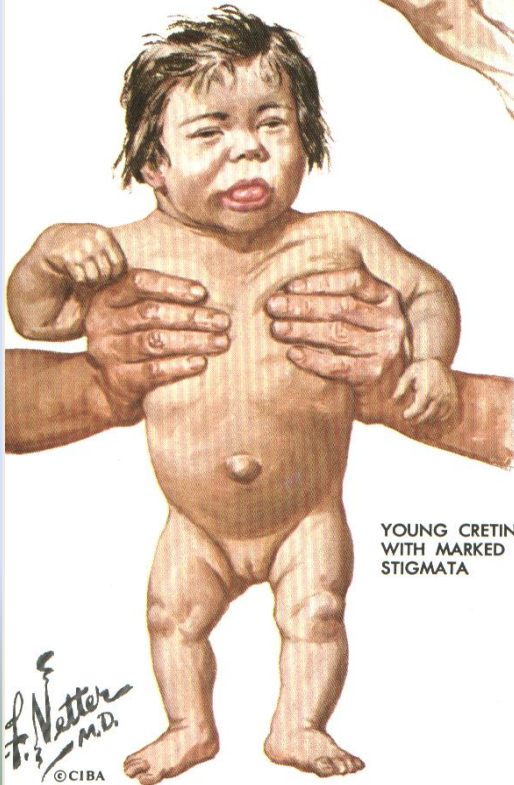
INFANT CRETIN WITH ONLY MILD STIGMATA



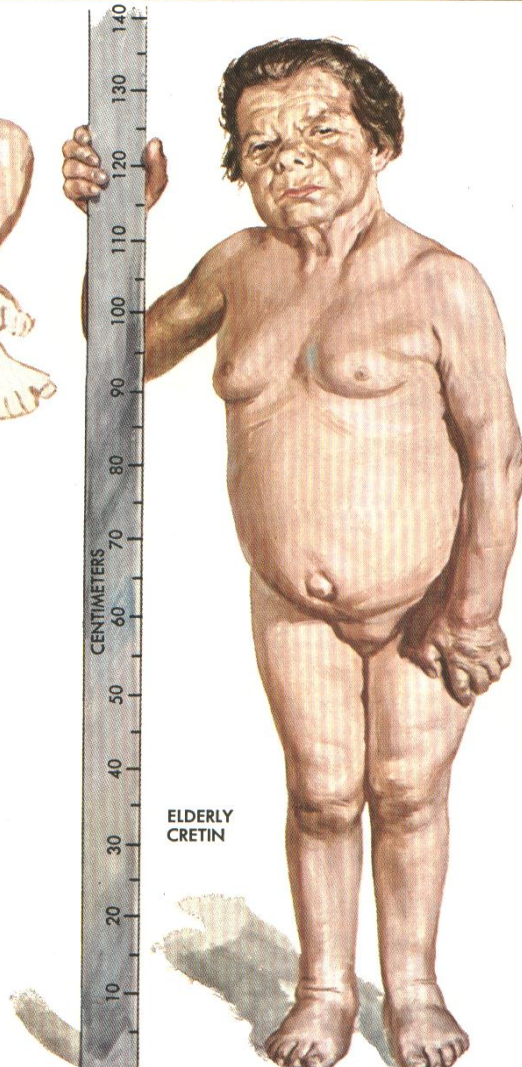
ATHYROTIC CRETINISM (SPORADIC)



GOITROUS CRETINISM (ENDEMIC)



YOUNG CRETIN WITH MARKED STIGMATA



ELDERLY CRETIN

*F. Netter M.D.*  
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# MENTAL DEVELOPMENT

- Thyroid hormones are essential for fetal and post-natal CNS development
  - development, number of cells
  - synapses development



# THYROID ONTOGENESIS

- 8 week – FETAL THYROID ACTIVITY — thyroglobulin synthesis
- 10 week – beginning of iodine capture— followed by thyrosine iodination
- 12 week – production of colloides
- **12 week** – fetal hypothalamic-pituitary-thyroid axis operates independently of maternal axis
- Maternal T3,T4,TSH cross the placenta in a **small amount**

**Although clinical presentation is known to all medical stuff, huge percentage of cases are revealed one month after birth.**

**Before the hypothyroidism screening tests were introduced in clinical practice, only 1/6 of cases have been revealed in the first quarter of life.**

# **SCREENING TESTS**

- 1. METHOD= TSH assessment (Europe, Japan)**
- 2. METHOD= T4 assessment**

# IODINE PROPHYLAXIS IN CROATIA

- 1930. – 1941. sporadic iodine prophylaxis
- **1953.** The first law on mandatory iodination of salt  
**10 mg KI/kg NaCl**
- Ten years after goiter incidence in Croatia decreased for three times and cretenism was eradicated

**9.10.1996.**

**NEW REGULATION  
ON SALT IODINATION**

**25 mg KI/kg NaCl**

**III According to the disease stage (clinical presentation)**

-Clinical

-Subclinical

**CLINICAL HYPOTHYROIDISM**  
**Clinical manifestations**



# Skin, connective tissue, nails and hair

- pale and cold
- dry and rough
- fullness of the face, bloated appearance, edema
- hoarse and husky voice



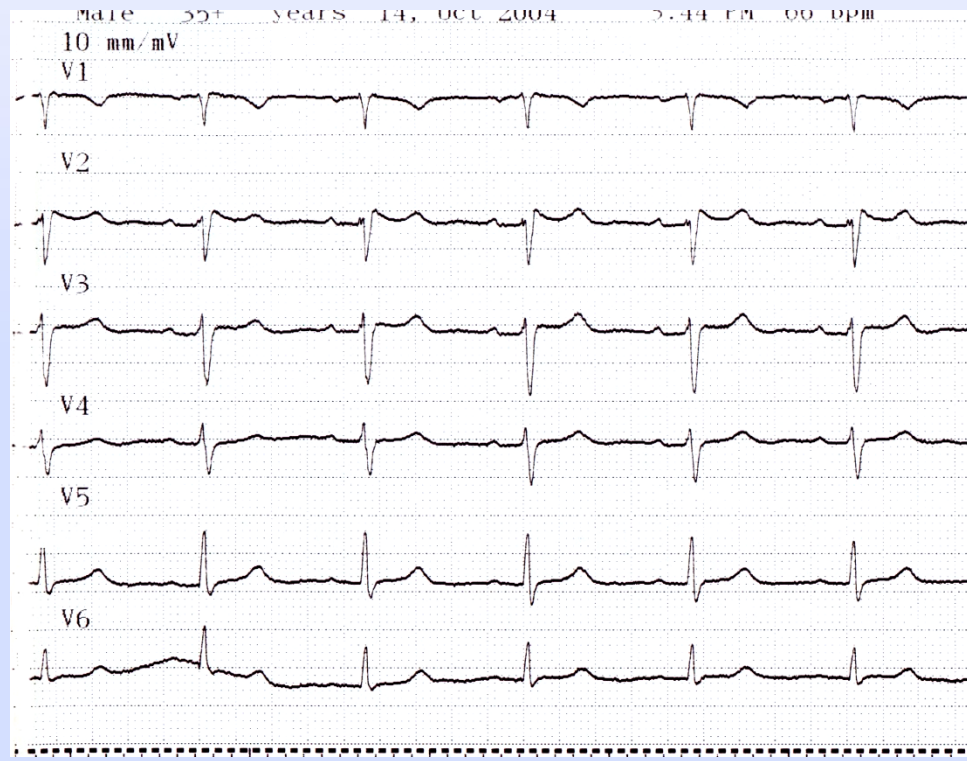
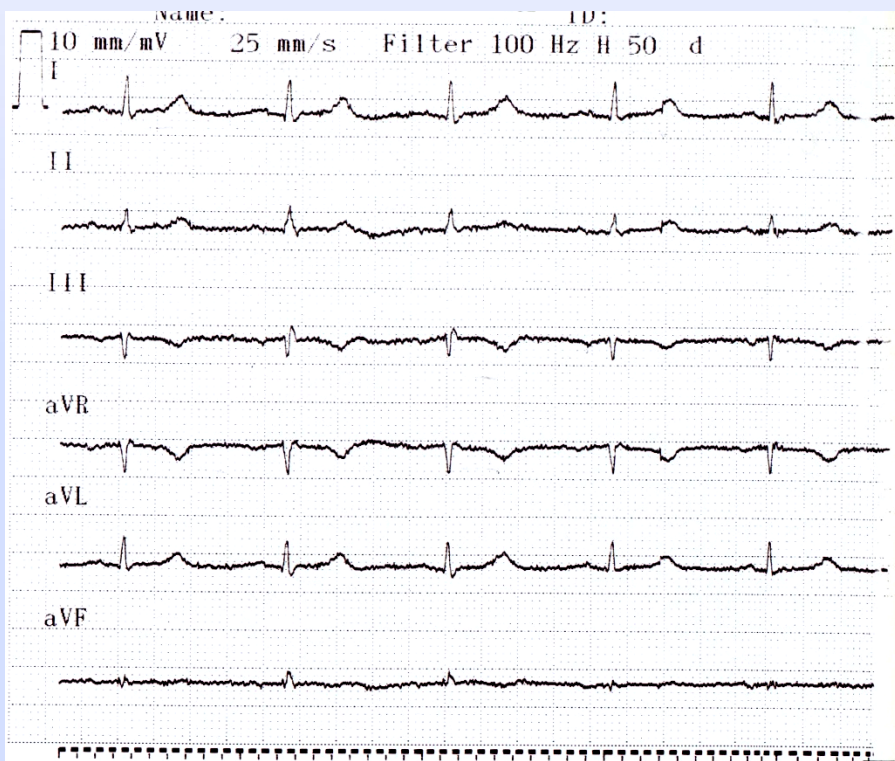
- hair and body hairs: dry, rough, lackluster, brittle, hair loss
- nails: thin, striated, brittle
- rarely cutted
- skin has some yellowish tone
- bruises propensity

# Cardiovascular system

- decreased MV, heart stroke volume, frequency, blood and plasma volume
- peripheral vasoconstriction
- decreased brain blood flow and oxygen consumption
- decreased ERPF and GFR up to 30%
- decreased metabolism up to 50%

- hypothermia
- cold intolerance
- bradycardia
- enlarged- dilatated heart, weak contractions
- pericardial effusion
- less audible heart sounds

- EKG: sinus bradycardia, low voltage, prolonged PQ interval, ST segment depression and negative T waves
- Rtg.: enlarged heart
- mild diastolic hypertension



# Respiratory system

- dyspnoea
- hypoxemia
- hypercapnia
- pleural effusion
- respiratory failure

# Gastrointestinal system

- slow intestinal movements
- meteorism
- opstipation
- weight gain despite decreased apetite
- tendency to cholelithiasis development



# CNS

- insufficient blood circulation in the brain that leads to hypoxia
- intellectual function slowdown
- slowed thinking, lack of concentration
- weak memory
- dullness

- headaches, syncope
- cold intolerance
- slowed and slurred speech
- somnolence
- limb stiffness, paresthesions

- slow reflexes, reduction of peripheral sensibility
- apathy, depression, aggression and maniacal attacks
- confusion, dementia, somnolence, lethargy, stupor, coma

# Muscular system

- stiffness and muscle aches
- slow movements and reflexes
- general weakness and fatigue
- increased level of muscle enzymes: CK, AST, LDH

# Skeletal system

- thyroid hormones are essential for the skeletal growth and development
  - slow growth and skeletal development - epiphyseal dysgenesis
- dwarfism

# Kidneys, water and electrolytes metabolism

- decreased ERPF and GFR up to 30%
- fluid retention, salt, mucopolysaccharides and proteins in interstitial space in every kind of tissue
  - edema, effusions, ascites
  - decreased plasma volume and MV (25%)
  - diastolic hypertension due to peripheral vasoconstriction (arteries)

# Hematopoietic system

- anemia – 30%
  - hypoplastic
  - sideropenic
  - pernicious
- increased capillary fragility –bruises



# Reproductive function

- in early childhood- sexual immaturity
  - women: irregular, profusely menstrual bleedig, anovulation, decreased fertility, ovarian atrophy, amenorrhea, decreased libido, abortions
  - men: decreased libido, impotence, oligospermia

# Pituitary and adrenal gland

- hyperprolactinemia
- galactorrhea and amenorrhea
- enlarged pituitary gland
- concentrations of other hormones in regular range, but decreased functional reserve

# The metabolism of proteins, carbohydrates and fats

- increased cholesterol
- increased triglycerides
- increased low-density lipoproteins
- atherosclerosis
- hypothermia

# The frequency of symptoms and signs (%)

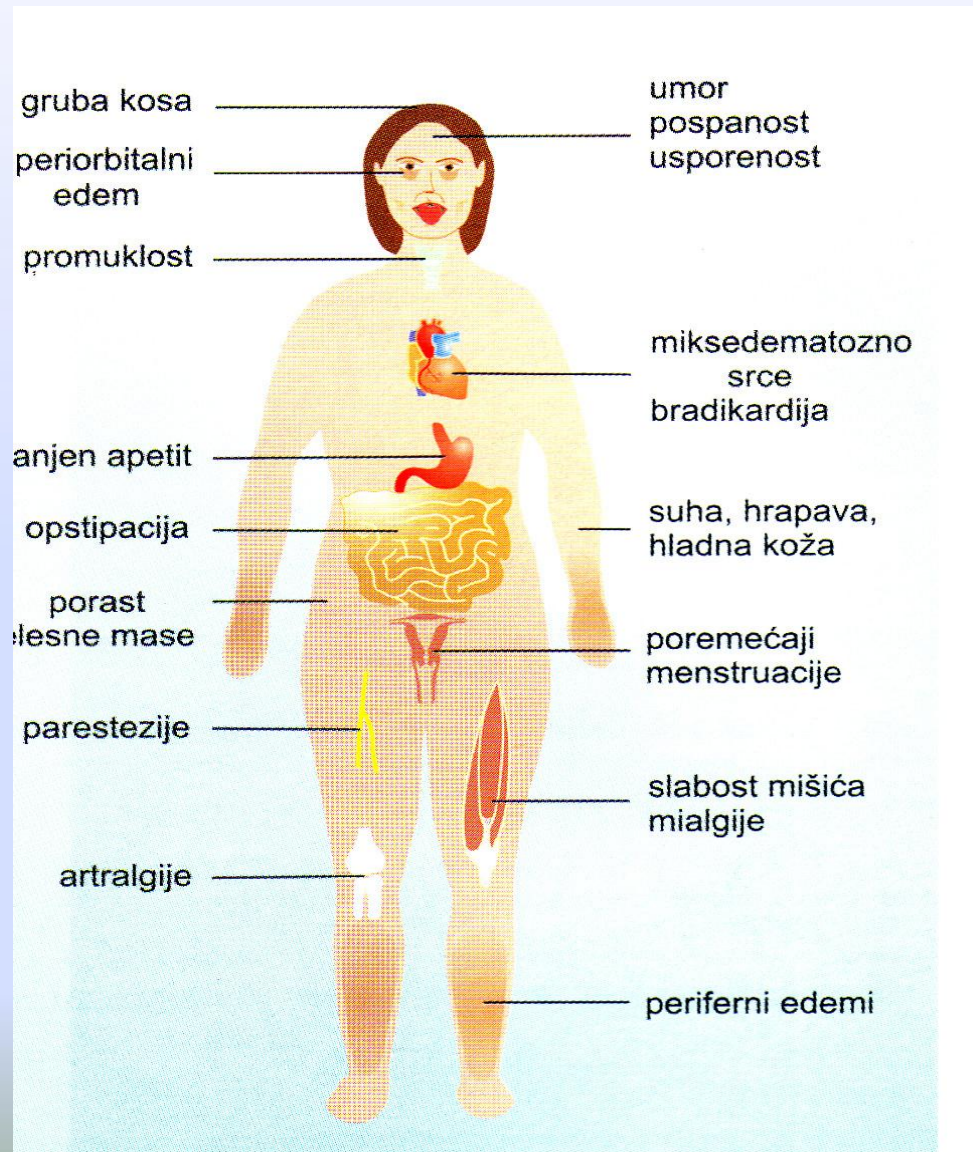
- faintness 99
- dry skin 97
- rough skin 97
- slowed speech 91
- swelling of the eyelids 90
- cold intolerance 89
- decreased sweating 89
- cold skin 83
- facial edema 79

# The frequency of symptoms and signs (%)

- brittle hair 76
- pale skin 67
- memory impairment 66
- constipation 61
- weight gain 59
- hair loss 57
- dispnoea 55
- peripheral edema 55
- hoarseness 52

# Clinical findings are due to slower metabolism

- coarse hair
- periorbital edema
- hoarseness
- decreased appetite, weight gain
- constipation
- paresthesia
- arthralgia
- myxomatous heart, bradycardia
- dry, rough, cold skin
- fatigue, drowsiness, slowness



# Diagnosis

- clinical presentation
- laboratory tests
- morphological diagnosis



# Thyroid gland

- decreased
- normal size
- increased

# Laboratory evaluation of thyroid function

- **TSH**, T4, T3
- Antibodies
- Biochemical tests (lipids, transaminases, iron....)

# TSH

- TSH third generation: high sensitivity
- Increased value:
  - HYPOTHYROIDISM- PRIMARY
  - PITUITARY ADENOMA
  - NON THYROID DISEASES
  - THYROXINE RESISTENCE
- decreased value:
  - THYROTOXYCOSIS...
  - HYPOTHYROIDISM- SECONDARY

# Thyroid hormones- T4

- The thyroid gland is the only source of endogenous T4
- T4 is an indicator of thyroid function
- ***T4 or FT4***

# TBG

INCREASED : T4



- contraceptives and other estrogen sources
- pregnancy
- neonatal age
- infectious icterus
- chronic active hepatitis
- biliary cirrhosis
- acute intermittent porphyria

DECREASED: T4



- androgens
- glucocorticoids
- chronic liver disease
- severe systemic disease
- nephrotic syndrome
- malnutrition

# Thyroid hormones– T3

- **T3**: 20% is from thyroid origin (10% synthesis, 10% by intrathyroid conversion of T4), 80 % is converted from T4 in the periphery
- 20-30% hypothyroid patients have T3\* in normal range
- 70% of hospitalized patients have low T3, without thyroid disease<sup>#</sup>
- **T3:T4 ratio** is changed in functional thyroid disorders and in systemic disorders

\* Larsen PR: Tests related to thyroid hormones in blood: thyroid hormone concentrations. u: Ingbar, Braverman ur. The Thyroid: Fundamental and clinical Text.

<sup>#</sup> Bermudez F, Surks MI, Oppenheimer JH. High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. J Clin Endocrinol Metab. 1975;41:27-40.

# ATD (Autoimmune thyroid disease)

- Mb. Graves-Basedow
- Autoimmune thyroiditis:
  - Hashimoto's thyroiditis
  - atrophic thyroiditis
- ATD is often associated with other autoimmune diseases: diabetes, anemia, RA, vitiligo.....
- Antibodies to thyroid antigens (thyroglobuline, peroxidase, TSH receptors)

# Thyroid antibodies

- In healthy population (26% f, 9% m.; elderly) –increased risk of hypothyroidism development
  - Microsomal antibodies or Anti-thyroid peroxidase antibodies (MSAt or antiTPO):
    - 90-95% patients with thyroiditis
    - 80% patients with Mb. Basedow
    - 15-20% patients with non-autoimmune thyroid disorder
  - Thyroglobulin antibodies (anti Tg):
    - 70-80% patients with thyroiditis
    - 30-40% patients with Mb Graves
    - 10-15% patients with non-autoimmune thyroid disorder
- Thyroid receptor antibody (stimulating, blocking) TRAb (Thybia)



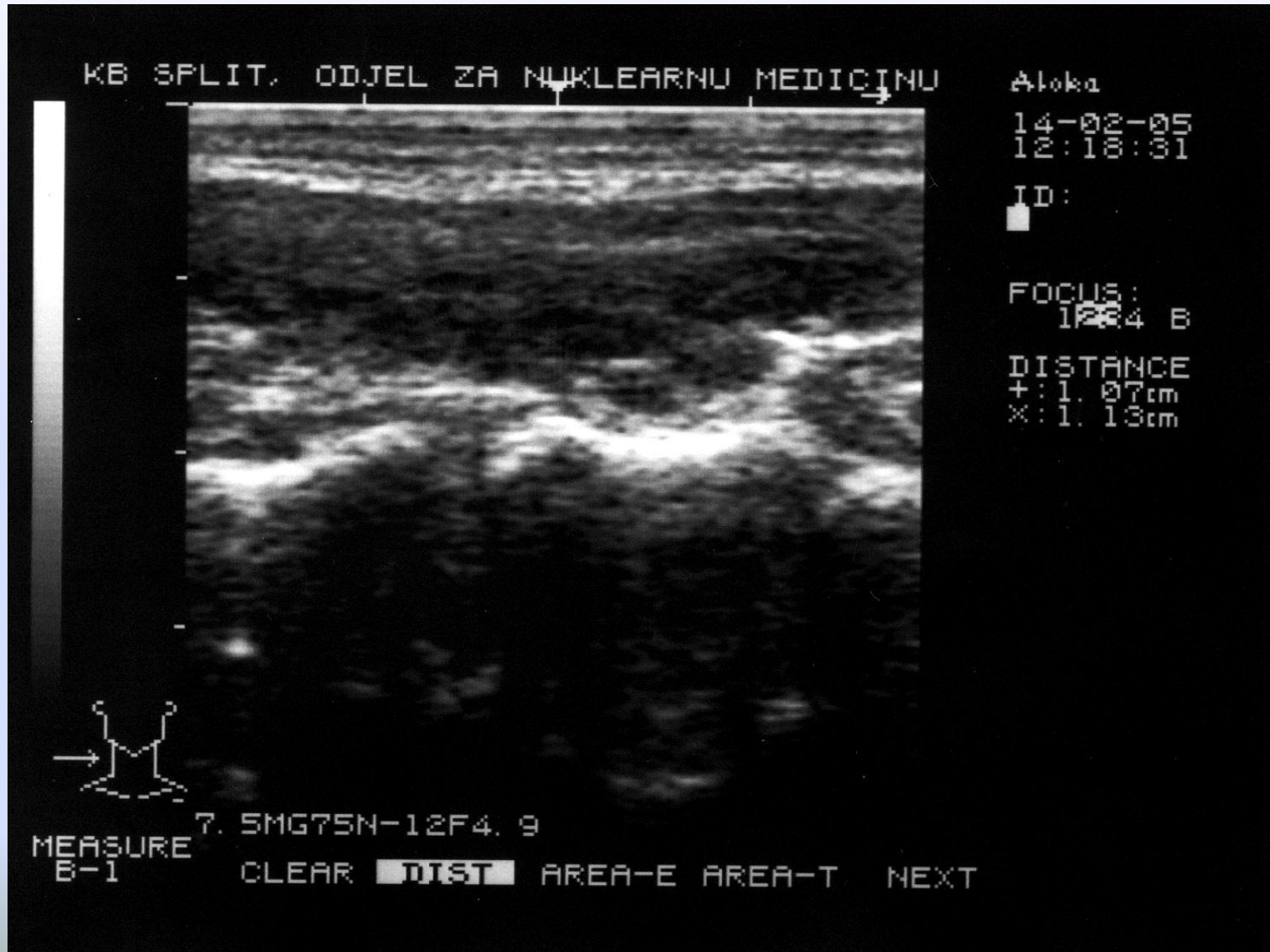
# Morphological diagnostic methods

- Ultrasonography
- FNAB: fine-needle aspiration biopsy
- Scintigraphy

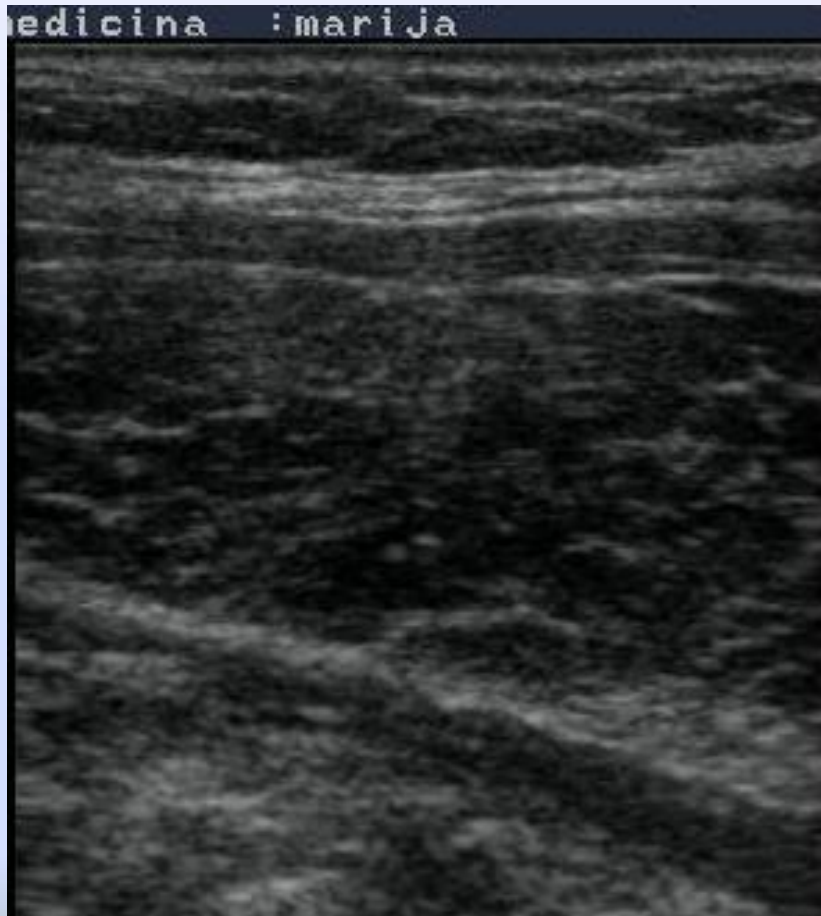
# Morphological diagnostic methods

- **ULTRASONOGRAPHY:** at first diagnosis evaluation, control US only in a case of a nodular changes in thyroid gland
- **SCINTIGRAPHY:** rarely, in a case of nodal changes, ectopic thyroid, mostly hypofunctional thyroid
- **FNAB:** diagnosis of thyroiditis, evaluation of nodal changes

# Thyroiditis



# Hashimoto's goiter



# Differential diagnosis

## **Nephrotic syndrome:**

similarity - pallor, edema, hypercholesterolemia, decreased T4 and T3

difference - massive proteinuria, severe hypoproteinemia

## **Chronic renal failure:**

similarity: anorexia, exhaustion, edema, periorbital edema, yellowish skin

difference: azotemia, changes in urine, arterial hypertension, retinopathy

## **Pernicious anemia :**

similarity: yellowish skin, limb stiffness and paresthesias, mental abnormalities, moderate macrocytic anemia, achlorhydria

difference: absent laboratory and clinical findings of hypothyroidism

**Neurosis:** due to distraction and non-specificity of early hypothyroid symptoms, patients may be declared neurotic

difference: absent laboratory and clinical findings of hypothyroidism

## **Parkinsonism:**

similarity: due to the expressionless faces elderly patients with hypothyroidism may be incorrectly diagnosed as being sick from parkinsonism

difference: absent laboratory and clinical findings of hypothyroidism

# Myxedema coma (crisis)

- the most difficult stage of hypothyroidism
- coma, hypothermia, respiratory and heart failure, myxoedema, bradycardia
- complication of long-standing, neglected hypothyroidism, elderly patients
- precipitating factor

## Myxedema coma treatment

1. immediate intravenous thyroid hormone replacement: levothyroxine in bolus dose (200-500  $\mu\text{g}$ ) - depending on the age - perorally or intravenously (po/iv)
2. L-triiodothyronine 10-15  $\mu\text{g}/8$  h perorally, levothyroxine 75- 100  $\mu\text{g}$  daily po/iv
3. Corticosteroids (Hydrocortisone 10 mg/h or 100 mg/12 h iv)
4. Antibiotics
5. Cardiotonic drugs
6. Correction of hyponatremia (isotonic or hypertonic NaCl solution)
7. Assisted ventilation,  $\text{O}_2$
8. Cautious expansion of circulating volume and vasopressors
9. Glucose intravenously 100 g/24 h

**In adults, early symptoms of hypothyroidism are nonspecific, with insidious beginning**

**Treatment: thyroxine replacement therapy to TSH normalisation**

**( $\approx 1,7 \mu\text{g}/\text{kg}$  for adults)**



# The goals of hypothyroidism treatment

- To achieve **complete clinical remission**, positive subjective feeling and absence of minor symptoms (fatigue).
- Complete physical and mental ability, especially for young patients
- To achieve normalization (ie optimization) in TSH levels, while normal and optimal values are not necessarily identical!
- Follow-up of patients on therapy:
  - TSH 1-2 times a year
  - TSH 8-10 weeks after changes in daily dose

# **HYPOTHYROIDISM**

## **Associated diseases**

- Lipid disorder
- Heart disease
- Mental disorders
- Autoimmune diseases
- Malignant diseases

# **HYPOTHYROIDISM**

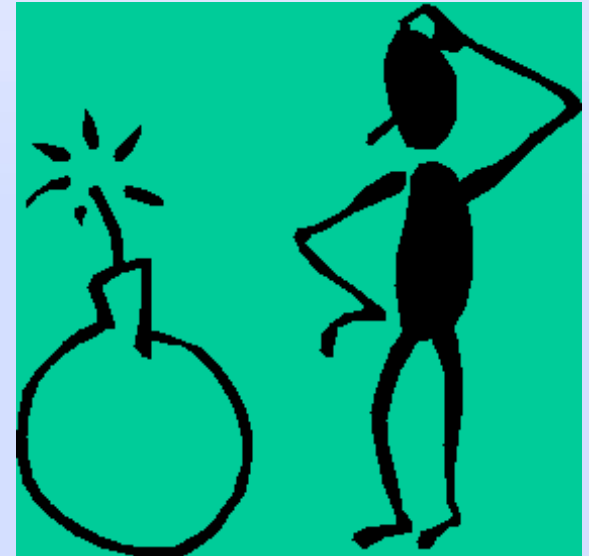
## **Associated autoimmune diseases**

- diabetes (insulin dependent)
- SLE
- rheumatoid arthritis
- Mb Addison
- myasthenia gravis
- sarcoidosis
- Sjögren's syndrome

# Amiodarone!

- 15% – 20% of patients develop hypothyroidism!
- 10% of patients manifest symptoms of hyperthyroidism!

Supervising- thyroid hormones level must be checked every three months!



# **HYPOTHYROIDISM- associated diseases**

## **Conclusions**

- hypothyroidism is systemic disease
- it is often associated with other, most commonly autoimmune disorders
- untreated hypothyroidism increases the risk of atherosclerosis and cardiovascular diseases
- hypothyroidism increases the risk of thyroid lymphomas, and reduces the risk of breast cancer

# SUBCLINICAL HYPOTHYROIDISM

What is subclinical hypothyroidism (nowdays more used phrase is “**mild**” **hypothyreosis**), is it a risk for health and and whether it should be treated?

- Elevated TSH with normal both total and free thyroid hormones
- Absence of clinical manifestations (dubious criterion, there is overlapping of asymptomatic, oligosymptomatic and symptomatic forms)
- It would be better to speak of "biochemical, laboratory" hypothyroidism, but the term subclinical become standard
- **High incidence!!!**
- **Progression toward clinical hypothyroidism(5-20% yearly?)**

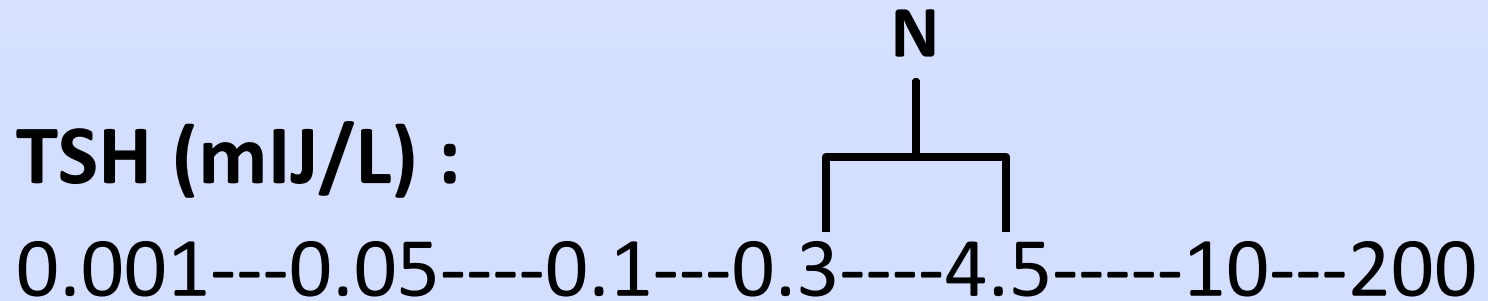
# TSH and subclinical thyroid disorders

(methodological problem)

T3 normal

T4 normal

No clinical manifestations



**IN SUBCLINICAL THYROID DISORDERS TSH LEVELS MAY VARY FROM 1000 UP TO 2000 TIMES**

# Is subclinical hypothyroidism pathological condition?

- There are growing evidence that subclinical hypothyroidism has negative effects on health
- Some studies have shown the correction of pathological parameters after LT4 treatment
- But there is **no unique answer** to whether and which patients with subclinical hypothyroidism must be treated!

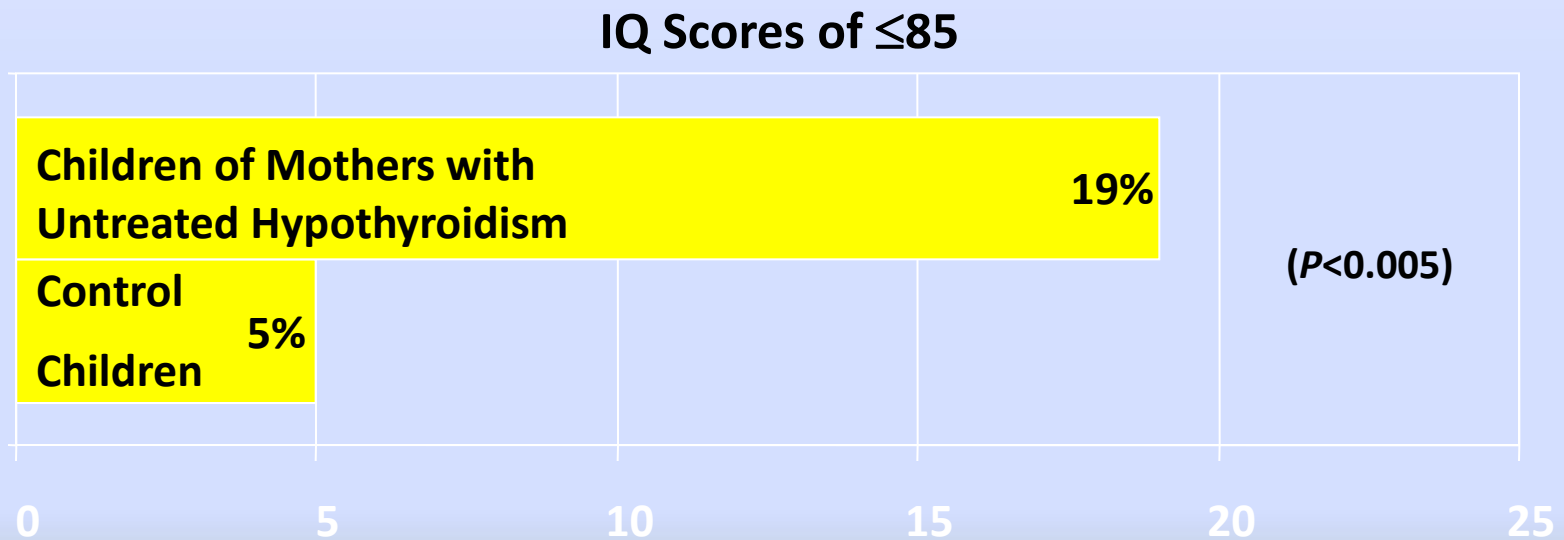


# Mild Thyroid Failure May Increase Cardiovascular Disease Risk

- Mild thyroid failure has been evaluated as a cardiovascular risk factor associated with
  - Increased serum levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels
  - Reduced high-density lipoprotein cholesterol (HDL-C) levels
  - Increased prevalence of aortic atherosclerosis
  - Increased incidence of myocardial infarction

# Consequences of Mild Hypothyroidism- Fetal Brain Development

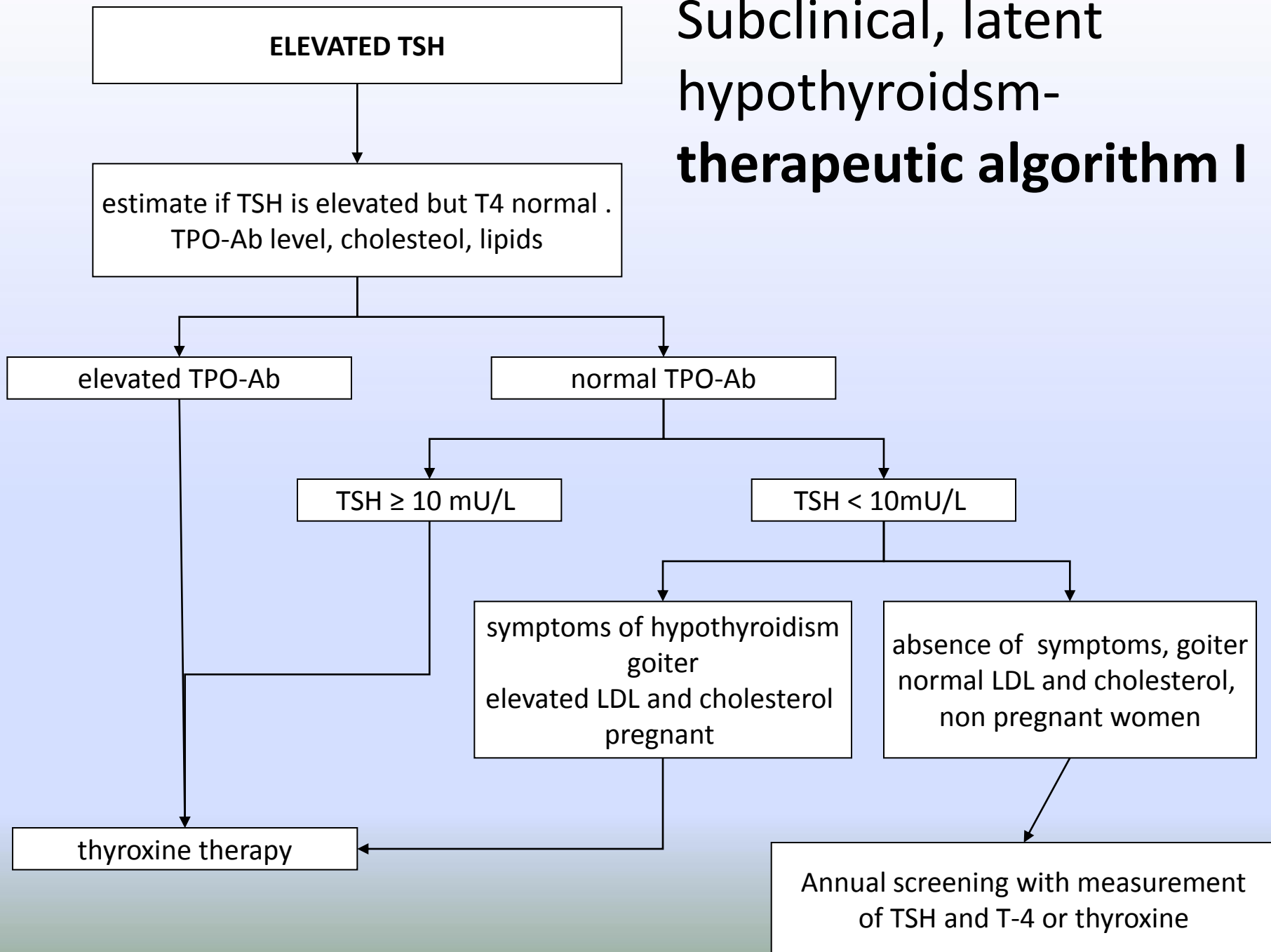
- Children of women with untreated hypothyroidism during pregnancy:
  - Averaged 7 points lower on IQ testing\*
  - Had a significant percentage (19%) of IQ  $\leq 85$



\*Full-scale Wechsler Intelligence Scale for Children.

Haddow JE, et al. *N Engl J Med.* 1999;341:549-555.

# Subclinical, latent hypothyroidism- therapeutic algorithm I



## Treatment options in subclinical hypothyroidism **therapeutic algorithm II**

- Young people with  $TSH > 3$  (or  $> 2.5$  ?). TSH in a range of 4.5-5 is not acceptable, especially if positive TPO-Ab
- The same is even more important for pregnant women and women planning pregnancy
- Every patient with  $TSH > 10$
- Every patient with  $TSH > 4.5$  and positive TPO-Ab

## **The proposed criteria that justify screening**

1. The disorder needs to be prevalent in the population
2. The disease is associated with significant morbidity / mortality.
3. The disease can not be recognised clinically in an early stage
4. The disease should be revealed early, treatment prevents progression.
5. Presence of a simple, safe, inexpensive, sensitive and specific test to diagnose the disease

**Subclinical hypothyroidism has all the criteria that justify screening!**

ORGANISATION	THROID FUNCTION SCREEING RECOMMENDATION
American thyroid association	all women and men over 35 years, screening every 5 yr.
American association of clinical endocrinology	eldery patients, especially women- screening is required
American Society for Clinical Pathology	women over 50 yr., if in need for medical help all eldery patients- screening during hospitalization, and at least every 5 years
American Academy of Family Physicians	patients over age of 60 yr- screening is required
The American College of Obstetrics and Gynecology	women in increased risk (autoimmune disorders, family history for thyriod disorders)- screening is required after age of 19 yr
The American Medical Association	women over 50 yr with incidental findings that are indicaive for overt thyroid disorder- evaluation required
The American College of Preventive Medicine	Insufficient evidence "for" or "against" screening
The Royal Society of Medicine	Screening over healthy adult population – is not justified



THE END