THYROID DISEASE IN CHILDREN

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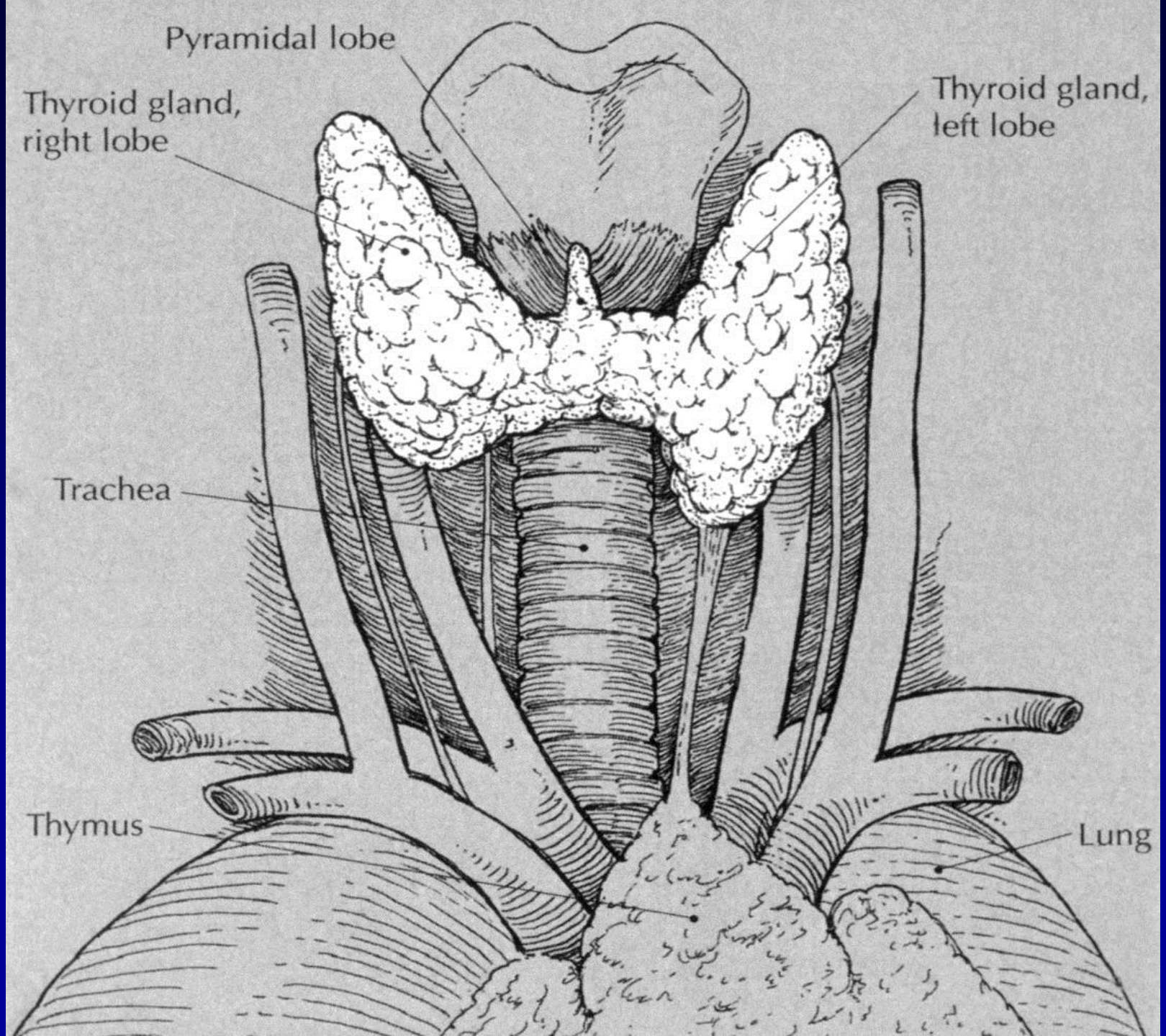
Neither I nor any immediate family members have any financial interests that may be construed as a conflict of interest with this presentation.

LEARNING OBJECTIVES

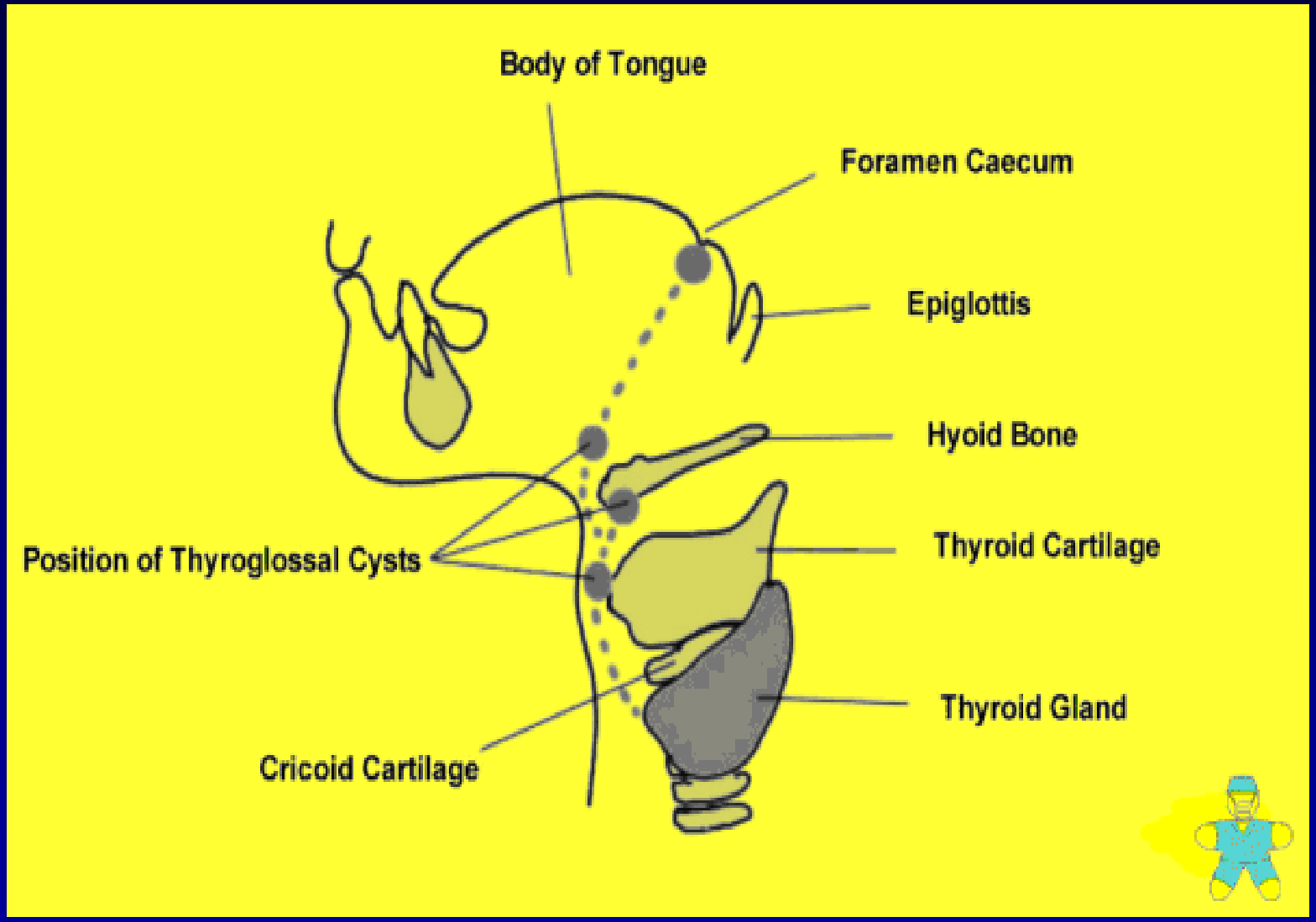
At the end of this lecture, participants will be able to:

1. Recognize and evaluate the following conditions in children:
   - congenital hypothyroidism
   - acquired hypothyroidism
   - hyperthyroidism
   - thyroid nodules
2. Initiate treatment for congenital hypothyroidism
3. Treat acquired hypothyroidism


Pyramidal lobe
Thyroid gland, right lobe
Thyroid gland, left lobe
Trachea
Thymus
Lung

Thyroid Development

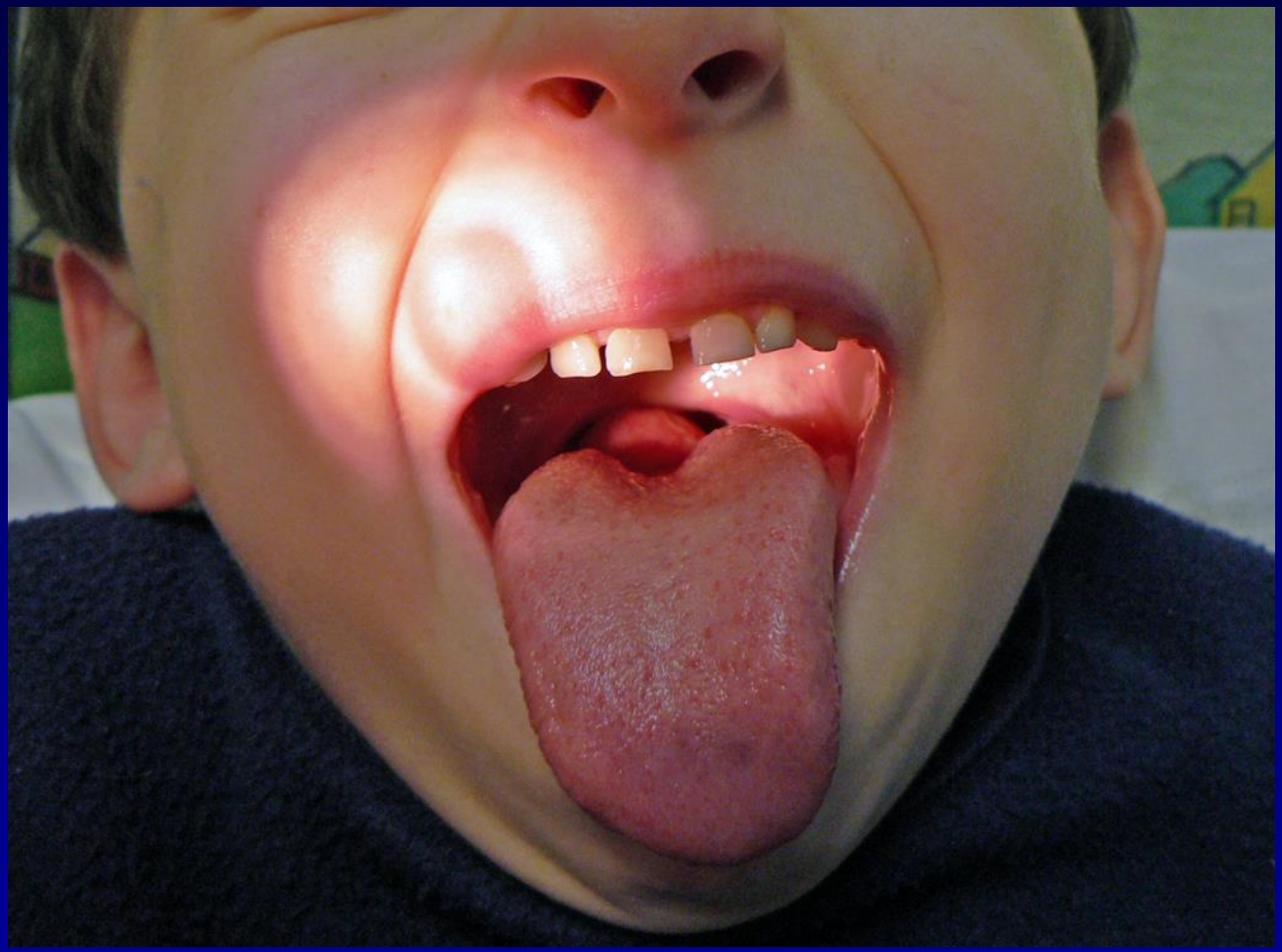
- Thyroid gland develops at 24 days gestation
- Starts development at the base of the tongue (foramen cecum)
- Connected to the tongue via thyroglossal duct
- Arises from an outpouching of the forgut (endoderm)
- Genes Involved:
  - NKX2.1 (TTF-1)
  - TTF-2 (FOXE1)
  - PAX-8


Body of Tongue
Foramen Caecum
Epiglottis
Hyoid Bone
Position of Thyroglossal Cysts
Thyroid Cartilage
Thyroid Gland
Cricoid Cartilage

Thyroid Development

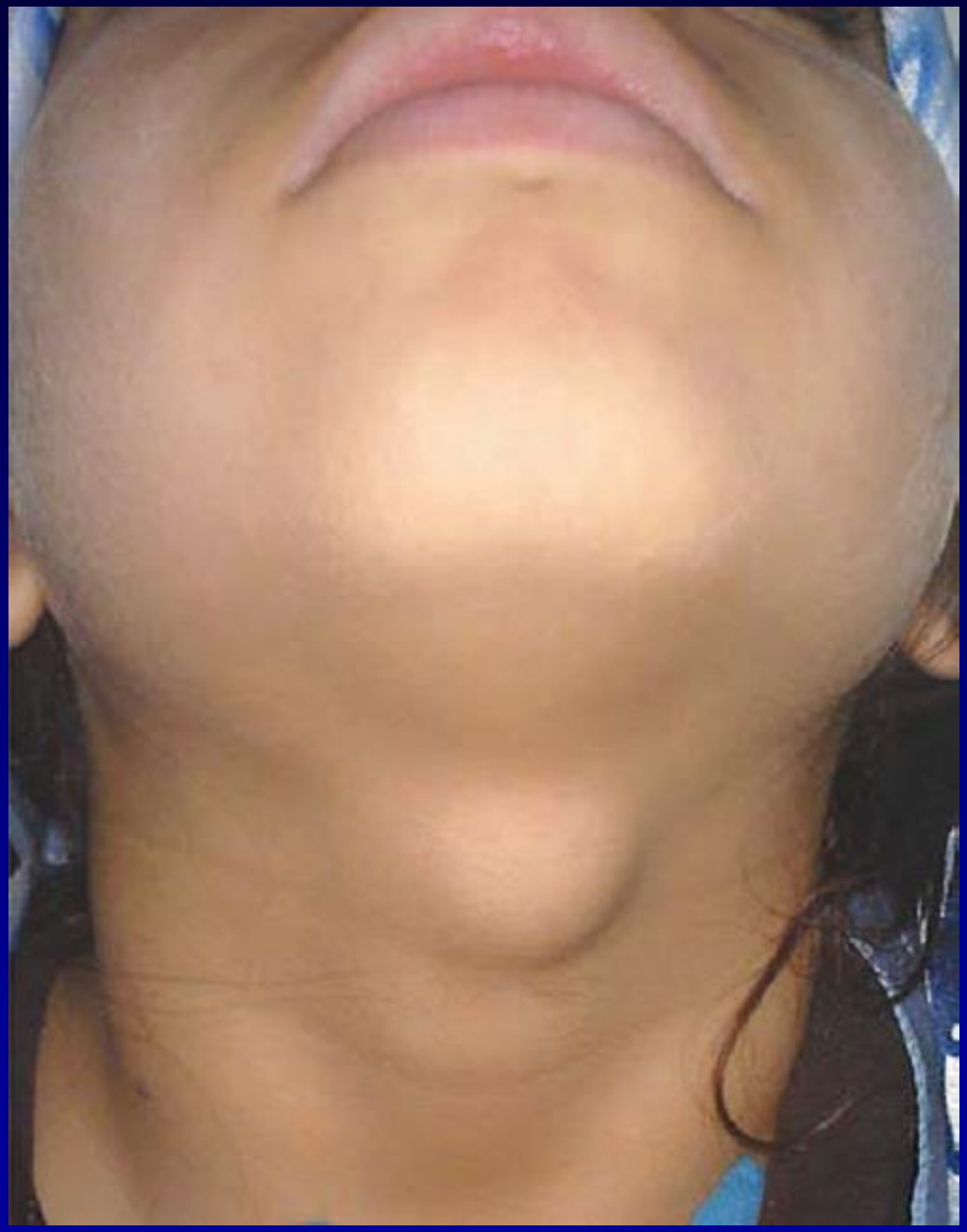
- Migrates down to the normal location over the thyroid cartilage by 8-10 weeks
- Thyroglossal duct is the remnant; involutes

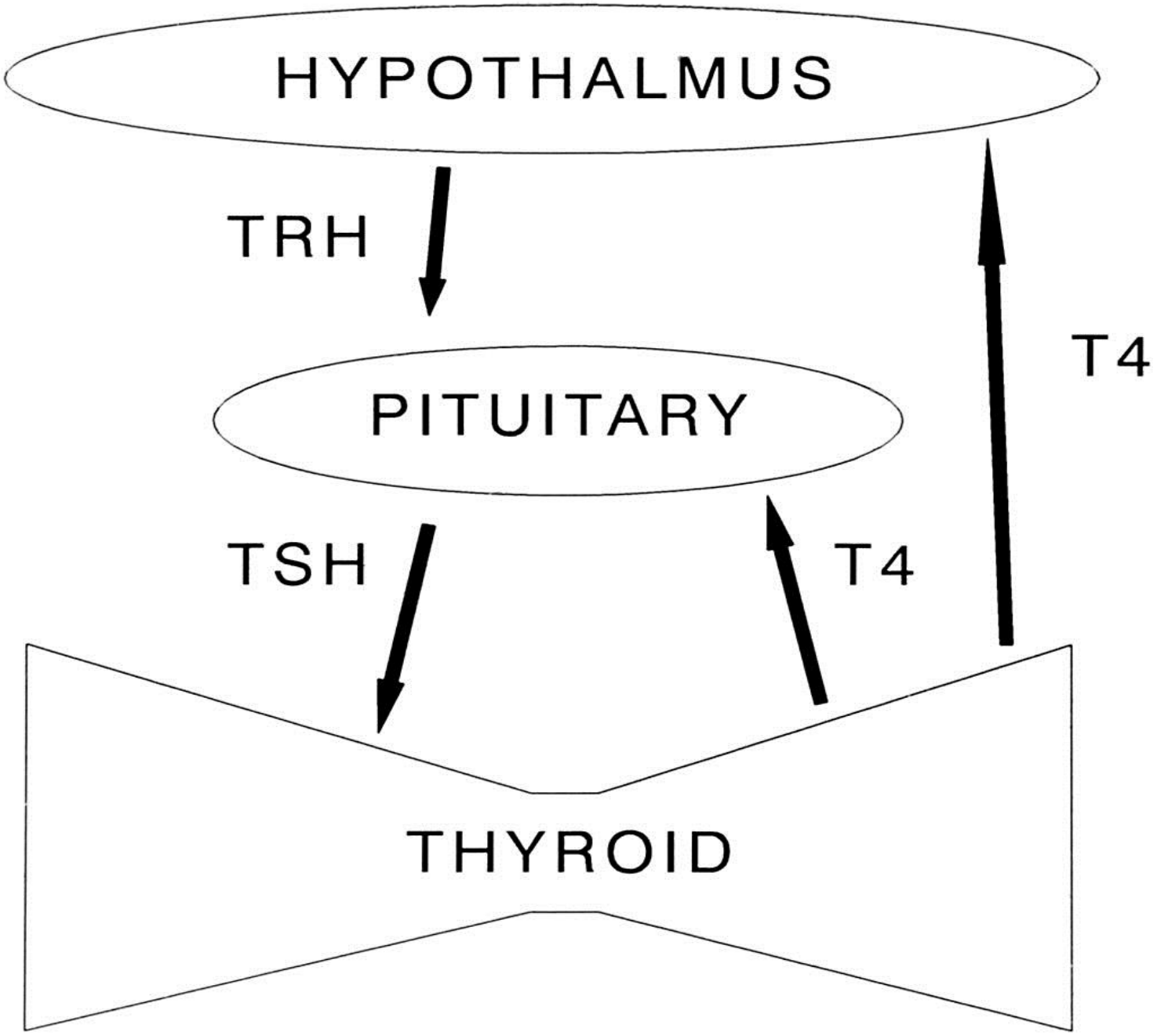
Lingual Thyroid

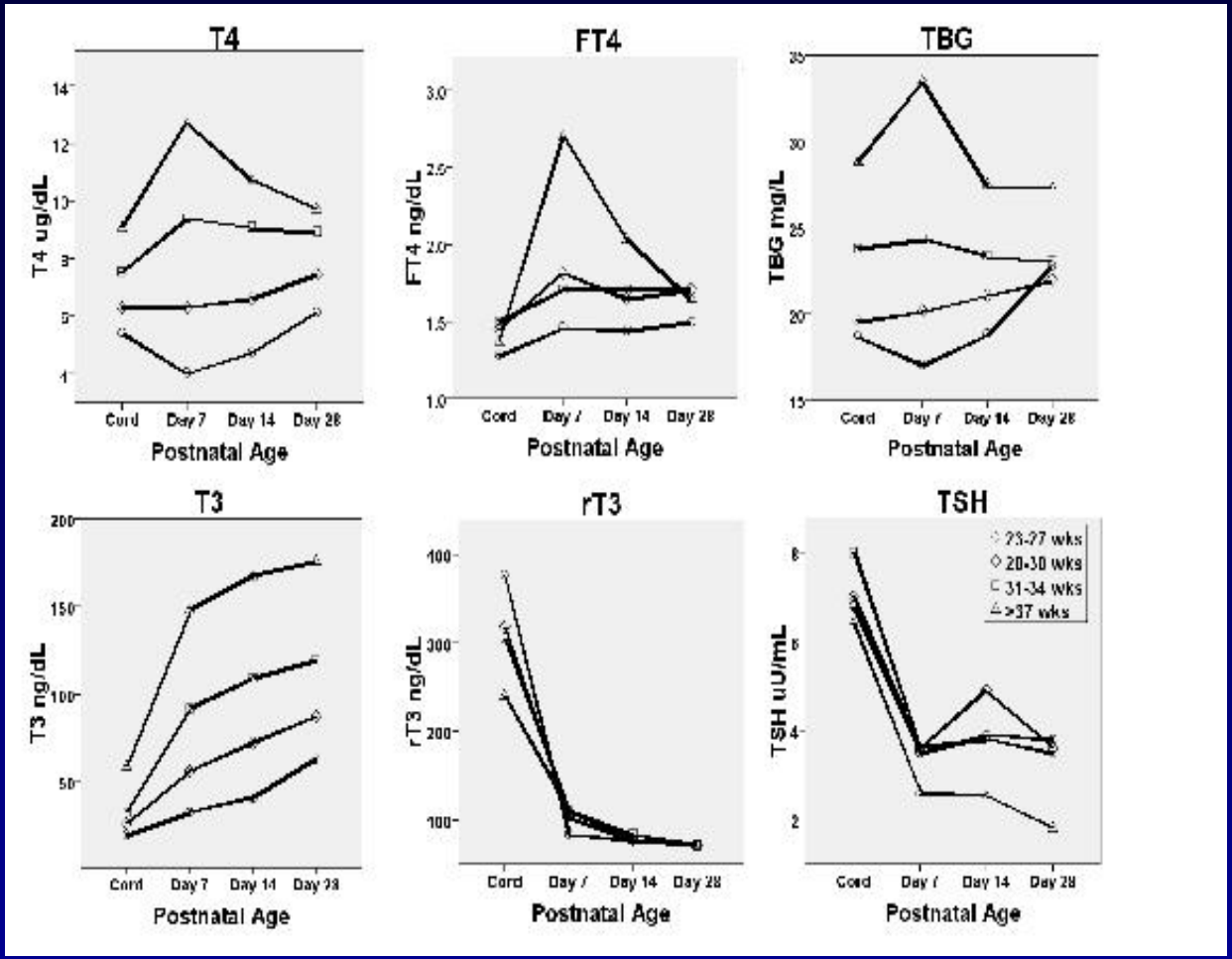


Courtesy of Dr. Dennis Brenner

Ectopic Thyroid




HYPOTHALMUS
TRH
PITUITARY
T4
TSH
T4
THYROID

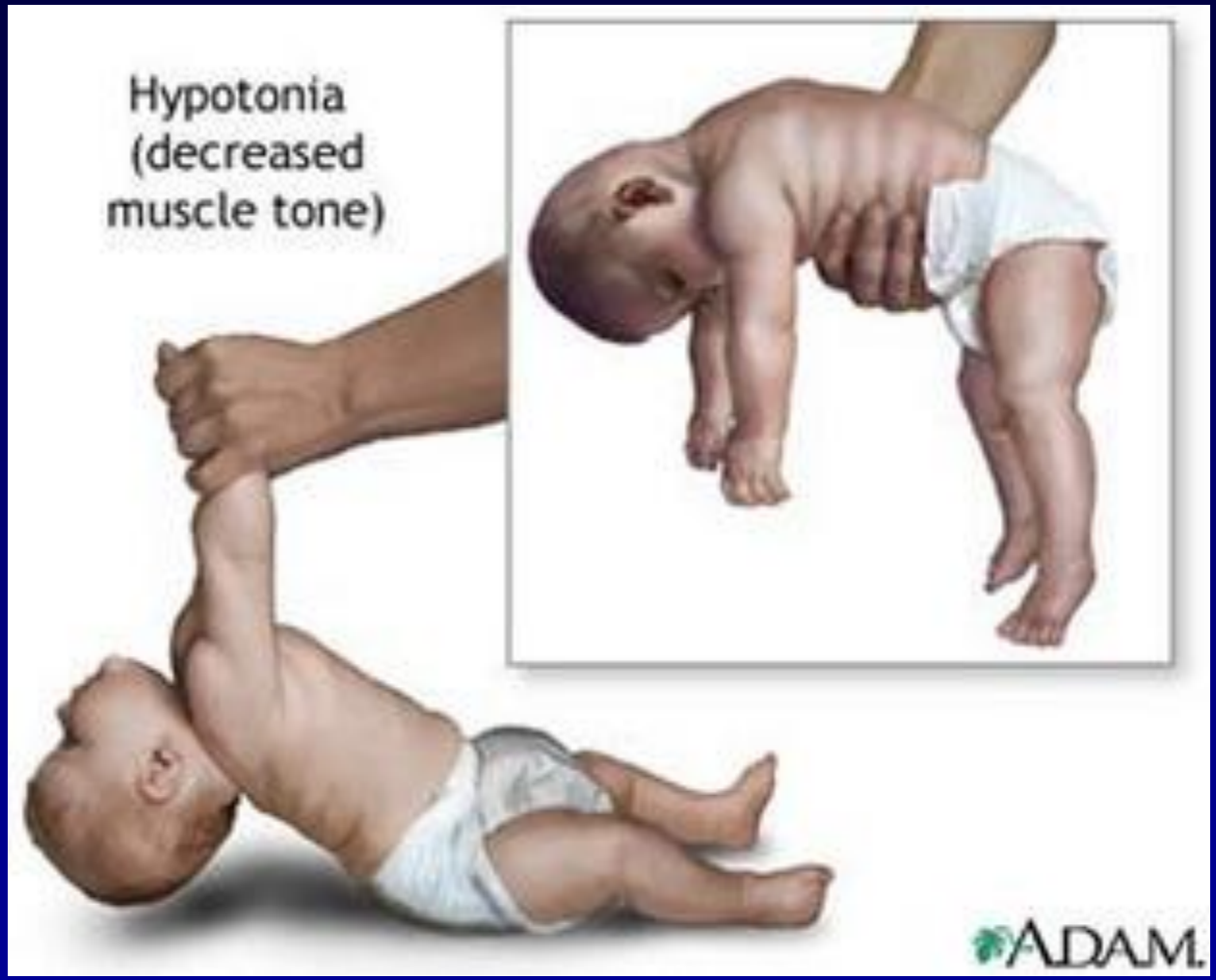


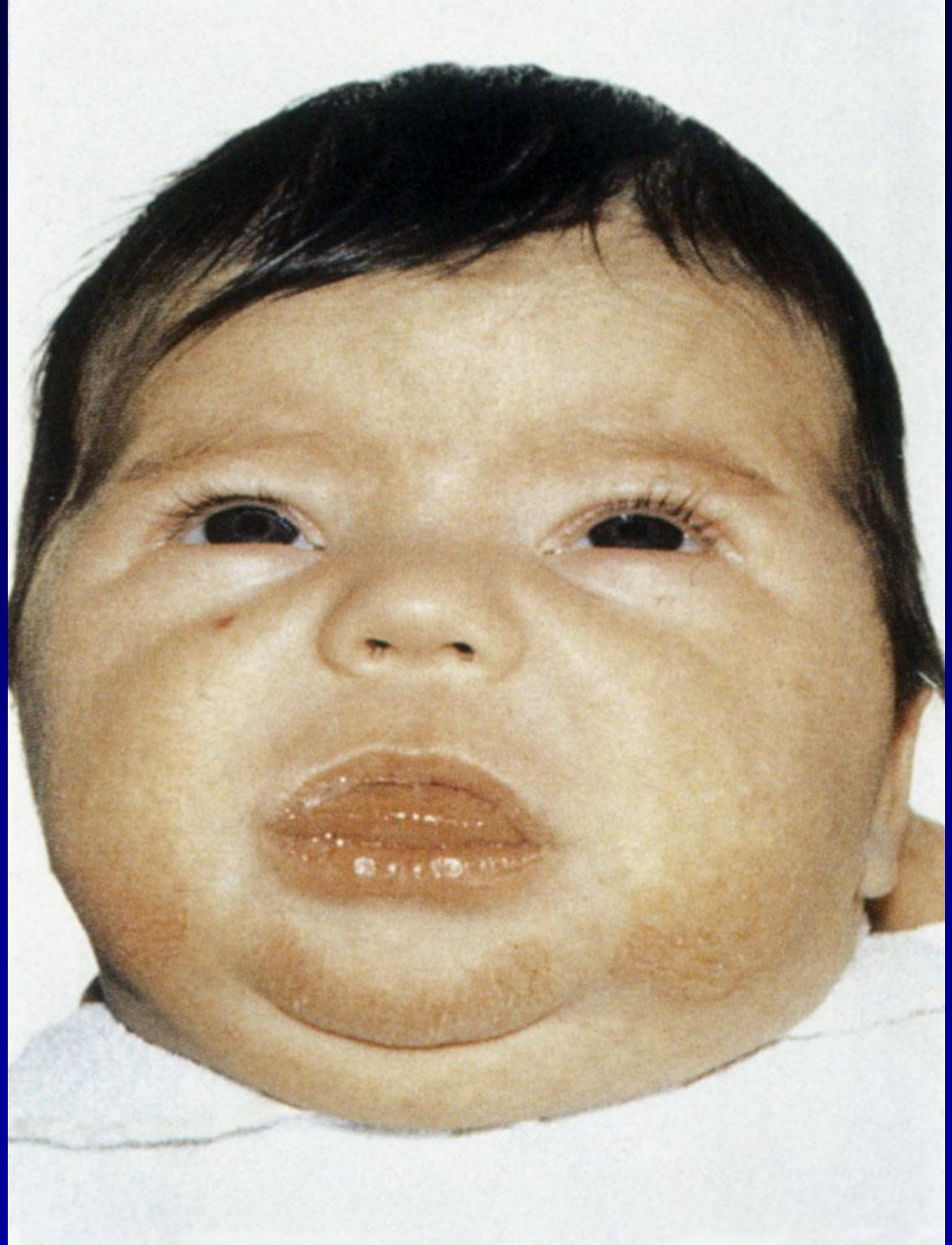
Rosalind S. Brown. Disorders of thyroid gland infancy, childhood, adolescence, march 21, 2012

SIGNS OF CONGENITAL HYPOTHYROIDISM

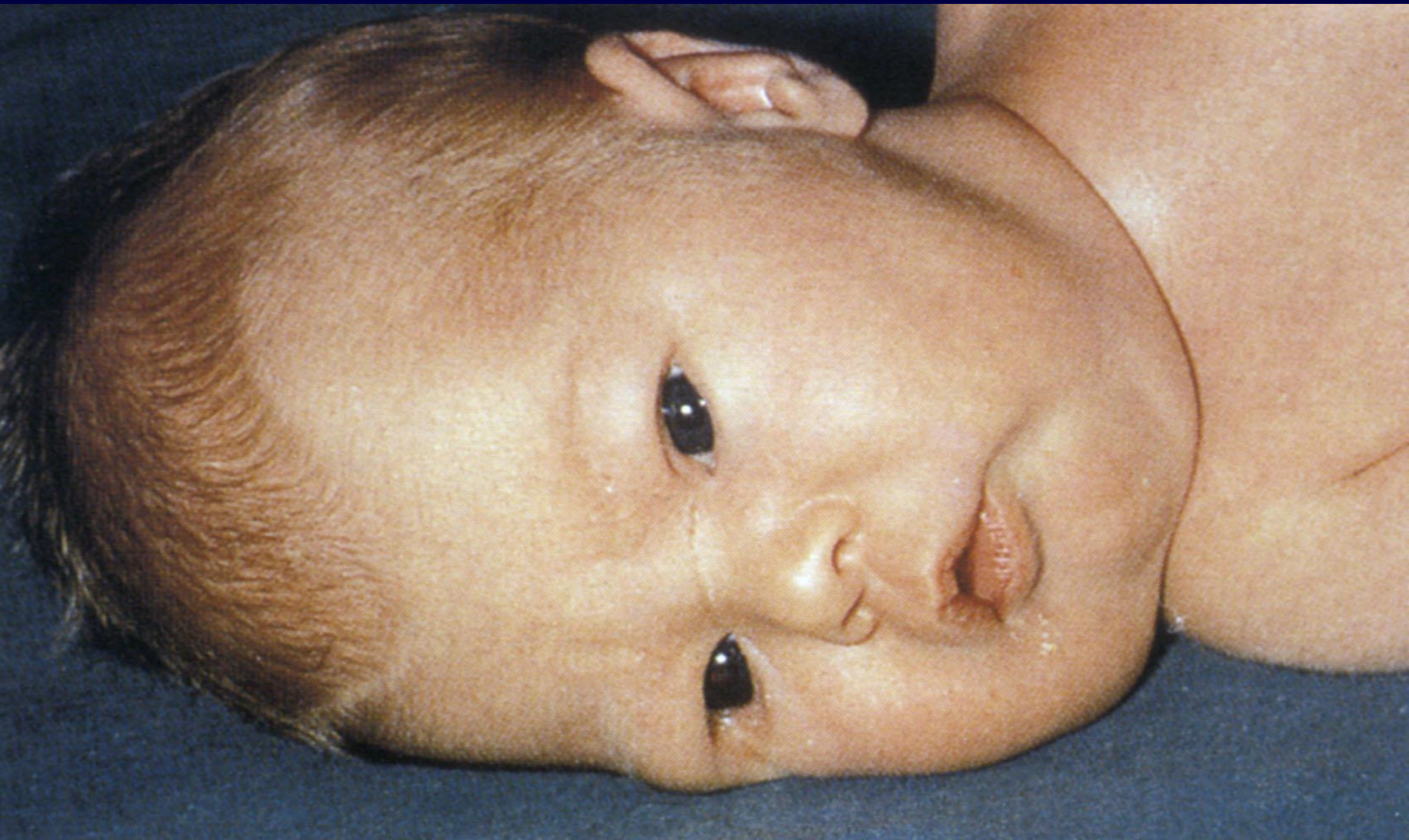
PERCENT WITH SIGN AT 5 WEEKS

- 31% prolonged jaundice
- 23% umbilical hernia
- 21% constipation
- 21% macroglossia
- 19% feeding problems
- 16% hypotonia
- 16% hoarse cry
- 13% large posterior fontanelle
- 10% dry skin
- 5% hypothermia
- 2% goiter
- 40% delayed bone age


Hypotonia
(decreased
muscle tone)
ADAM.



Congenital hypothyroidism occurs in 1:4000 infants.



Congenital hypothyroidism

- Wordwide iodine deficiency is the most common cause of congenital primary hypothyroidism and of preventable mental retardation

Figure 5. Endemic Goiter due to Dietary Iodine Deficiency

Dr Paul W. Ladenson Johns Hopkins University.
Goiter and thyroid nodules2008-06-10

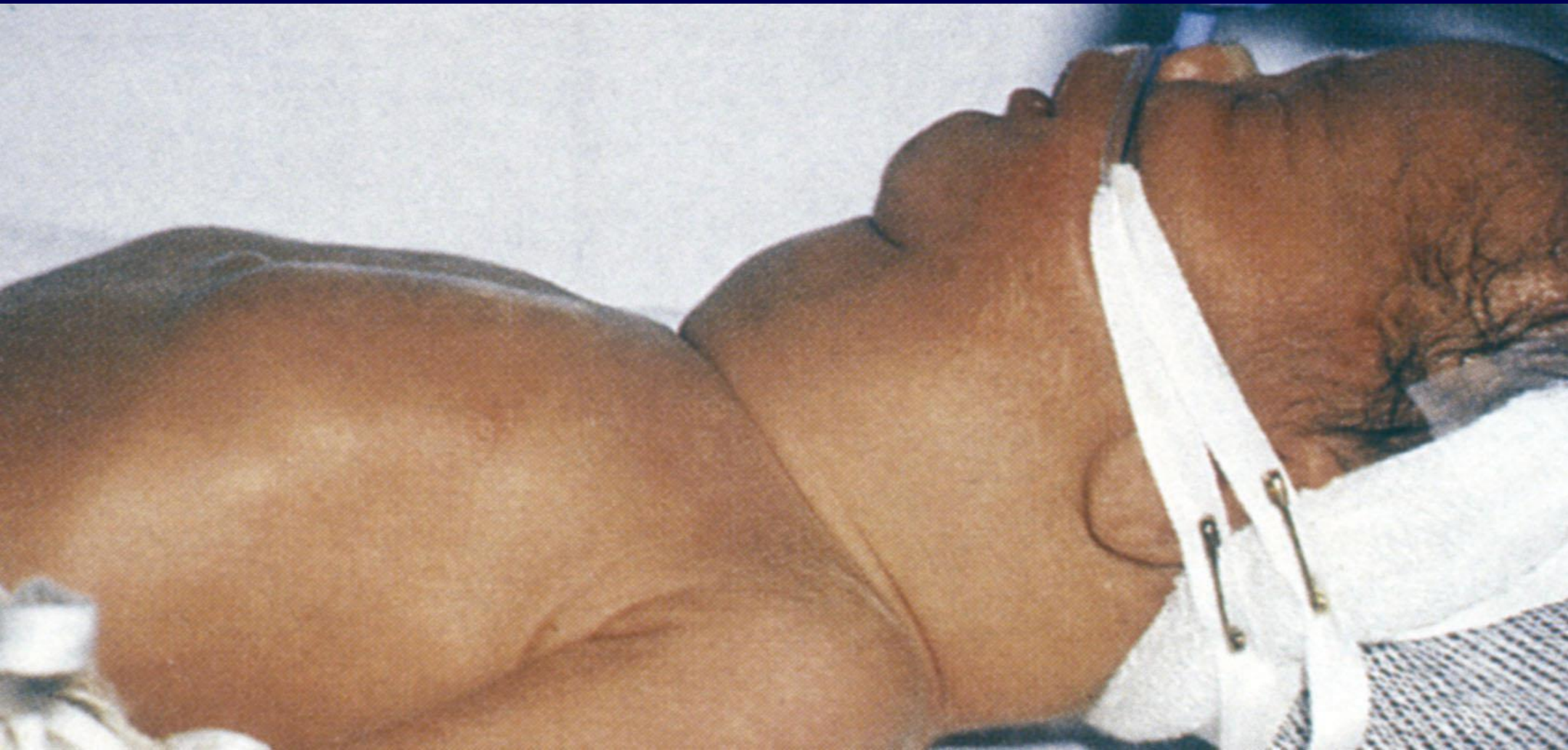
Congenital hypothyroidism

- Thyroid dysgensis-98% sporadic
- Agenesis: failure of thyroid gland to develop
- Most common in iodine sufficient areas

Pendred syndrome

- Autosomal recessive
- Most common cause of syndromic deafness
- Mutation in chloride-iodide transport protein "Pendrin"
  - Expressed in thyroid & cochlea
- Presents as euthyroid goiter, deafness

Congenital hypothyroidism with goiter due to maternal PTU.



Congenital hypothyroidism

- Maternally transmitted TSH receptor- blocking antibodies (TRB-Ab) can be a cause of transient congenital hypothyroidism
- Incidence approximately 1,100,000
- Transient congenital hypothyroidism resolves in 4-12 weeks

MANAGEMENT OF CONGENITAL HYPOTHYROIDISM

- Documentation
  - Free T4, TSH
- Thyroid scan, ultrasound *(optional)*
- Treatment *(normal size full term)*
  - start L-thyroxin at 10-15mcg/Kg daily
  - Monitor TSH every 2-3 months during first 2 years of life.

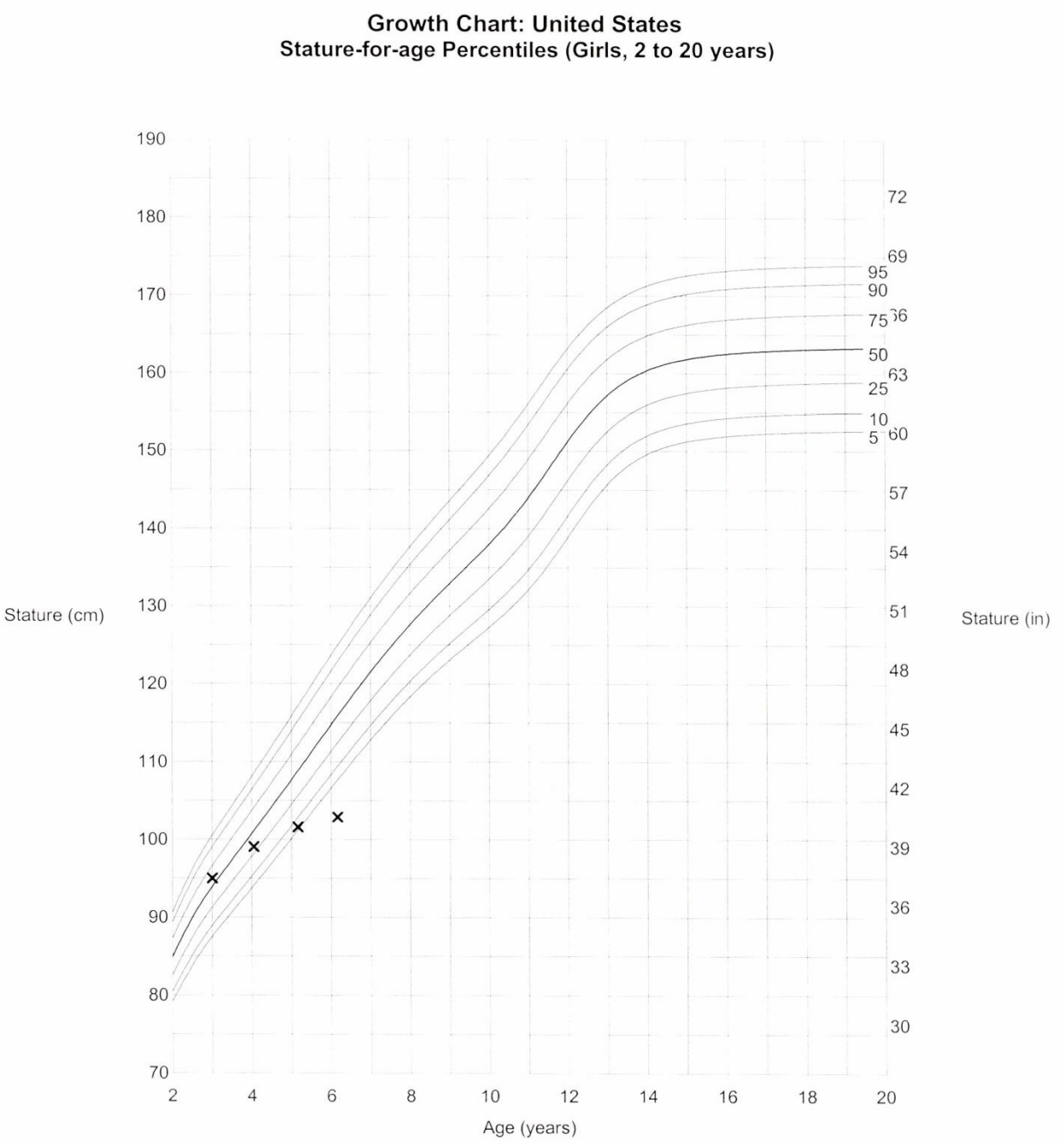
SYMPTOMS OF ACQUIRED HYPOTHYROIDISM

- Weakness
- Lethargy
- Decreased appetite
- Cold intolerance
- Constipation
- Weight gain

SIGNS OF ACQUIRED HYPOTHYROIDISM

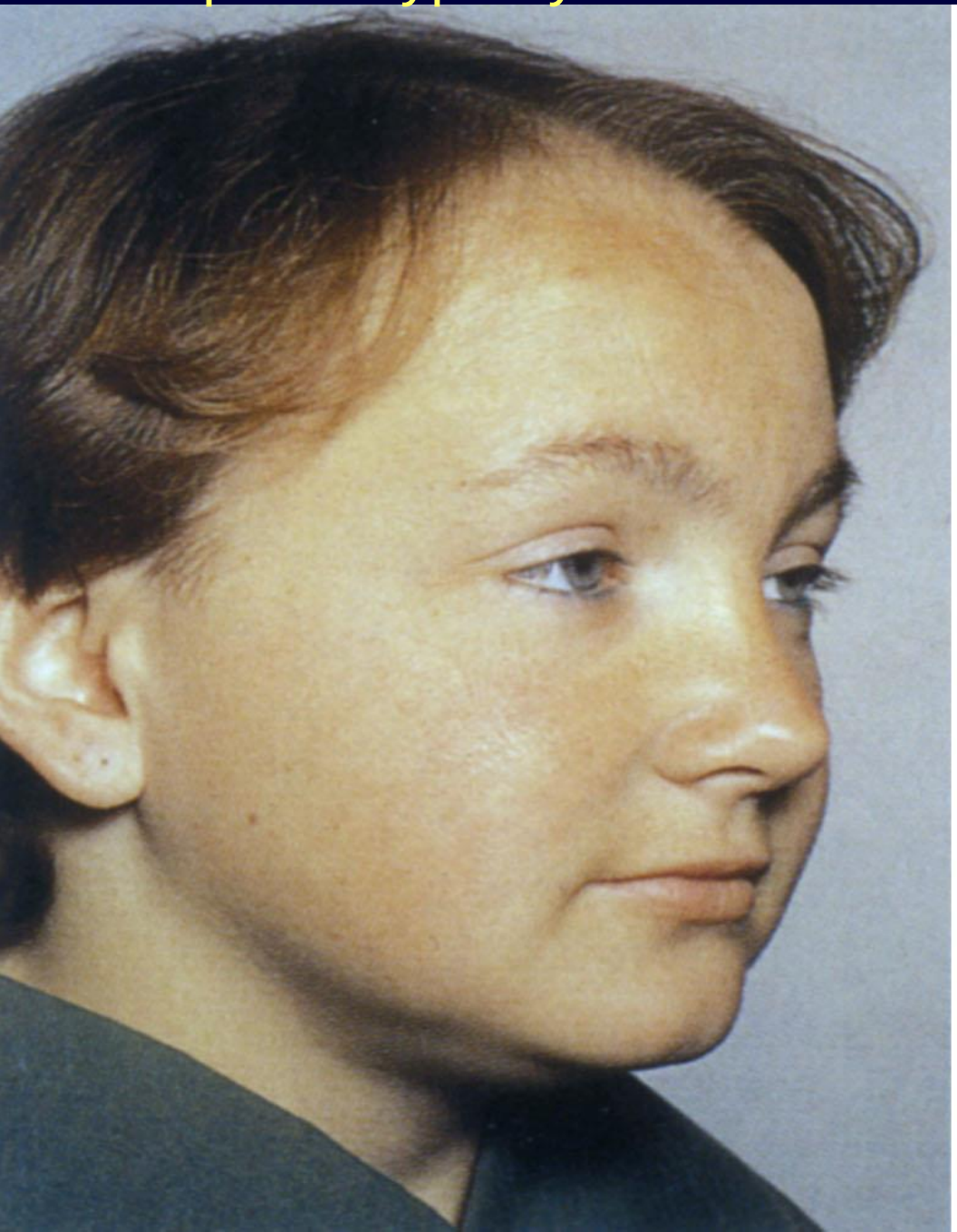
- Goiter
- Growth failure
- Delayed dentition
- Delayed or precocious puberty
- Galactorrhea
- Carotenemia
- Pale dry skin

Girl with TSH of 366.51

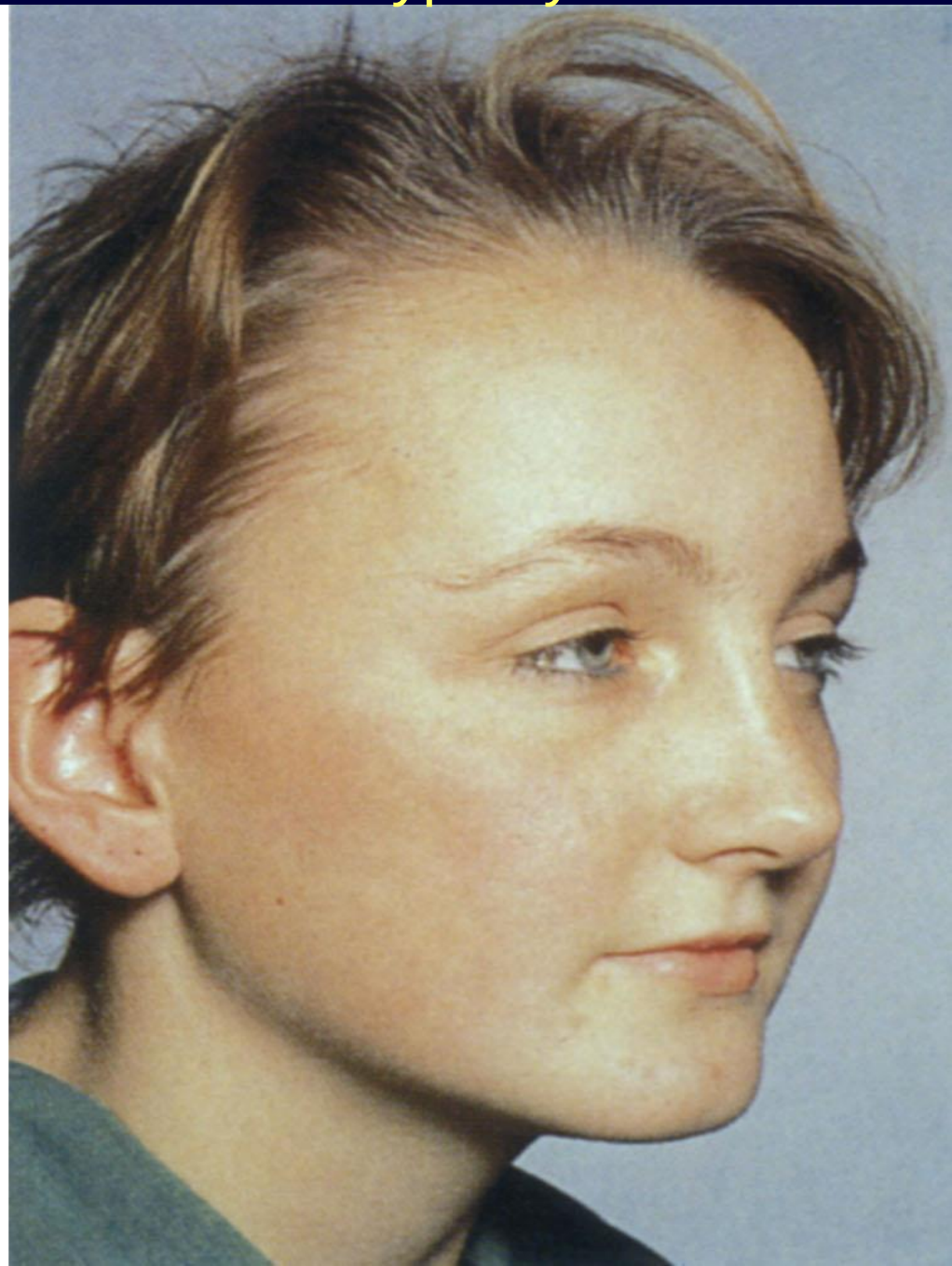


TSH
366.51
RESULT CHECKED AND VERIFIED

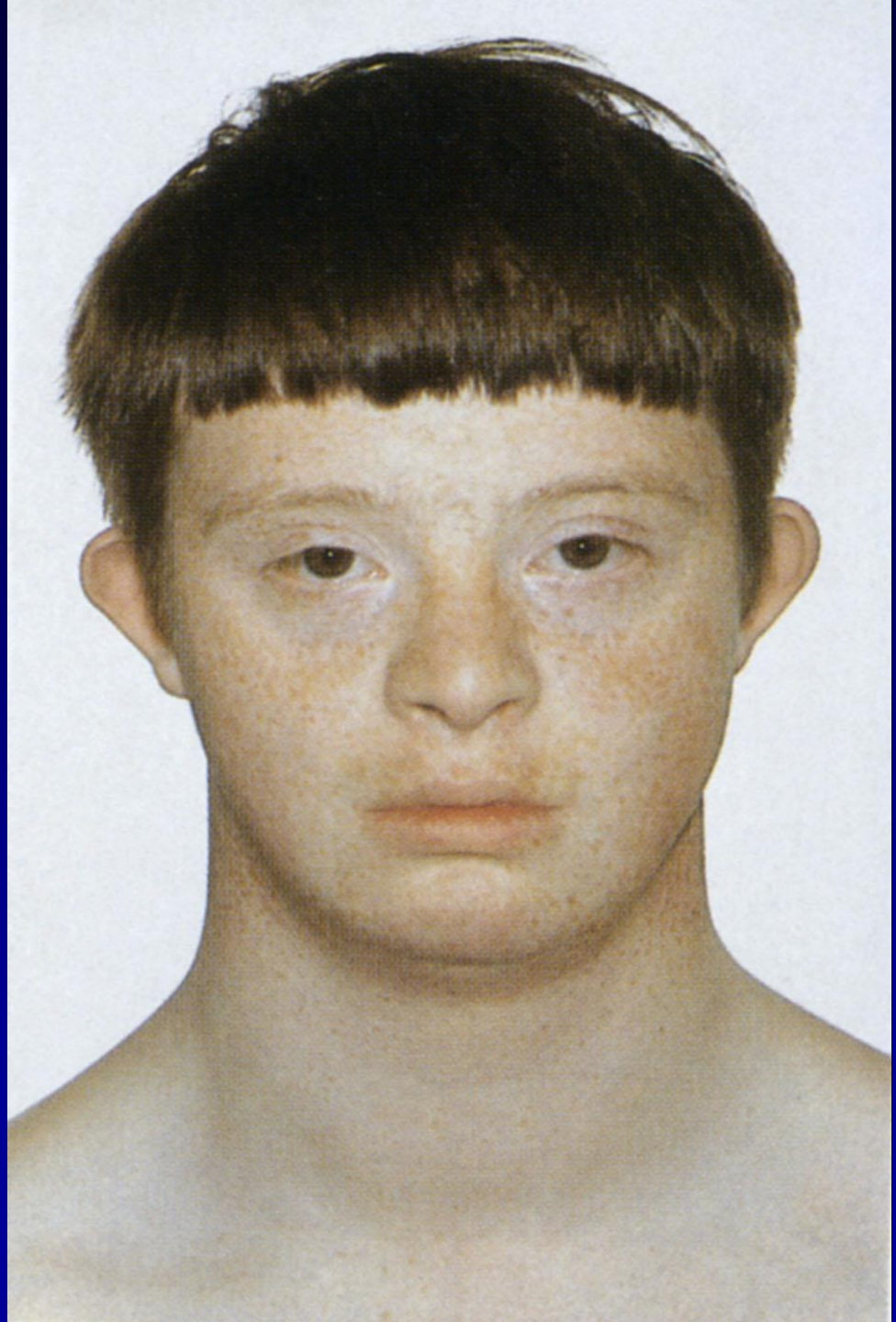
Acquired hypothyroidism



Treated hypothyroidism



All forms of thyroid disease are more common in children with Down syndrome.



EVALUATION OF ACQUIRED HYPOTHYROIDISM

- Documentation
  - TSH
  - Free T4
  - Microsomal antibodies

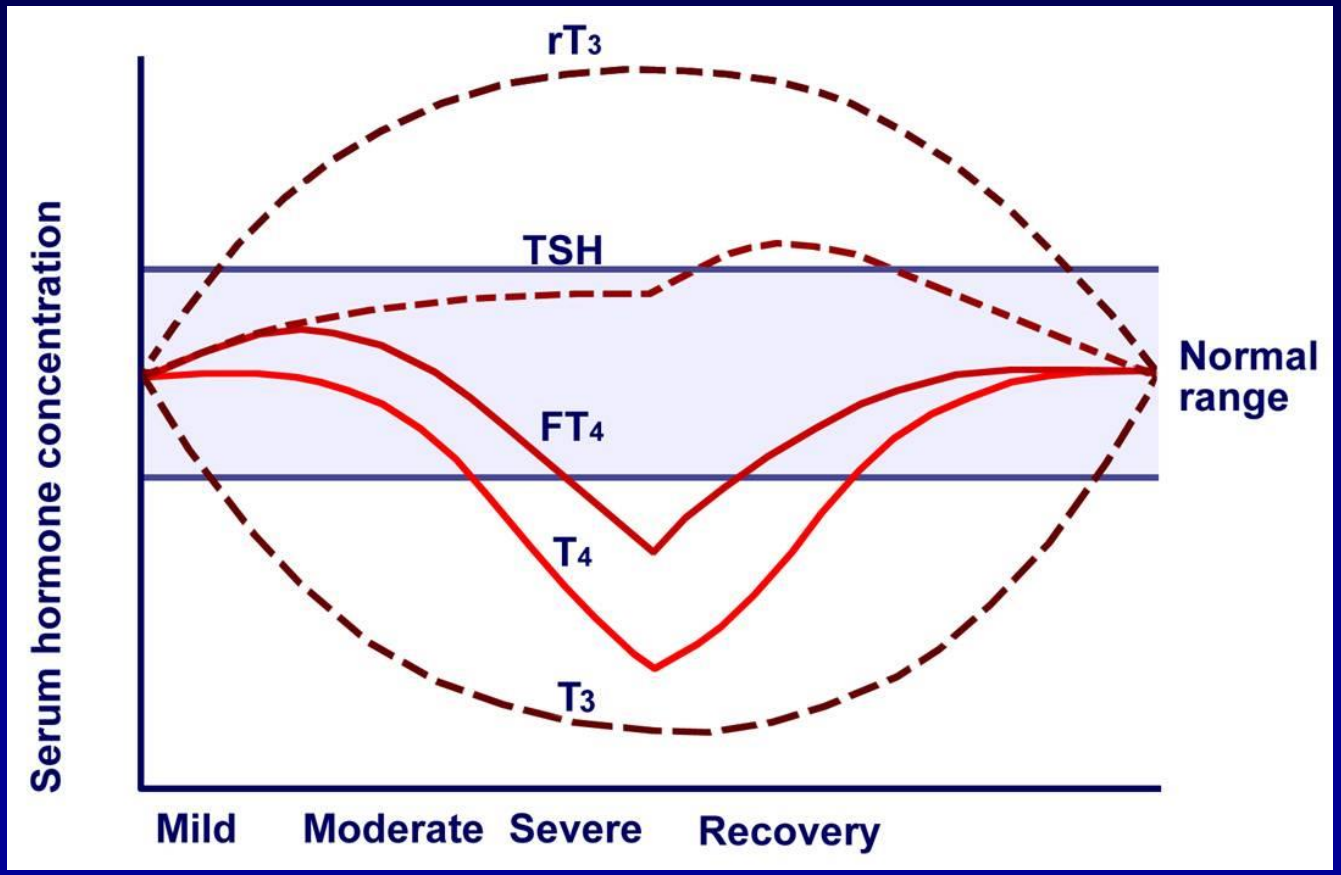
TREATMENT OF ACQUIRED HYPOTHYROIDISM

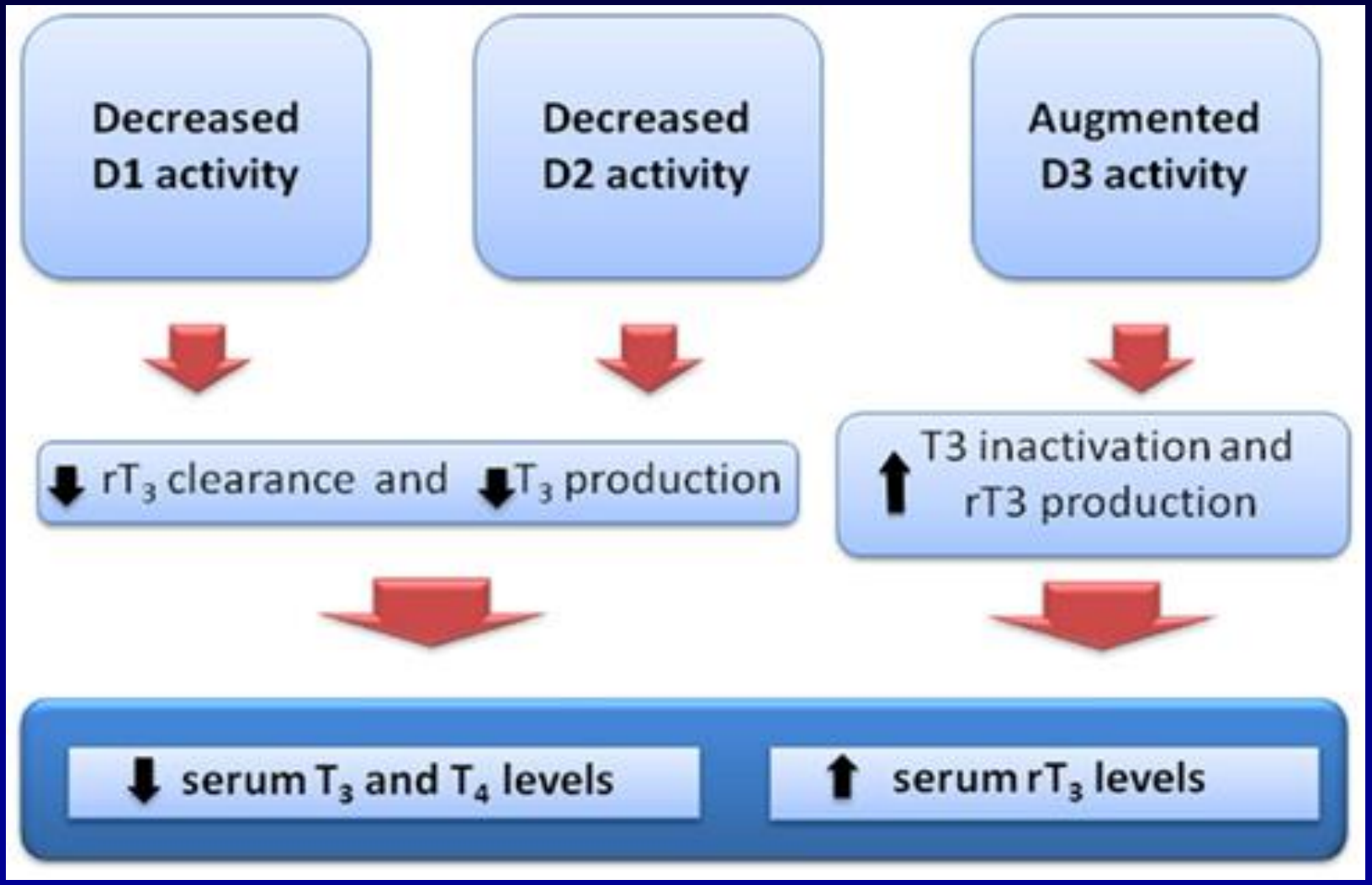
- L-thyroxine
  - start with a low dose
  - 0.025 or 0.05 mg daily
- Monitor TSH level every 4 - 6 weeks
- Increase L-thyroxine by 0.0125 mg increments until TSH is normal.
- Monitor TSH every 6 months

Euthyroid Sick Syndrome

- Changes in thyroid function occur within 12 hours of illness
- The lower the T3 the more severe the illness

Euthyroid Sick Syndrome





Wajner ,Maia**New insights toward the acute non-thyroidal illness syndrome**
Front. Endocrinol., 26 January 2012

SICK EUTHYROID SYNDROME

	T4	T3	rT3	TSH
Sick euthyroid	Low	Low	High	Low or Normal
Hypothyroidism	Low	Low	Low	High

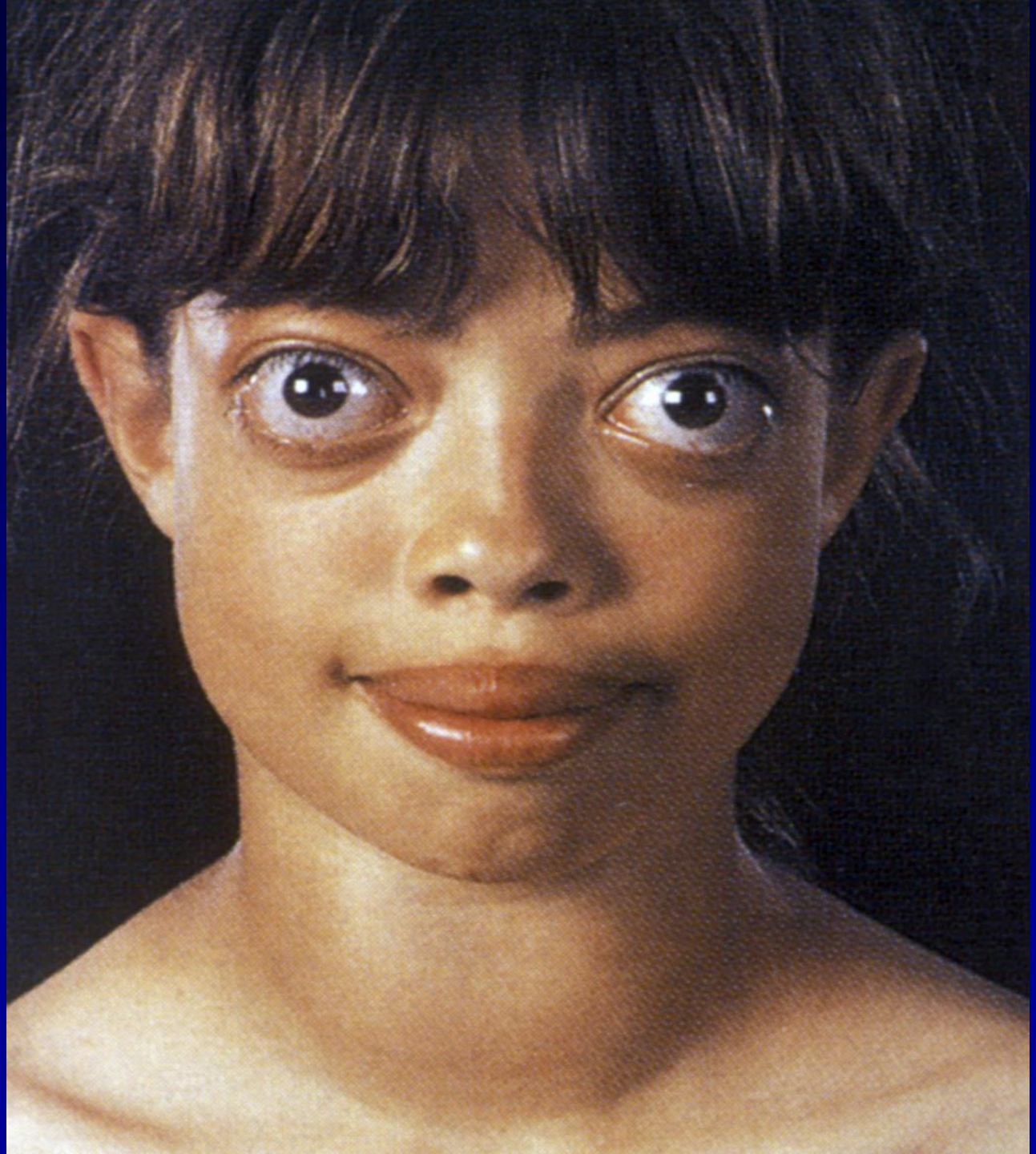
CAUSES OF HYPERTHYROIDISM

- Excess production of T4
  - Graves' disease
  - toxic adenoma
  - pituitary resistance to T4
  - McCune-Albright syndrome
  - TSH receptor mutations
  - TSH producing pituitary tumor
- Excess release of T4
  - Subacute thyroiditis
  - Hashimoto's toxic thyroiditis
  - iodine induced hyperthyroidism

SIGNS AND SYMPTOMS OF GRAVES' DISEASE IN ADOLESCENTS

- 98% goiter
- 82% tachycardia
- 82% nervousness
- 80% increased pulse pressure
- 65% proptosis
- 60% increased appetite
- 52% tremor
- 50% weight loss
- 30% heat intolerance

Graves' disease



EVALUATION OF HYPERTHYROIDISM

- Documentation
  - Free T4, TSH
- Determine etiology
  - thyroid stimulating immunoglobulins
  - radioactive iodide uptake scan

TREATMENT OF GRAVES' DISEASE

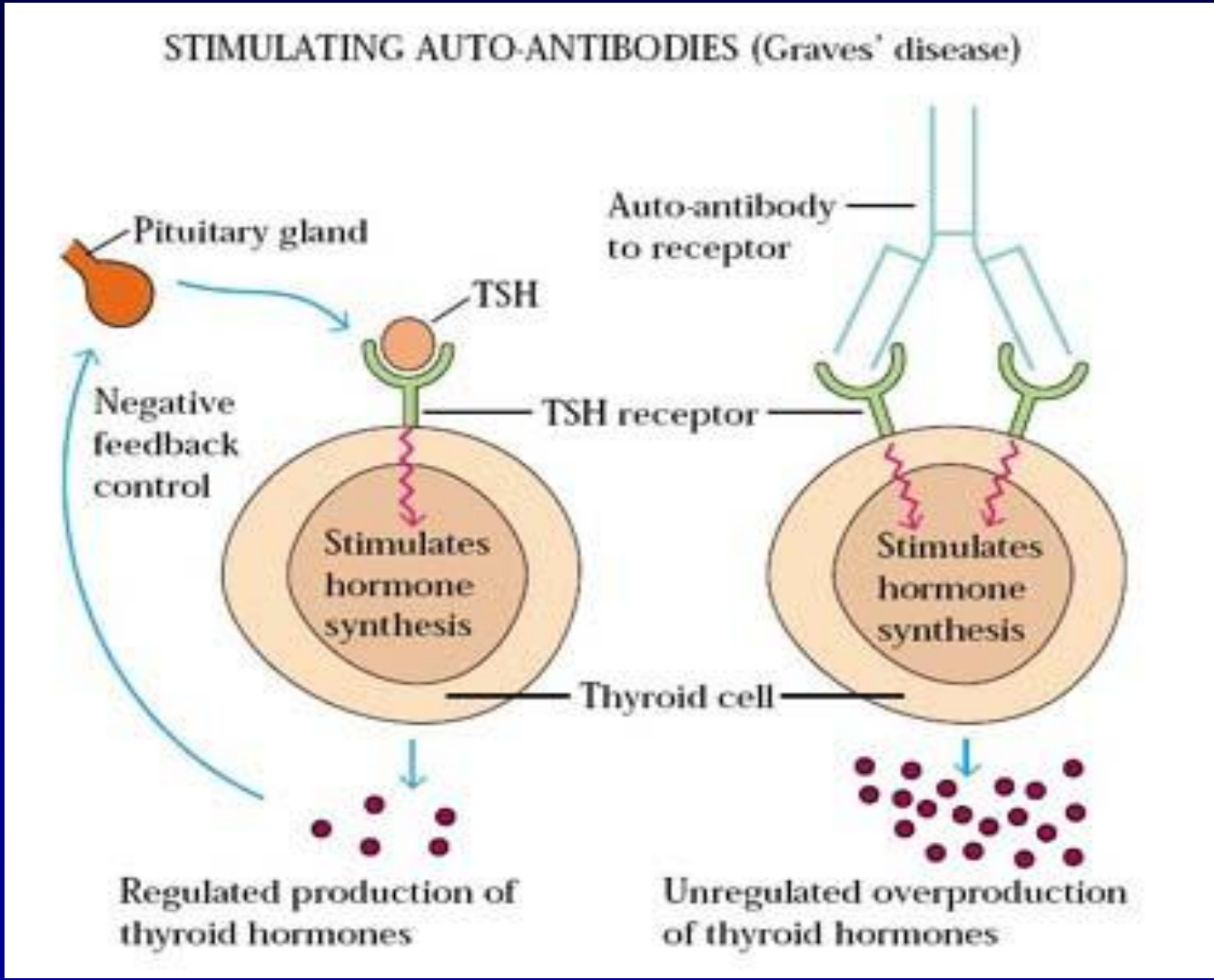
- Antithyroid medications
  - PTU 5-10 mg/Kg divided t.i.d.
    - Not recommended due to liver toxicity
  - Methimazole 0.5-1 mg/Kg daily
- ^{131}I radioactive ablation
- Thyroidectomy

SIDE EFFECTS OF ANTITHYROID DRUGS

- Rash
- Nausea
- Headache
- Puritis
- Lupus
- Arthritis
- Alopecia
- Hepatic toxicity
- Agranulocytosis

Anti-idiotype antibody

It is possible to make an antibody that is directed against the antigen binding site of another antibody (i.e., the antigen binding site is the epitope). This type of antibody is called an anti-idiotype antibody. In this case, the antigen binding site of the anti-idiotype antibody can be similar in structure to the original antigen (they both recognize the same antibody.)


STIMULATING AUTO-ANTIBODIES (Graves' disease)
Pituitary gland
TSH
Auto-antibody to receptor
Negative feedback control
TSH receptor
Stimulates hormone synthesis
Stimulates hormone synthesis
Thyroid cell
Regulated production of thyroid hormones
Unregulated overproduction of thyroid hormones

Neonatal Graves' Disease

Fetal Thyroid Dynamics

- Early in gestation T4 crosses the placenta from mother to fetus
- Late in gestation fetal T4 is almost exclusively from fetus
- Fetus makes T4 prior to TSH

Thyroid Autoantibodies in Pregnancy

- Up to 20% of pregnant mothers have thyroid autoantibodies
- Risk from thyroid autoantibodies
  - Maternal hypothyroidism
  - Preeclampsia
  - Placental abruption
  - IUGR

Neonatal Thyrotoxicosis

- Life threatening neonatal emergency
- 10% of infants born to mother with Graves disease have increased thyroid hormone
- Neonatal thyrotoxicosis occurs in 1-2% of neonates born to mothers with Graves disease
- Due to transplacental passage of TSI
- Mother can have active or inactive Graves
- All mothers should have TSI levels done at end of 2nd trimester
- TSI greater than 500% strongly correlated

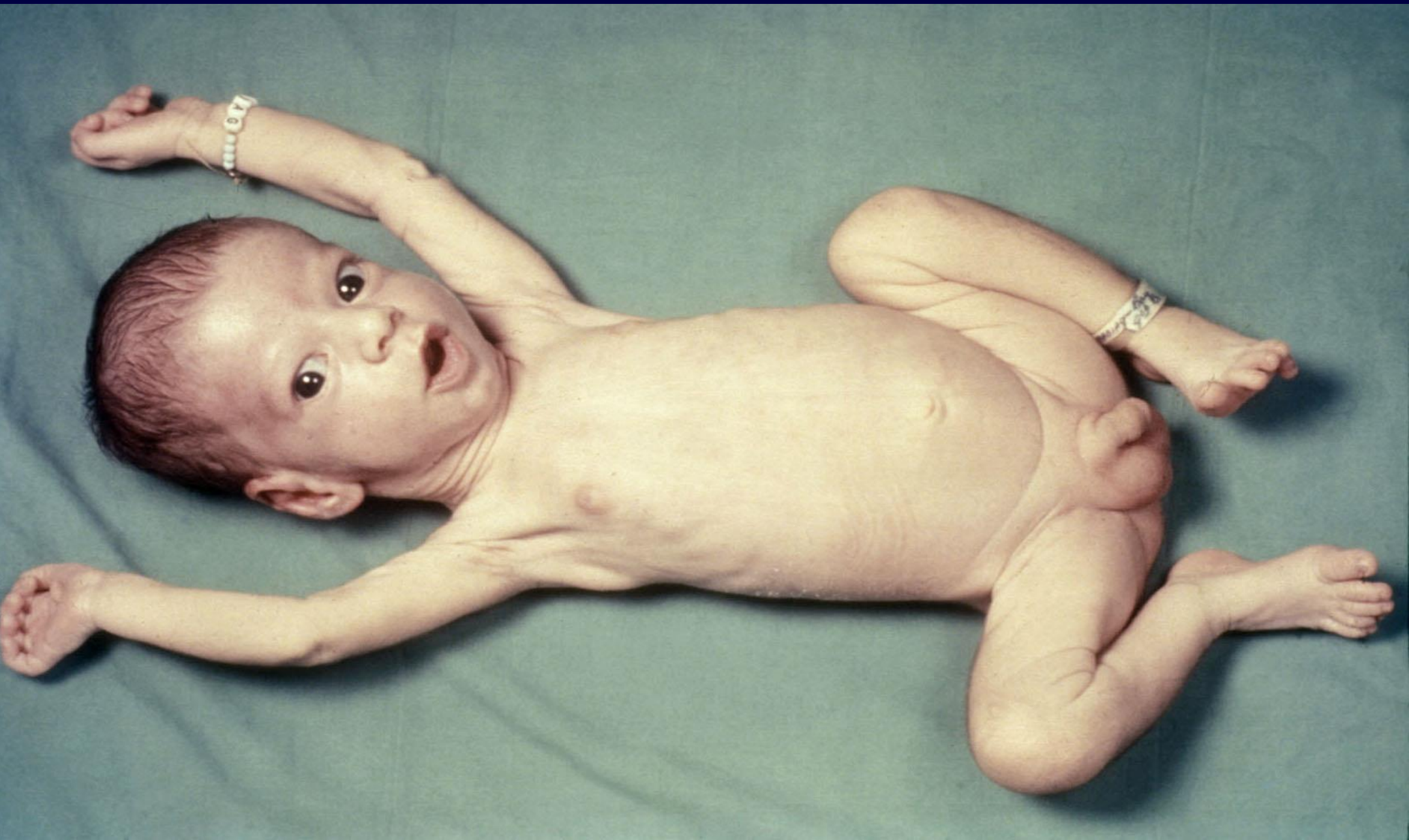
Neonatal Thyrotoxicosis

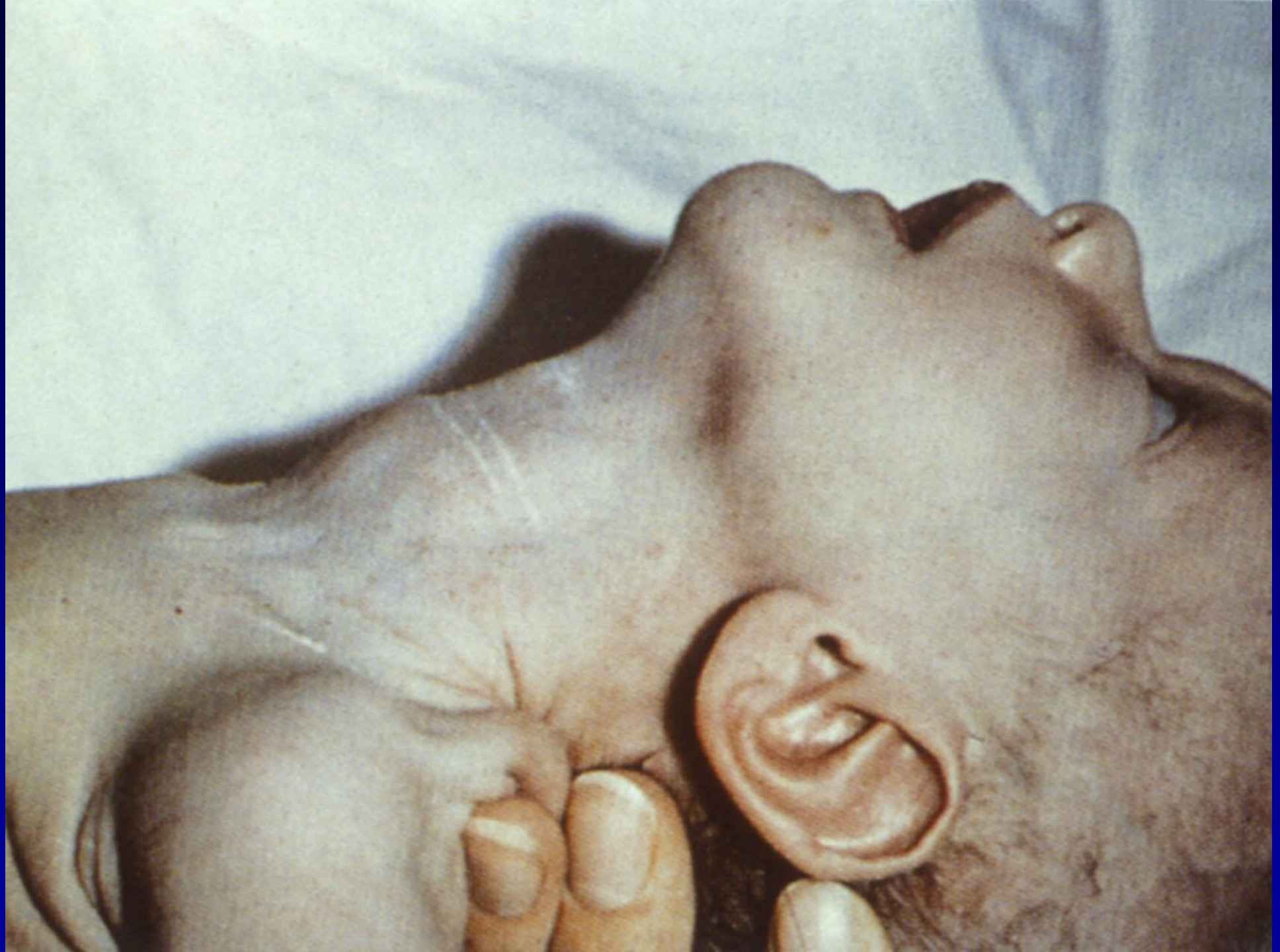
- Onset is usually day 2-9 of life
- If Thyrotropin Binding Inhibitory Immunoglobulins (***TBII***)) also present can be delayed for 4-6 weeks

SIGNS AND SYMPTOMS OF NEONATAL GRAVES' DISEASE

- Premature birth
- Low birth weight
- Goiter
- Restlessness and irritability
- Fever, flushing
- Tachycardia, cardiomegally, heart failure
- Lid retraction, proptosis, periorbital edema
- Poor weight gain, or weight loss
- Increased gastrointestinal motility, frequent stooling

Neonatal Graves' disease





Question- Neonatal Hyperthyroidism

- A baby girl born at term weighing 3500 gm. No prenatal problems or problems with delivery. She is now 14 hours old and has a blood sugar 30 mg/dl and is jittery and irritable. In retrospect you find that mother had Graves disease and underwent total thyroidectomy 8 years ago. You suspect neonatal Graves' disease and order which of the following?
- A. Thyroid Ultrasound
- B. Serum thyroglobulin
- C. TPO antibodies
- D. Cord blood TSH, thyroid stimulating immunoglobulin

Question 2-Neonatal Graves

- What would you use to treat this baby?

A. Lugol Solution

B. Methimazole

C. Levothyroxine

D. Glucocorticoids

TREATMENT OF NEONATAL GRAVES' DISEASE

- Acutely may require beta-blocker, prednisone and Lugol's solution.
- Methimazole 0.5 – 1mg/Kg daily
  - Goal is to completely suppress the thyroid gland
- Must give L-thyroxin
  - Usually start 25mcg daily
    - Adjust to keep free T4 and TSH in normal range
- Treat for 6 months
  - Maternal antibodies will be cleared by that time
  - Stop Methimazole and L-thyroxin at same time.

SUBACUTE THYROIDITIS

- Physical exam
  - painful swelling of the thyroid
  - signs of hyperthyroidism
- Laboratory evaluation
  - high T4, low TSH, high ESR, absent TSI
  - decreased radioactive iodide uptake scan
- Treatment
  - beta blockers
  - ASA, glucocorticoids

Exogenous Thyroid Hormone

- High free T4, high T4, high T3, low TSH
- Can you test for this?

Exogenous Thyroid Hormone

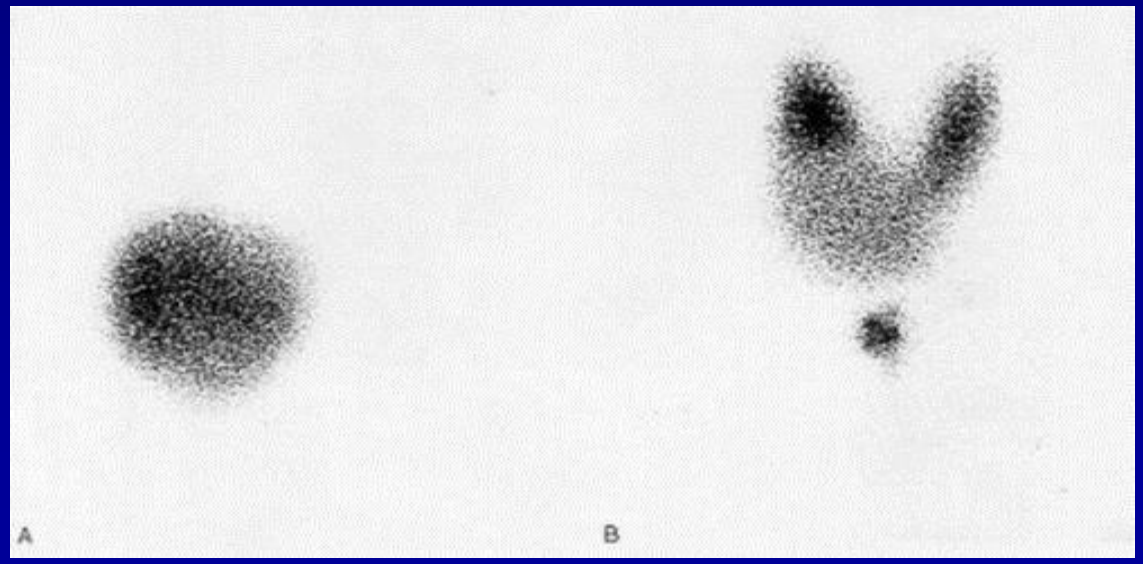
- plasma thyroglobulin level will be undetectable or extremely low in patients chronically abusing thyroid hormone
- may be used to differentiate cause

Autonomous Thyroid Nodule

- Functions independent of normal pituitary control
- Occur from somatic mutations in either the alpha subunit of the G-protein or TSH receptor
- Mutation results in constitutive activation of adenylyl cyclase and unregulated production of cAMP
- Rare in children

Autonomous Thyroid Nodules

- Radionuclide image using I-123 can help differentiate between a hot or cold nodule
- Hot nodule will accumulate radioisotope in the nodule and decreased or absent uptake in the surrounding tissue

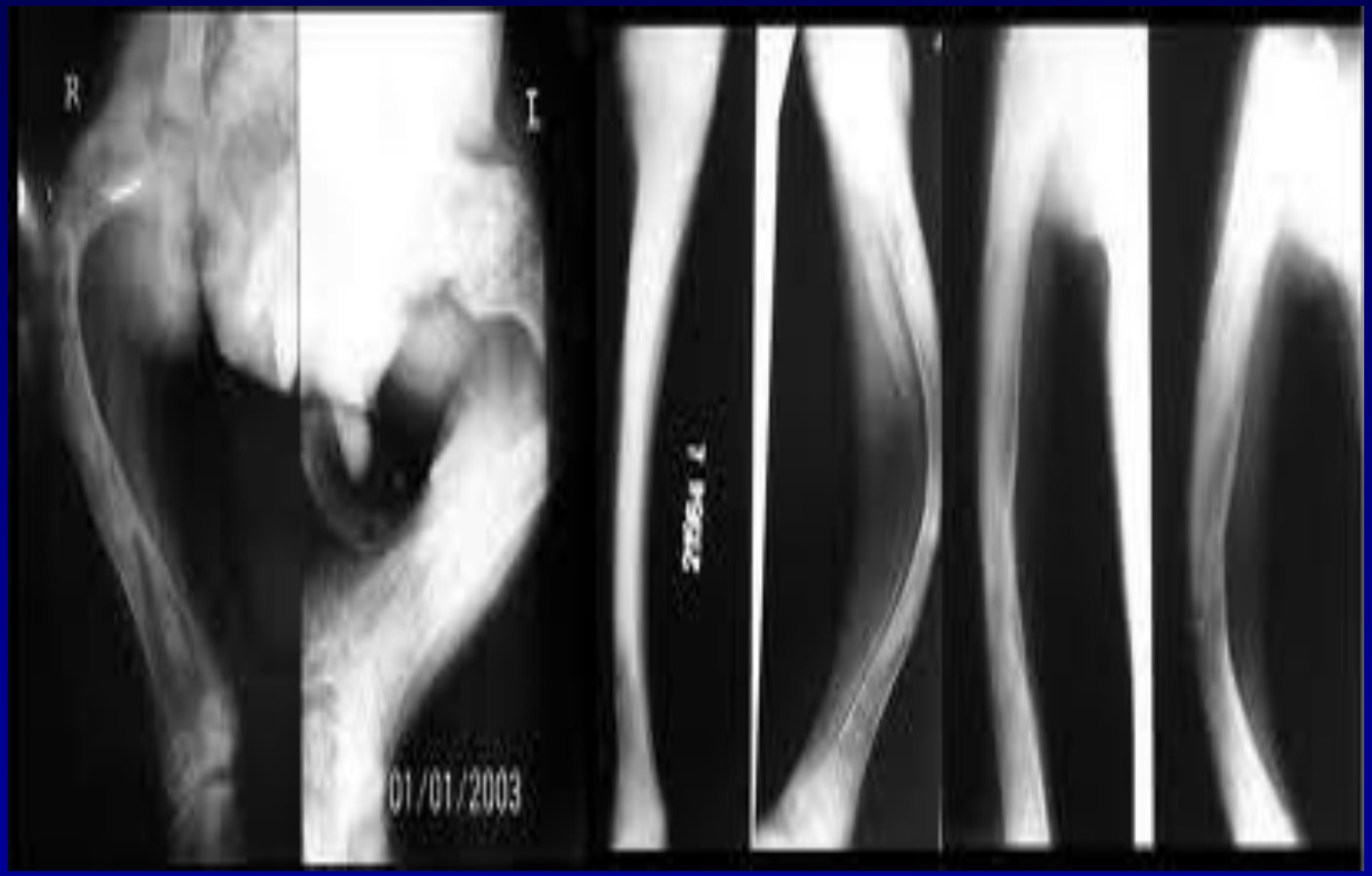


McCune-Albright Syndrome

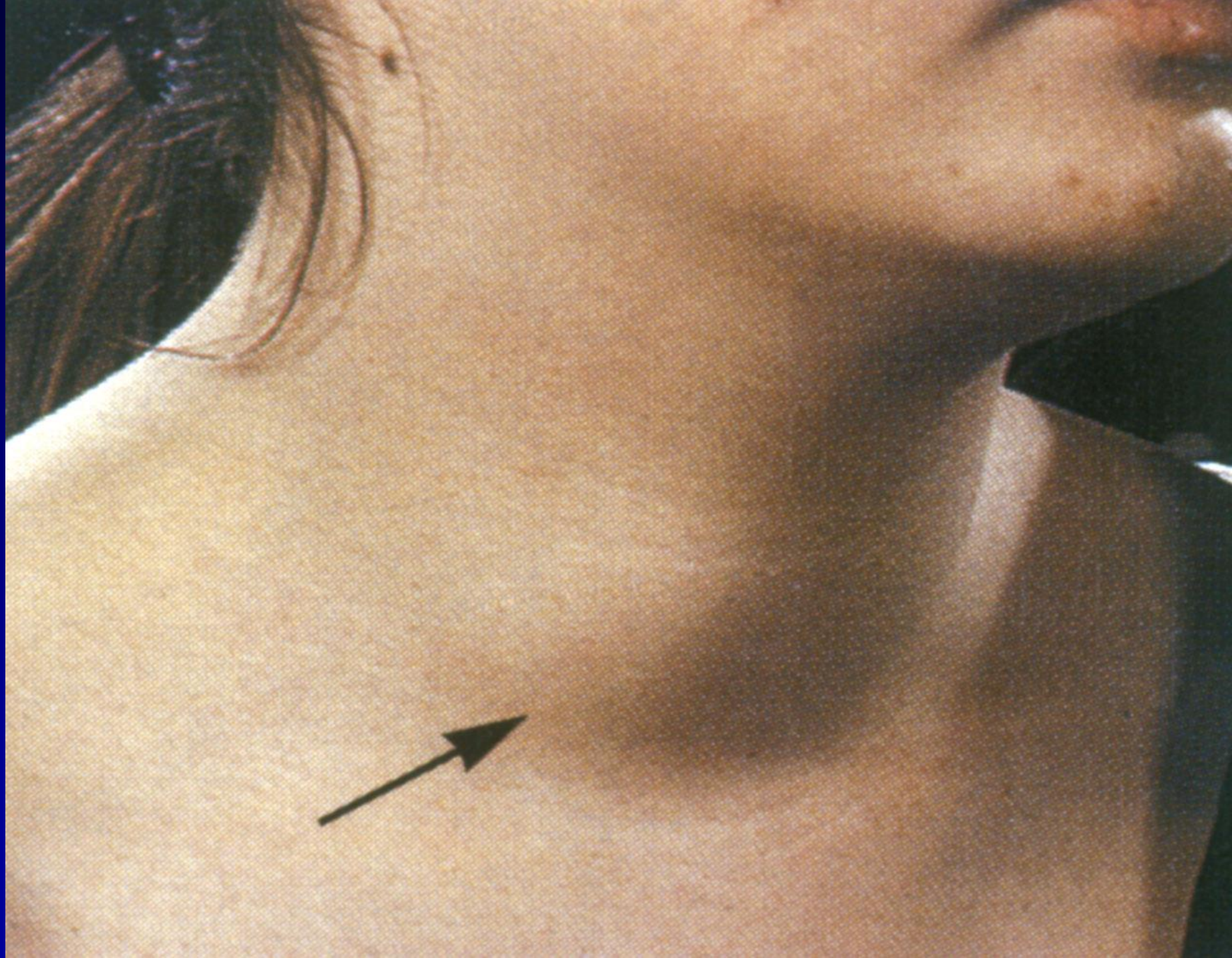
- Single or multiple hyperfunctioning adenomatous nodules
- Usually between 3-12 years
- Equal in boys and girls
- Overproduction of LH, FSH, TSH, GHRH, ACTH, and PTH seen in MAS are all receptors that are couple to G-proteins

McCune-Albright Syndrome

McCune-Albright Syndrome



Thyroid nodule



Thyroid Nodules

- 1% of Children
- 26% of thyroid nodules in children are malignant
- US & FNA best tools to identify cancer
- most benign nodules remain benign
- Prevalence of nodules is greater following radiation exposure
- Majority of thyroid cancers in children are papillary thyroid cancer

THYROID NODULES IN CHILDREN

Carcinoma	Adenoma		
35%	52%	Hayles	1956
20%	25%	Adams	1968
40%	24%	Kirkland	1973
17%	58%	Scott	1976

Question -Thyroid Nodules

- 15 year old female with 2.8 cm palpable firm mass in the right lobe of the thyroid gland. There is no fever, erythema or tenderness. The free T4 and TSH are normal. Microsomal antibodies are positive. What tests would you order?

a) Thyroglobulin antibody
b) Thyroid ultrasound
c) Serum calcitonin
d) 131 iodine uptake and scan

M.E.N. SYNDROMES

- M.E.N. 1
  - parathyroid, pituitary, and pancreatic adenomas
- M.E.N. 2a
  - medullary thyroid carcinoma, pheochromocytoma, parathyroid adenoma
- M.E.N. 2b
  - medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, intestinal neuromal dysplasia, marfanoid habitus
- Familial medullary thyroid carcinoma

M.E.N. 2

- M.E.N. 2a
  - Due to mutations in the extra-cellular region of the RET receptor.
  - Usually autosomal dominate inheritance.
  - Recommend thyroidectomy at age 3 years.
- M.E.N. 2b
  - Due to mutations in the intra-cellular region of the RET receptor.
  - Usually sporadic mutations.
  - Earlier development of medullary thyroid cancinoma.
  - Thyroidectomy done as soon as diagnosis made.

MEN 2b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EXPECTED BLOOD TEST RESULTS IN PEDIATRIC THYROID DISEASE

Condition	Free T4	TSH	Antibodies
Congenital hypothyroidism			
athyrotic	low	high	
nonathyrotic	normal / low	high	
Acquired hypothyroidism	normal / low	high	microsomal
Euthyroid sick syndrome	low	normal/ low	absent
Graves' disease	high	low	T.S.I.
Subacute thyroiditis	high	low	absent

Question 1

A 16 y.o. girl complains of weight loss, nervousness and tenderness in her anterior neck. Which of the following will clearly differentiate Graves' disease from subacute thyroiditis?

A Free T4

B T3

C TSH

D radioactive iodide uptake scan

Question 2

Which of the following medications is NOT helpful in treating subacute thyroiditis?

A PTU

B Propanolol

C Aspirin

D Prednisone

Question 3

A goiter (thyroid enlargement) is usually NOT present in which of the following?

A Hashimoto's thyroiditis

B Congenital hypothyroidism

C Graves' disease

D Subacute thyroiditis

Question 4

A 15 y.o. girl complains of constipation, tiredness and galactorrhea. On exam you note an enlarged firm thyroid gland. What is the most cost effective blood test to confirm your suspicion of hypothyroidism?

A TSH

B T4, TSH, microsomal antibodies

C Free T4, TSH, prolactin

D T4, T4RU, TSH, thyroglobulin antibodies

Question 5

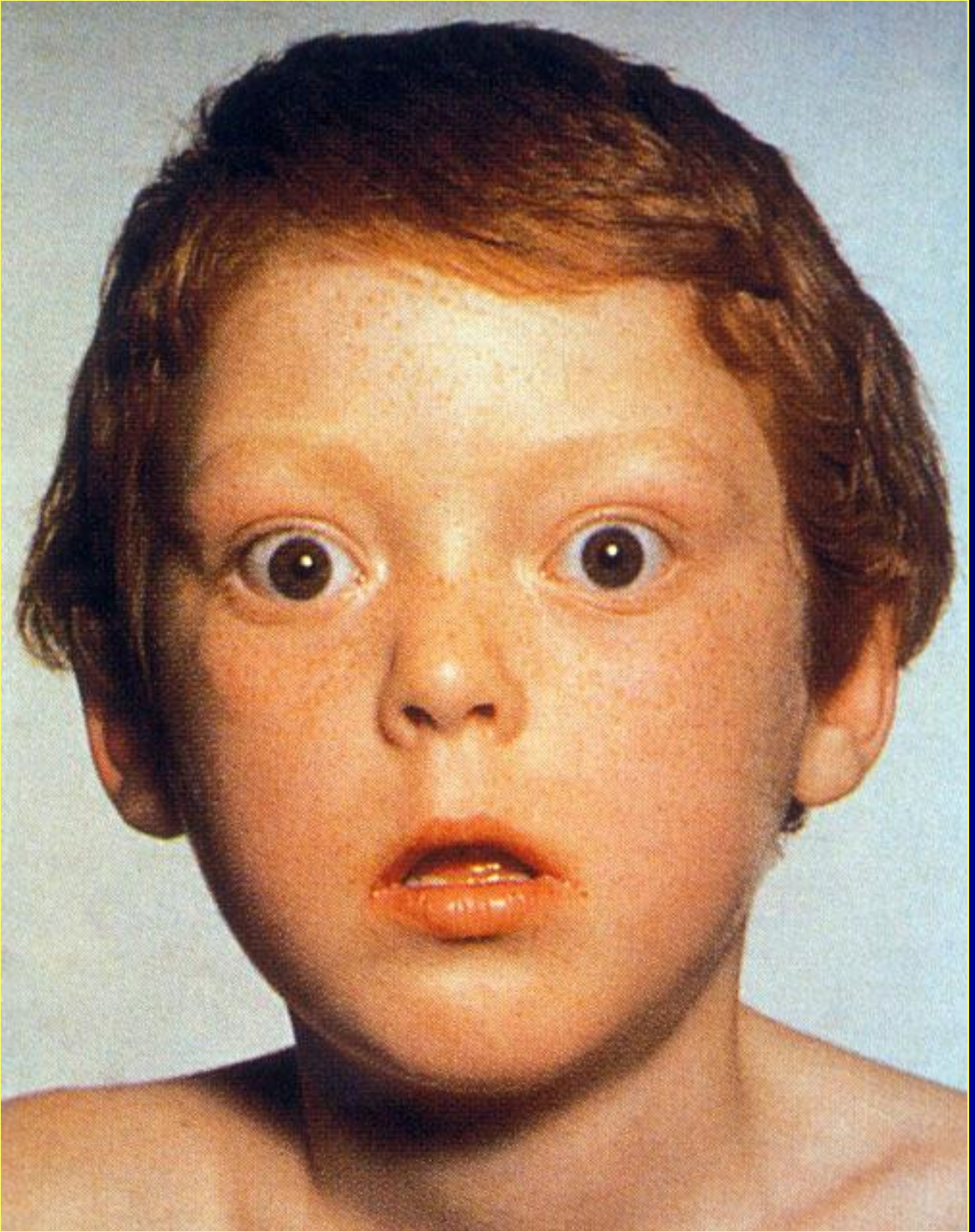
A child's father has M.E.N. 2. Which screening test should be performed?

A Fasting calcitonin level

B Calcitonin level after calcium infusion

C 24 hour urine for metanephrines

D Genetic testing on both the father and child



Question 6

This boy has:

A) just broken a neighbor's window with his baseball

B) just watched the movie "Halloween"

C) subacute thyroidits

D) Graves' eye disease

Graves Opthalmopathy

- clinically evident in over half of children and adolescents
- Usually mild
- may include
  - lid lag
  - lid retraction
  - stare, proptosis
  - conjunctival injection,
  - periorbital edema

Graves Opthalmopathy

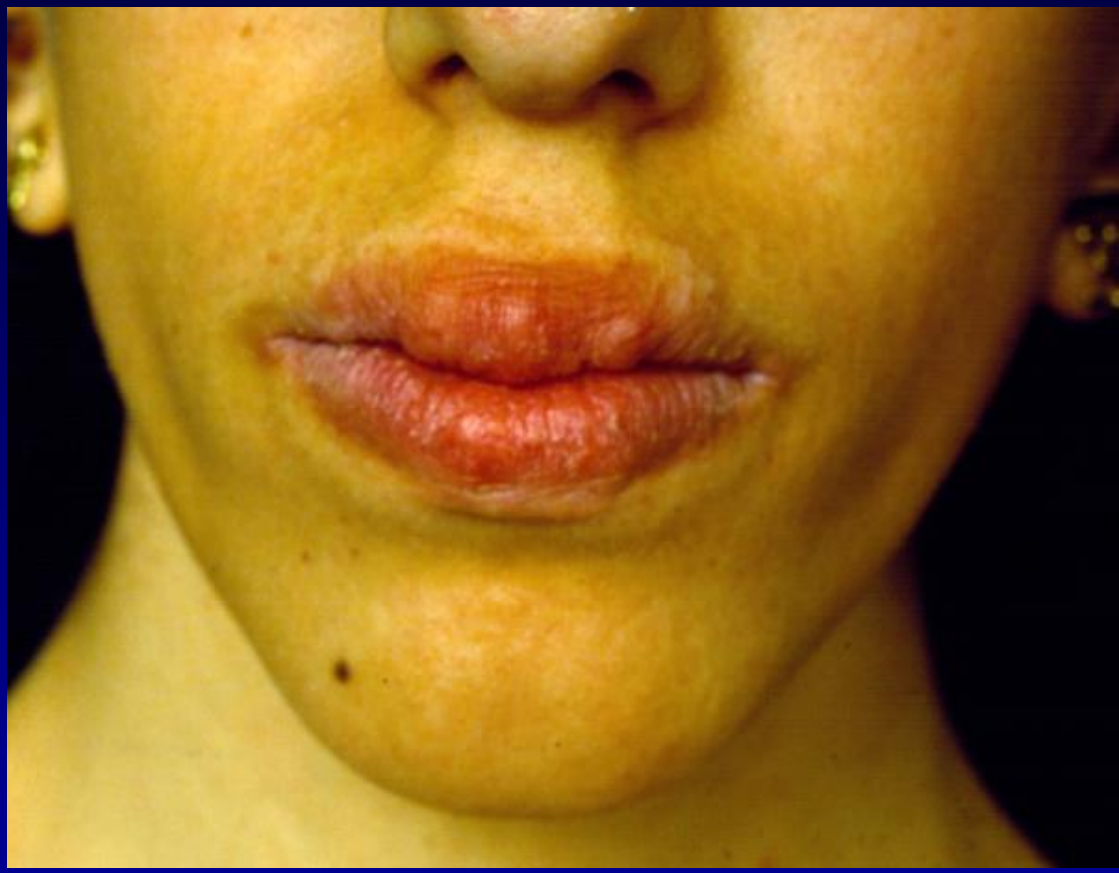
- explained by mechanical effects of an increase in tissue volume within the bony orbit
- caused by accumulation of glycosaminoglycans (GAGs) in the connective tissue of the orbital fat and muscles
- Orbital fibroblasts are the primary targets of the autoimmune attack and thought to share similar antigen structure with thyroid

Graves Opthalmopathy

- treatment not needed for mild cases
- eye drops or ointment needed to prevent corneal drying
- severe ophthalmopathy
  - Oral corticosteroids
  - orbital irradiation
  - surgical decompression

Question 7.

An adolescent female complains about her tall stature. On physical exam you notice some nodules on her lips and tongue. She has a history of severe constipation. No other family members have similar problems or findings.



What is your next step.

A. Obtain RET mutation analysis
B. Exam patient's parents.
C. Obtain calcitonin and CEA levels
D. Obtain Ca^{++} and PTH levels.


Iz a thyroid problem..
now give me cupcake