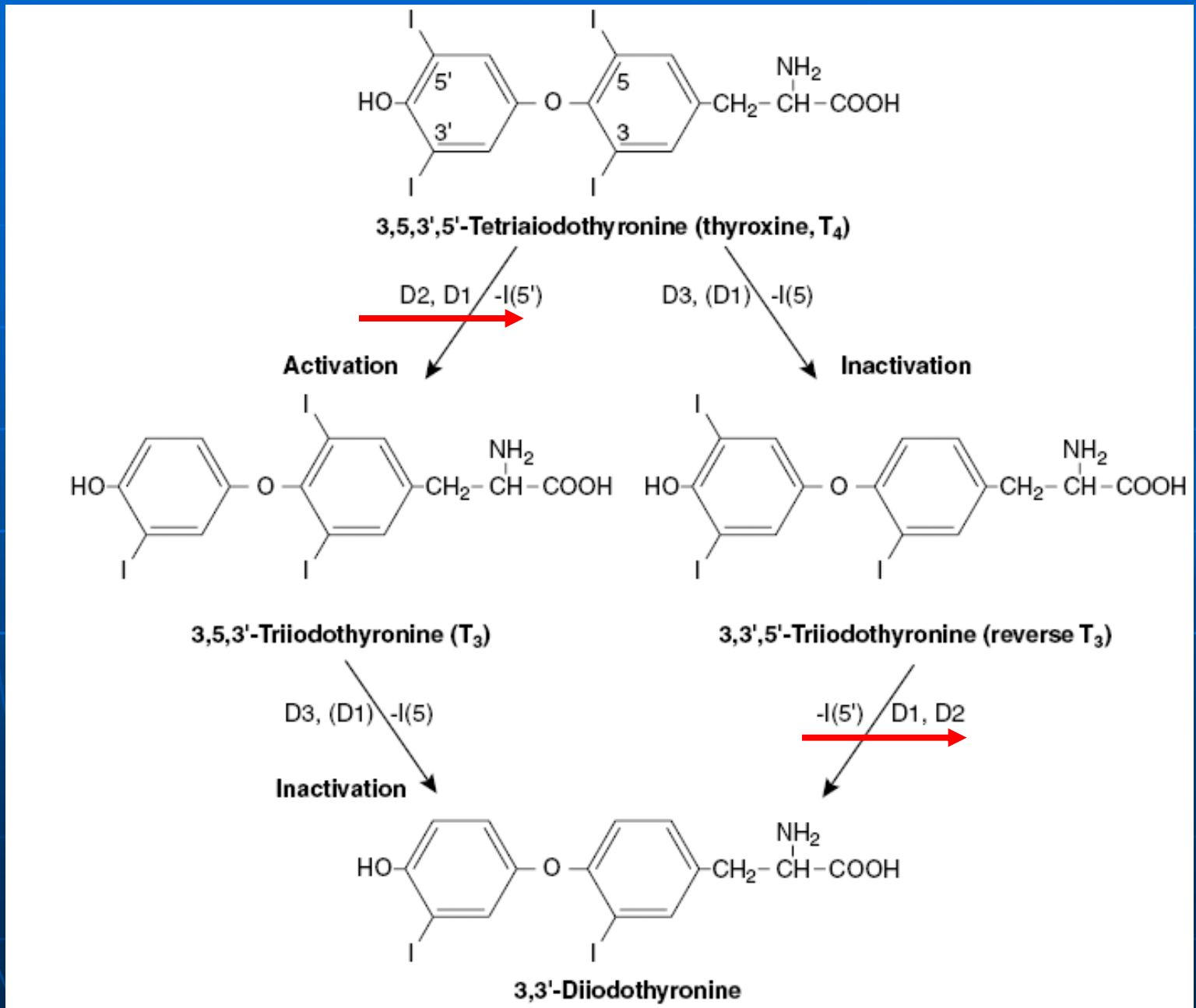
內分泌新陳代謝科復習 (Endocrinology)

國軍左營總醫院內科部新陳代謝科

Thyroid


3,5,3',5'-Tetriaiodothyronine (thyroxine, T4)
D2, D1 -I(5')
Activation
D3, (D1) -I(5)
Inactivation
3,5,3'-Triiodothyronine (T3)
3,3',5'-Triiodothyronine (reverse T3)
D3, (D1) -I(5)
Inactivation
-I(5') D1, D2
3,3'-Diiodothyronine

Non-Thyroid Illness (NTI)
(Euthyroid sick syndrome)

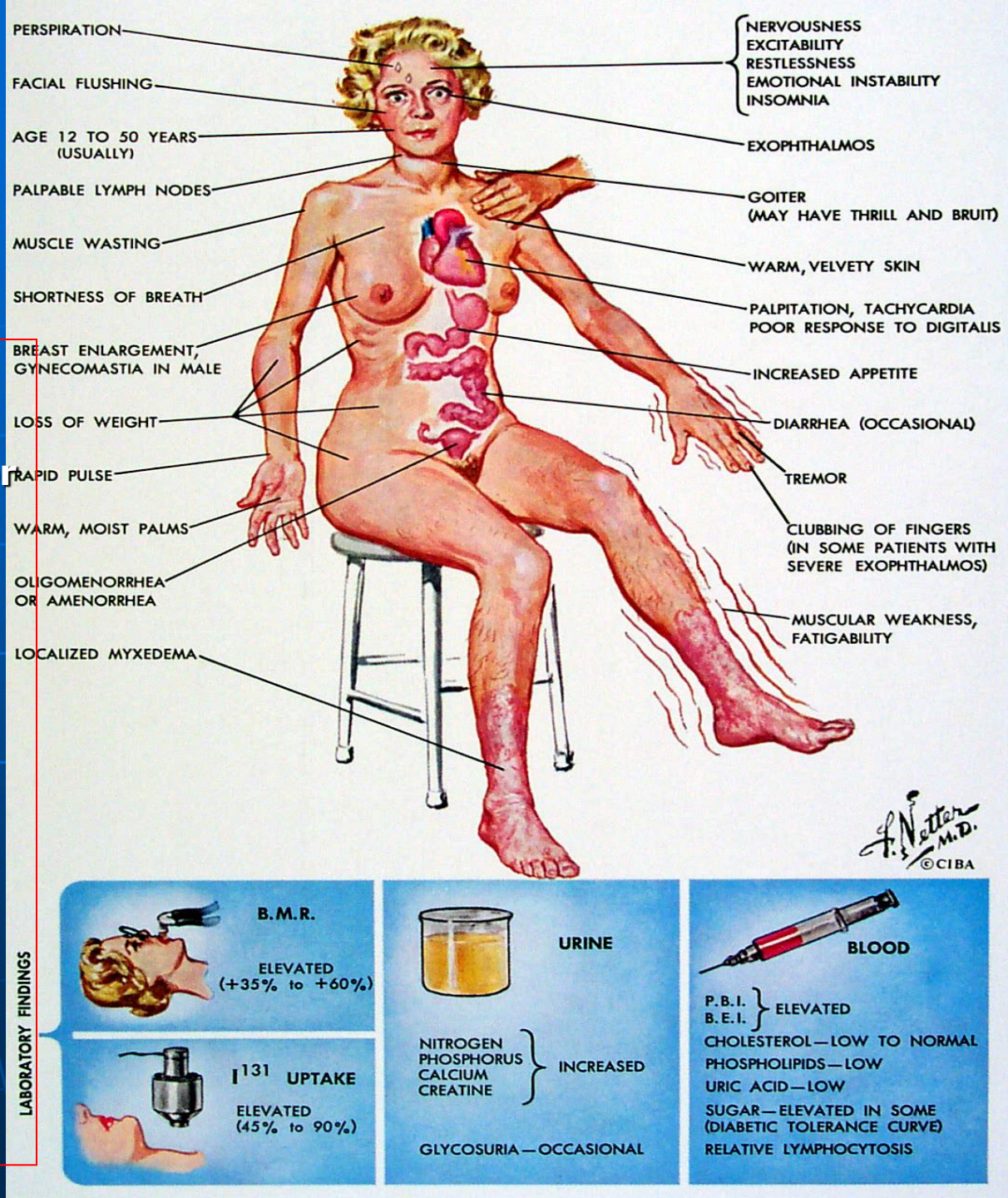
- NTIs（非甲狀腺病患）指因其他疾病就診之病患，包括輕微之非躺臥性病患至嚴重之ICU垂危病患，範圍很廣。
- 輕度或中度病患，如果懷疑有甲狀腺高能症或低能症，其甲狀腺功能之判讀大致與普通甲狀腺病患相同。

Non-Thyroid Illness (NTI)
(Euthyroid sick syndrome)

- 重度病患，尤其 ICU 病人之甲狀腺功能，約70%-80% T3降低，30%-50% T4 降低，這些T4低病患，其FT4約50%-70%正常，其餘偏低。
- 以上變化是由於 5’-deiodinase 活性降低，THBI (Thryroid hormone binding inhibitor)存在，TBPs降低等引起。而TSH 大部份是正常的，只約20%異常，其中2/3降低，而1/3升高，TSH 降低可能是為適應疾病狀態或使用 dopamine or glucocorticoid 等藥物使身體處於central hypothyroidism之狀態；TSH 偏高，則是在NTIs恢復期反彈所致

The S/S of Hyperthyroidism – multi-systemic involvement

Symptoms	Signs
Nervousness	Hyperactivity
Fatigue	Tachycardia or atrial arrhythmia
Weakness	Systolic hypertension
Increased perspiration	Warm, moist, smooth skin
Heat intolerance	Stare and eyelid retraction
Tremor, Hyperactivity	Tremor, Hyperreflexia
Appetite change, Weight change	Muscle weakness
Menstrual disturbance	



Causes of thyrotoxicosis

- Autoimmune
  - Graves' disease (60-90%) Hashimoto's disease
- Autonomous
  - toxic mulitinodular goitre
  - solitary toxic adenoma
- Thyroiditis (transient)
  - post-partum thyroiditis
  - subacute thyroiditis
  - paniless thyroiditis
- Drug induced
  - iodine- induced(Jod-Baseddow)
  - thyroxine ('factitous')
- Secondary (very rare)
  - TSH secreting tumour
  - HCG dependent (as in hyperemesis gravidarum)
- Thyroid hormone resistance
- Ectopic
  - struma ovarii
  - metasttic follicular carcinoma

Table 10–16. Common Thyroid Autoantibodies (Ab)

Antigen	Molecular Size	Abbreviation	Notes
TSH receptor	100 kd	TSHRAb	Antibody that causes Graves' disease
		TSHR-blocking Ab	Present in some thyroiditis patients
Thyroglobulin	330 kd	TgAb	Often undetectable using older techniques
Thyroid peroxidase	107 kd	TPOAb	Useful diagnostic marker

Prevalence of Thyroid Auto-Ab(%)

	TRAb	ATA	AMA
General Population	0	5-20	8-27
Graves' disease	80-95%	50-70	50-80
Hashimoto's thyroiditis	10-20	90-95	90-100
Relatives of Patients	0	40-50	40-50
Type 1 DM	0	40	40
Pregnant women	0	14	14

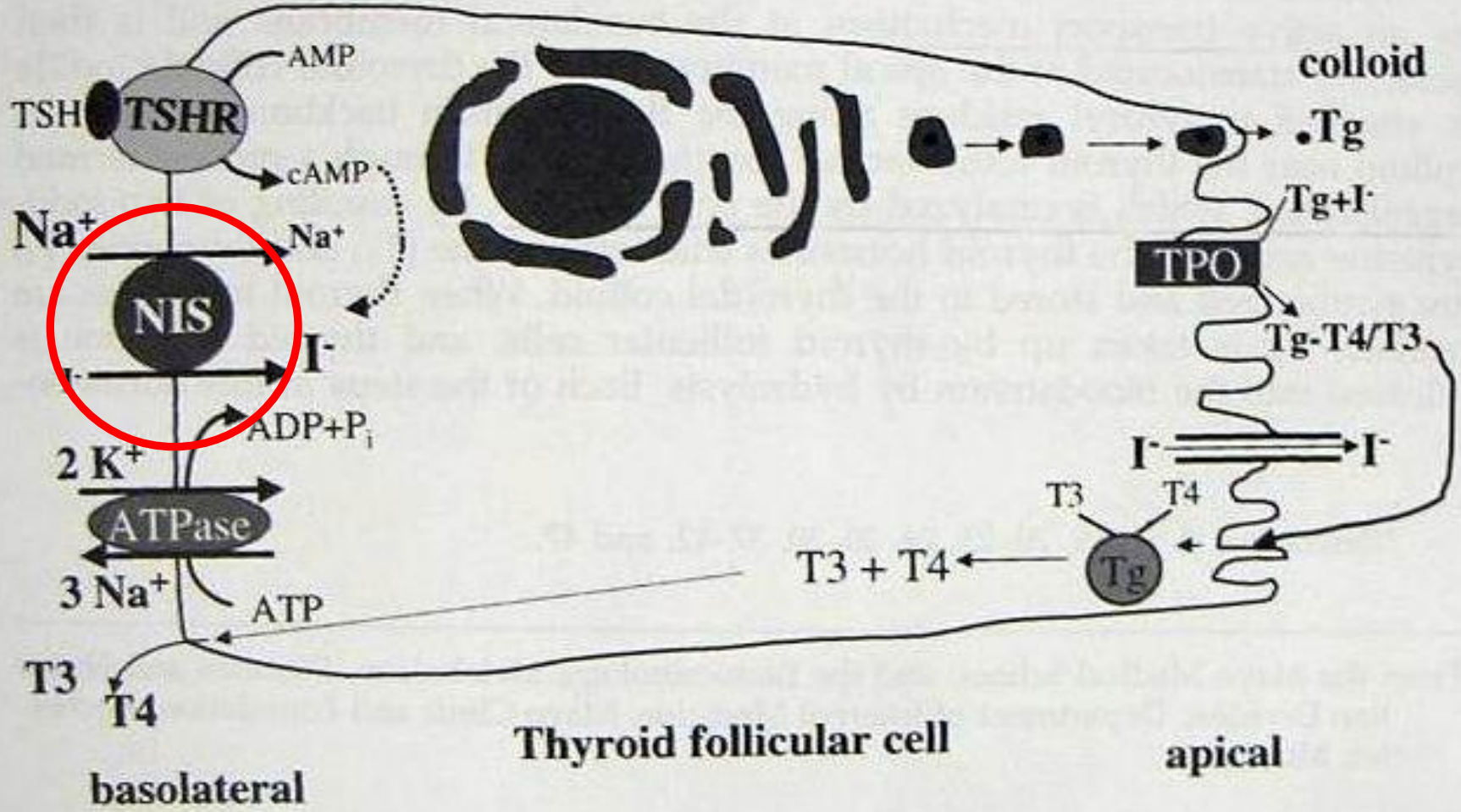


Figure 1. A thyroid follicular cell showing the key aspects of thyroid hormone synthesis. TSHR = TSH-receptor; NIS = sodium iodide symporter; TPO = thyroid peroxidase; Tg = thyroglobulin; T3 = triiodothyronine; T4 = thyroxine.

Endocrinology And Metabolism Clinics of North America 2000; 29(2):390

Recognition of Impending Storm: Diagnostic Criteria

Temperature dysfunction

Temp	
99-99.9	5
100-100.9	10
101-101.9	15
102-102.9	20
103-103.9	25
>=104.0	30

GI-Hepatic dysfunction

Absent	0
Moderate	10
diarrhea	
Nausea/vomiting	
Abdominal pain	
Severe	20
Unexplained jaundice	

CV dysfunction

Tachycardia	
90-109	5
110-119	10
120-129	15
130-139	20
>=140	25
CHF	
Absent	0
Mild	5
pedal edema	
Moderate	10
bibasilar rales	
Severe	15
pulmonary edema	
Atrial fibrollation	
Absent	0
Present	10

CNS effects

Absent	0
Mild	10
Agitation	
Moderate	20
Delirium, psycosis	
Extreme lethergy	
Severe	30
Seizure	
Coma	

Precipitiant Hx

Negative	0
Positive	10

Score > 45 -- thyroid storm, Score of 25-44 -- impending storm
Score < 25 -- unlikely to represent thyroid storm

PRECIPITANTS OF THYROID STORM

Rapid Rise In Thyroid Hormone Levels

- Thyroid surgery
- withdrawal of antithyroid drug therapy
- radioiodine therapy
- vigorous thyroid palpation
- iodinated contrast dyes

Acute or Subacute Nonthyroidal Illness

- Nonthyroidal surgery
- Infection
- CVA
- Pulmonary thromboembolism
- Parturition
- DKA
- Emotional stress
- Trauma.

Thyrotoxic Periodic Paralysis (TPP)

- Oriental man, 20-40 years, summer, high CHO diet,heavy exercise.
- Onset at 9 pm ~ 9 Am , any kinds of endogenous hyperthyroidism, not related to severity of hyperthyroidism.
- Na-k ATPase pump → Na-K interchange , Ca pump (?), genetic(?)
- Tx: (1) Acute stage: K replacement, rebound hyperkalemia (2) Propranolol : prevention (3) ATD

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  - TSH secreting tumour
  - HCG dependent (as in hyperemesis gravidarum)
- Thyroid hormone resistance
- Ectopic
  - struma ovarii
  - metasttic follicular carcinoma

Indications for RAI therapy:

- Age- people (>40).
- Huge goiter.
- Recurrent hyperthyroidism.
- Toxic goiter.

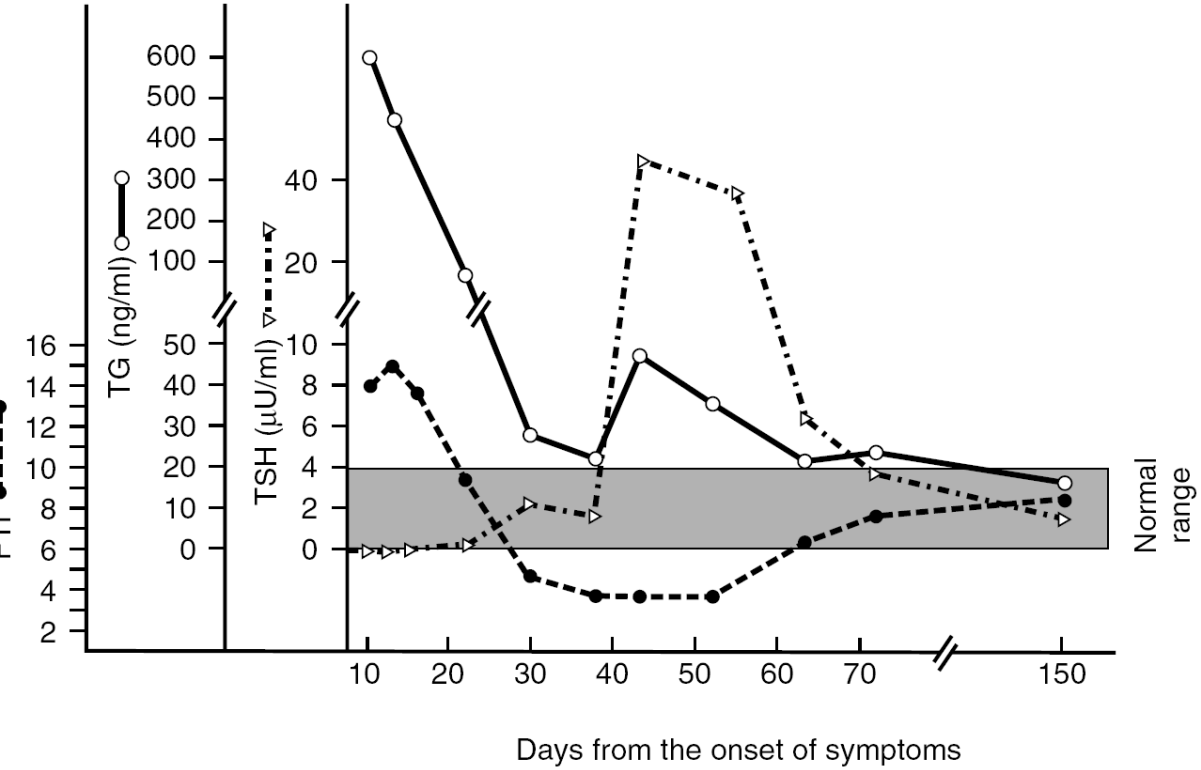


Figure 11–26. Thyroid function in a patient in the course of de Quervain's (subacute) thyroiditis. During the thyrotoxic phase (days 10 to 20) the serum thyroglobulin (TG) concentration was elevated, the free thyroxine index (FTI) was high, and thyrotropin (TSH) was suppressed. The erythrocyte sedimentation rate was 86 mm/hour, and the thyroidal radioactive iodine uptake was 2%. The Tg level and FTI declined in parallel. During the phase of hypothyroidism (days 30 to 63), when the FTI was below normal, the serum Tg level transiently increased in parallel with the increase in serum TSH. All parameters of thyroid function were normal by day 150, 5 months after the onset of symptoms. (From DeGroot LJ, Larsen PR, Hennemann G [eds]. Acute and subacute thyroiditis. In The Thyroid and Its Diseases, 6th ed. New York, Churchill Livingstone, 1996, p 705.)

Treatment

In mild cases,aspirin, nonsteroidal anti-inflammatory drugs, or cyclooxygenase-2 inhibitors generally control the symptoms.In more severe cases,glucocorticoids (e.g., prednisone up to 40 mg/day) alleviate the manifestations but do not influence the underlying disease process.

Acute Infectious Thyroiditis

- Congenital abnormalities of the piriform sinus
- Underlying autoimmune disease
- Immunocompromise of the host
- The etiology may be any bacterium,including *Staphylococcus*, *Pneumococcus*, *Salmonella*,or *Mycobacterium tuberculosis;* certain fungi, including *Coccidioides immitis*, *Candida*,or *Aspergillus* and *Histoplasma* have been reported.

D/DX of acute & subacute throiditis

Table 12–6. *Features Useful in Differentiating Acute Suppurative Thyroiditis and Subacute Thyroiditis*

	Characteristic	Acute Thyroiditis	Subacute Thyroiditis
History	Preceding upper respiratory infection	88%	17%
	Fever	100%	54%
	Symptoms of thyrotoxicosis	Uncommon	47%
	Sore throat	90%	36%
Physical examination of the thyroid	Painful thyroid swelling	100%	77%
	Left side affected	85%	Not specific
	Migrating thyroid tenderness	Possible	27%
	Erythema of overlying skin	83%	Not usually
Laboratory	Elevated white blood cell count	57%	25–50%
	Elevated erythrocyte sedimentation rate (>30 mm/hr)	100 %	85%
	Abnormal thyroid hormone levels (elevated or depressed)	5–10%	60%
	Alkaline phosphatase, transaminases increased	Rare	Common
Needle aspiration	Purulent, bacteria or fungi present	~100%	0
	Lymphocytes, macrophages, some polyps, giant cells	0	~100%
	^{123}I uptake low	Uncommon	~100%
Radiologic	Abnormal thyroid scan	92%	—
	Thyroid scan or ultrasound helpful in diagnosis	75%	—
	Gallium scan positive	~100%	~100%
	Barium swallow showing fistula	Common	0
	CT scan useful	Rarely	Not indicated
Clinical course	Clinical response to glucocorticoid treatment	Transient	100%
	Incision and drainage required	85%	No
	Recurrence following operative drainage	16%	No
	Piriform sinus fistula discovered	96%	No

From DeGroot LJ, Larsen PR, Hennemann G. Acute and subacute thyroiditis. In The Thyroid and Its Diseases, 6th ed. New York, Churchill Livingstone, 1996,

Causes of Thyroid Nodules

- Benign
  - Colloid or adenomatous
  - Cyst
  - Lymphocytic thyroiditis
  - Granulomatous thyroiditis
  - Neoplasm (follicular or Hurthel cell)
- Malignant
  - Papillary
  - Follicular
  - Medullar
  - Anaplastic
  - Lymphoma
  - Metastatic

Thyroid nodule

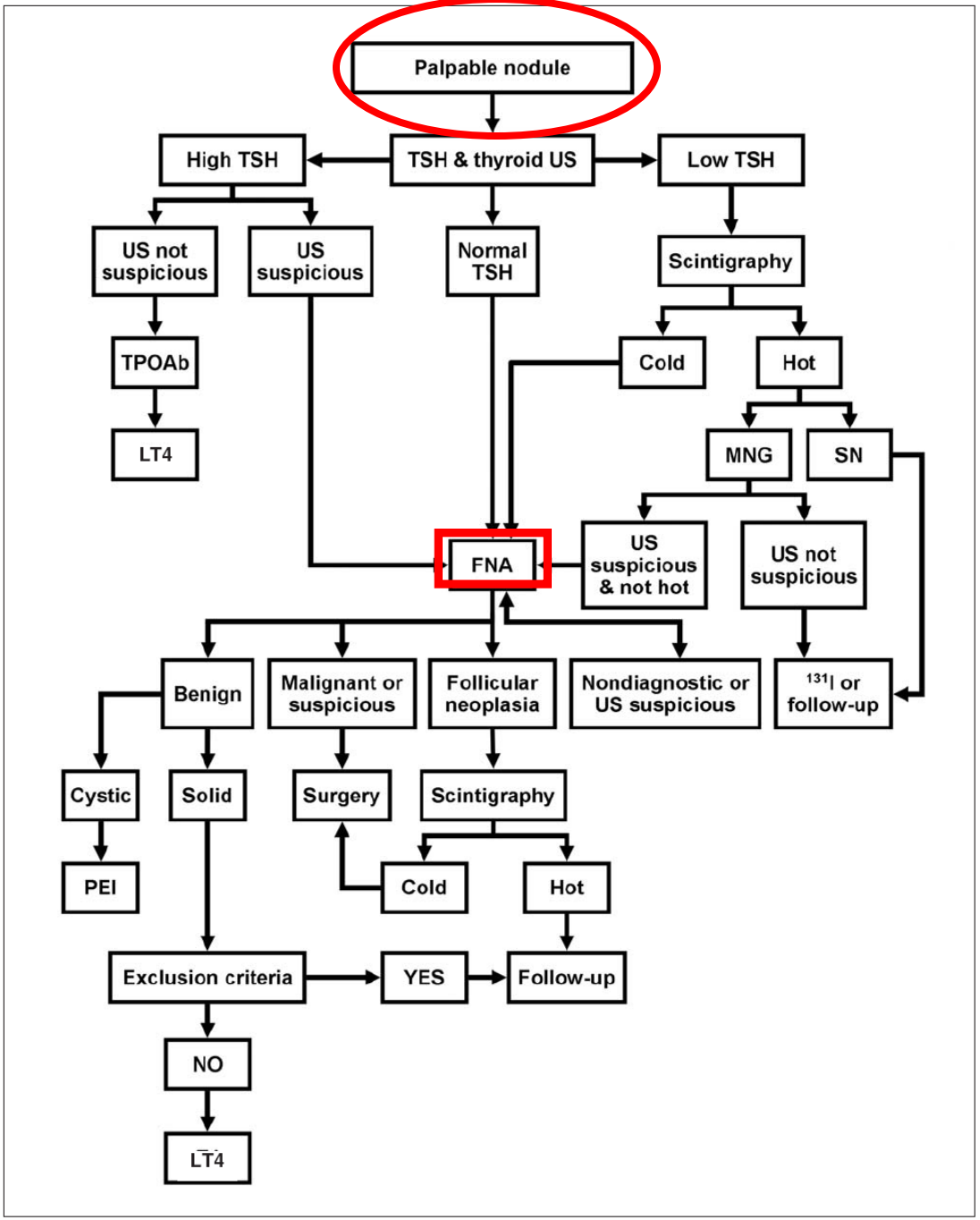


Fig. 1. Flowchart, indicating scheme for the diagnosis and management of palpable thyroid nodules. *FNA* = fine-needle aspiration; LT_4 = levothyroxine; *MNG* = multinodular goiter; *PEI* = percutaneous ethanol injection; *SN* = single nodule; *TPOAb* = thyroid peroxidase antibody; *TSH* = thyroid-stimulating hormone (thyrotropin); *US* = ultrasonography.

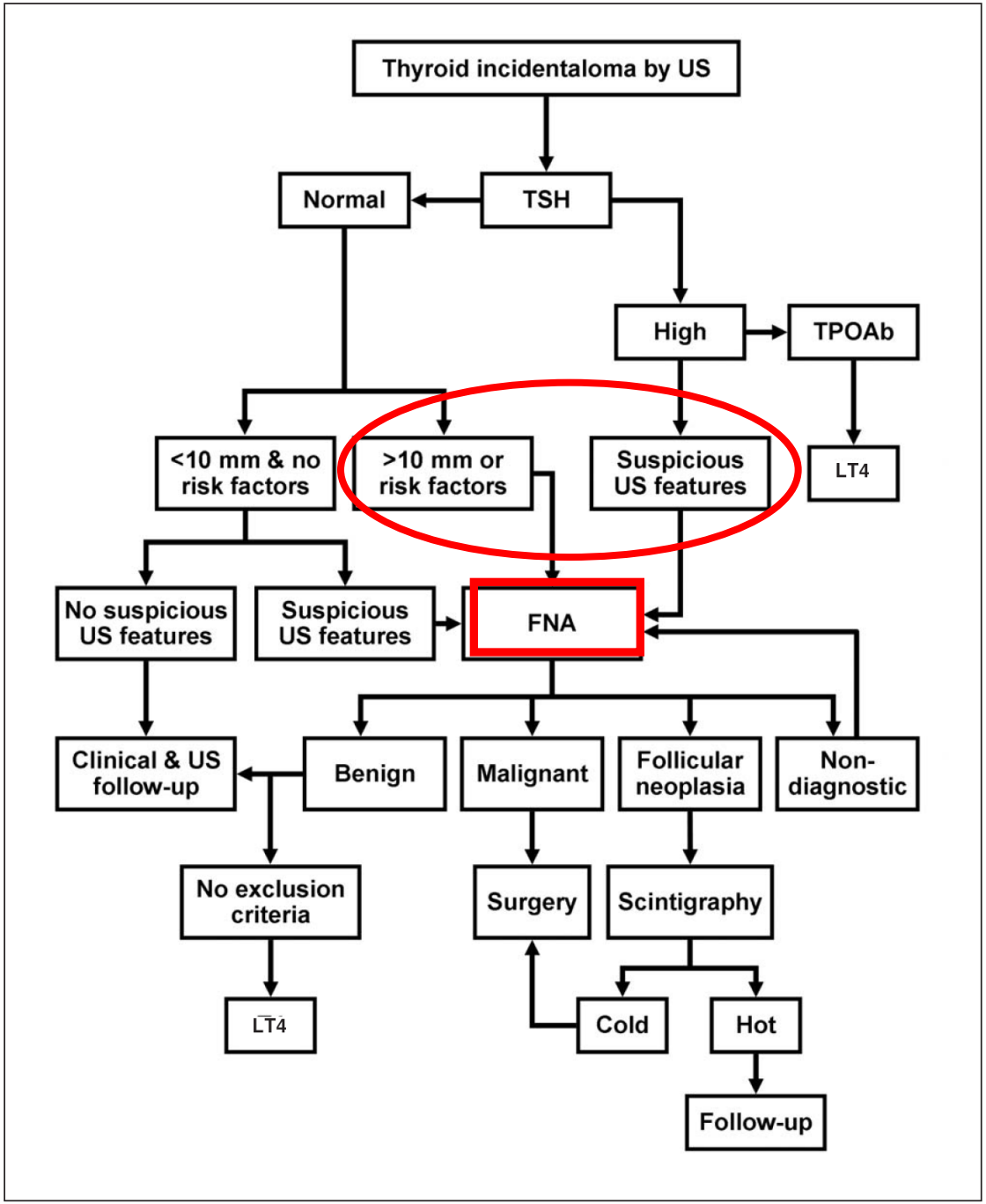
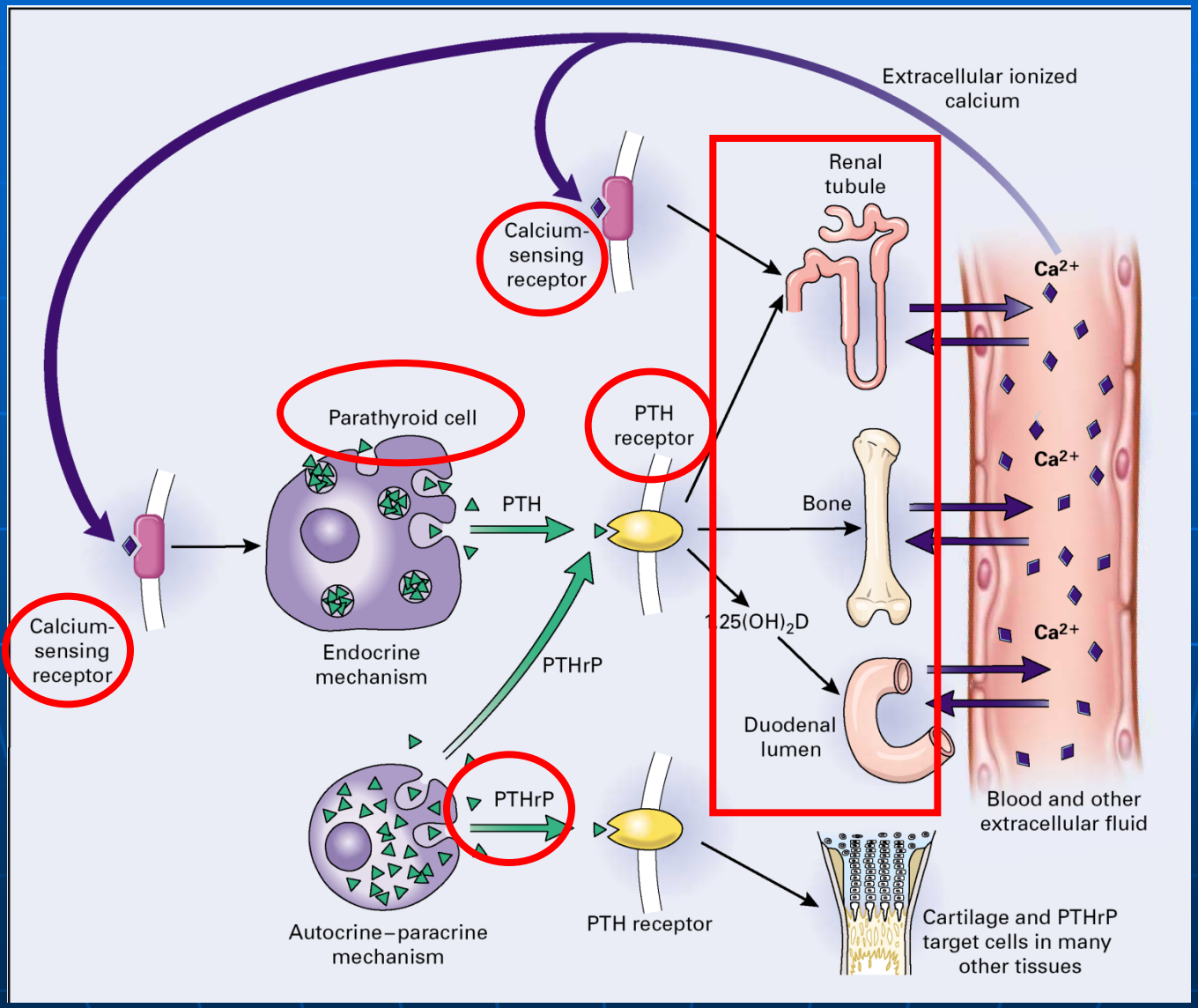


Fig. 2. Flowchart, showing recommended scheme for the diagnosis and management of ultrasonography-determined thyroid incidentalomas. *FNA* = fine-needle aspiration; LT_4 = levothyroxine; *TPOAb* = thyroid peroxidase antibody; *TSH* = thyroid-stimulating hormone (thyrotropin); *US* = ultrasonography.

Parathyroid, PTH and malignant

Calcium Homoeostasis



The parathyroid axis

NEJM 2000; 343:1863-1875

Actions of the Hormones Involved in Calcium Homeostasis

TABLE 1

Actions of the Hormones Involved in Calcium Homeostasis

Hormone	*Effect on bones*	*Effect on gut*	*Effect on kidneys*
Parathyroid hormone ↑Ca^{++}, ↓PO_4 levels in blood	Supports osteoclast resorption	Indirect effects via ↑calcitriol from 1-hydroxylation	Supports Ca^{++} resorption and PO_4 excretion, activates 1-hydroxylation
Calcitriol (vitamin D) ↑Ca^{++}, ↑PO_4 levels in blood	No direct effects Supports osteoblasts	↑Ca^{++} and PO_4 absorption	No direct effects
Calcitonin causes ↓Ca^{++}, ↓PO_4 levels in blood when hypercalcemia is present	Inhibits osteoclast resorption	No direct effects	Promotes Ca^{++} and PO_4 excretion

Ca^{++} = calcium; PO_4 = phosphate radical.

Am Fam Physician 2003;67:1959-66

Clinical Manifestations

Renal "stones"
- Nephrolithiasis
- Nephrogenic diabetes insipidus
- Dehydration
- Nephrocalcinosis

Skeleton "bones"
- Bone pain
- Arthritis
- Osteoporosis
- Osteitis fibrosa cystica in hyperparathyroidism (subperiosteal resorption, bone cysts)

Gastrointestinal "abdominal moans"
- Nausea, vomiting
- Anorexia, weight loss
- Constipation
- Abdominal pain
- Pancreatitis
- Peptic ulcer disease

Neuromuscular "psychic groans"
- Impaired concentration and memory
- Confusion, stupor, coma
- Lethargy and fatigue
- Muscle weakness
- Corneal calcification (band keratopathy)

Cardiovascular
- Hypertension
- Shortened QT interval on electrocardiogram
- Cardiac arrhythmias
- Vascular calcification

Other
- Itching
- Keratitis, conjunctivitis

<11.5 mg/dL

Asymptomatic

11.5-12 mg/dL

Common

>13 mg/dL

Calcification in kidneys, skin, vessels, lungs, heart, and stomach

>15 mg/dL

Coma and cardiac arrest

Am Fam Physician 2003;67:1959-66

Harrison's Principles of Internal Medicine - 16th Ed. (2005)

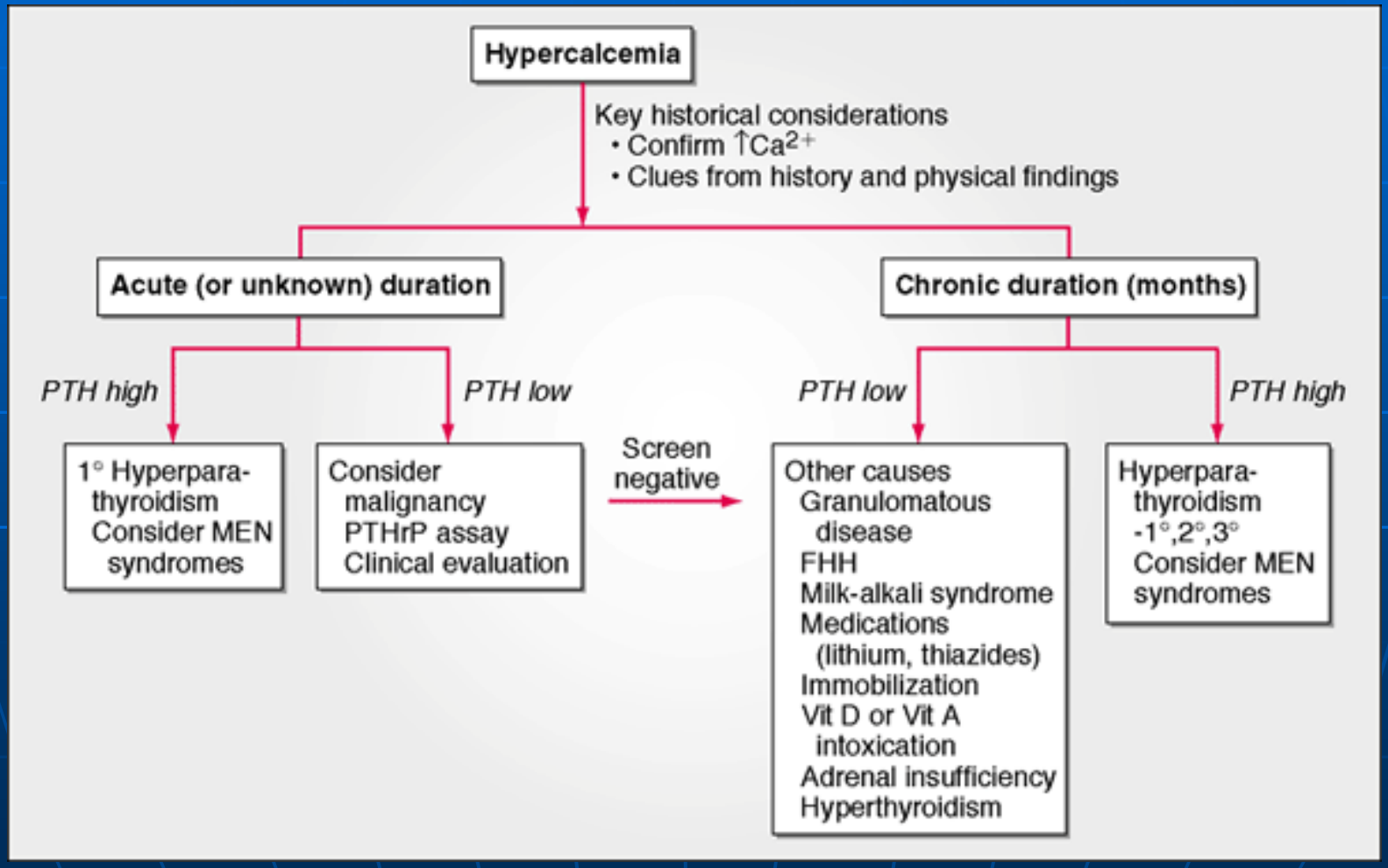
TABLE 332-1 Classification of Causes of **Hypercalcemia**

I. Parathyroid-related
A. Primary hyperparathyroidism
1. Solitary adenomas
2. Multiple endocrine neoplasia
B. Lithium therapy
C. Familial hypocalciuric **hypercalcemia**
II. Malignancy-related
A. Solid tumor with metastases (breast)
B. Solid tumor with humoral mediation of **hypercalcemia** (lung, kidney)
C. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)
III. Vitamin D-related
A. Vitamin D intoxication
B. ↑ $1,25(OH)_2D$; sarcoidosis and other granulomatous diseases
C. Idiopathic **hypercalcemia** of infancy
IV. Associated with high bone turnover
A. Hyperthyroidism
B. Immobilization
C. Thiazides
D. Vitamin A intoxication
V. Associated with renal failure
A. Severe secondary hyperparathyroidism
B. Aluminum intoxication
C. Milk-alkali syndrome

Table 26–2. Causes of Hypercalcemia

Parathyroid-Dependent Hypercalcemia
Primary hyperparathyroidism
Tertiary hyperparathyroidism
Familial hypocalciuric hypercalcemia
Lithium-associated hypercalcemia
Parathyroid-Independent Hypercalcemia
Neoplasms
Parathyroid hormone–related protein–dependent
Other humoral syndromes
Osteolytic metastases and multiple myeloma
Excess vitamin D/1,25$(OH)_2$D
Vitamin D ingestion
1,25-Dihydroxyvitamin D intoxication
Topical vitamin D analogues
Granulomatous disease
Williams' syndrome
Thyrotoxicosis
Adrenal insufficiency
Renal failure
Acute renal failure
Chronic renal failure with aplastic bone disease
Immobilization
Jansen's disease
Drugs
Vitamin A intoxication
Milk-alkali syndrome
Thiazide diuretics
Theophylline

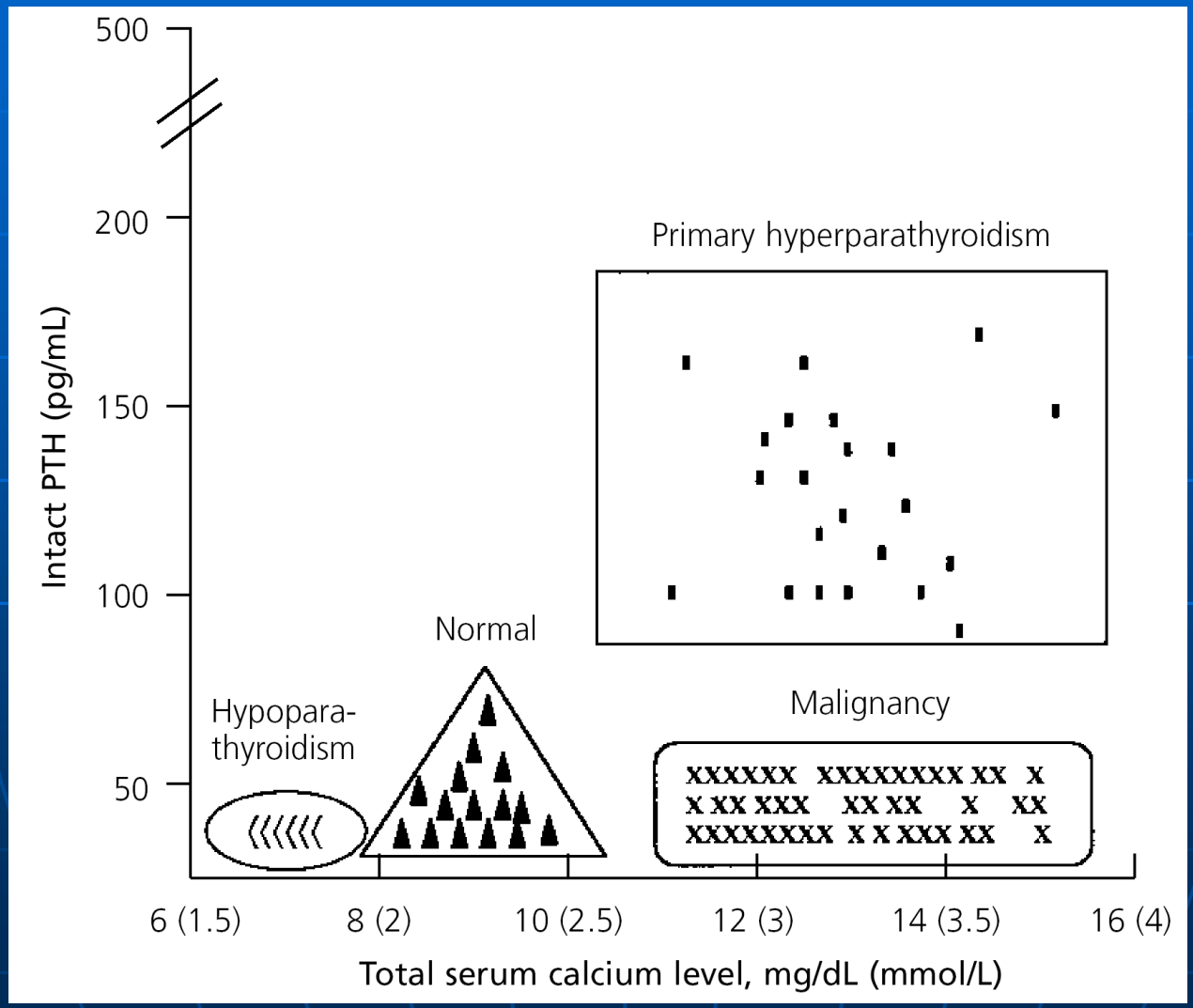
Evaluation of Hypercalcemia



Harrison's 16th Edi Chapter 332

Differential diagnosis

Representative Normogram for Interpreting Serum Intact PTH Levels



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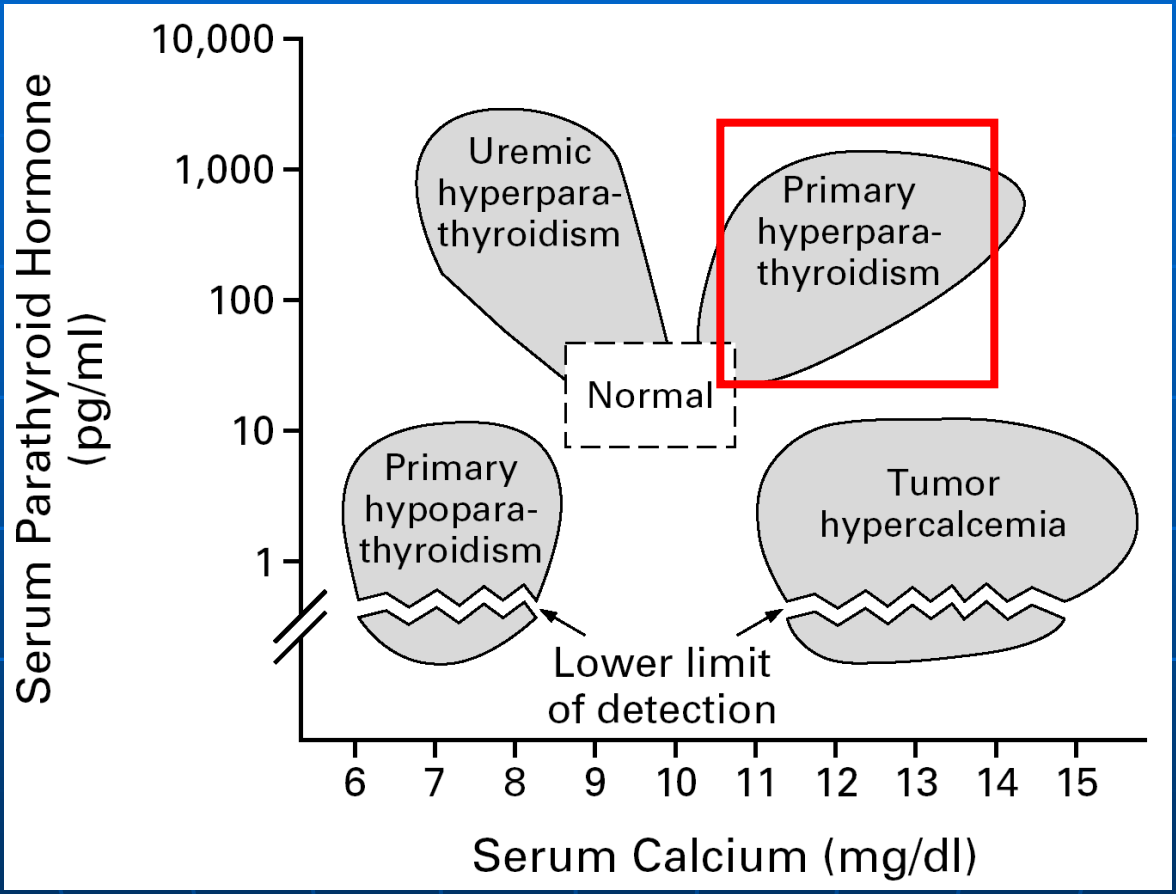
Hyperparathyroidism-Diagnosis



- High PTH, hypercalcemia, and low phosphate level

Hyperparathyroidism

TABLE 1. CATEGORIES OF PRIMARY HYPERPARATHYROIDISM.*

CHARACTERISTIC	SPORADIC ADENOMA	MULTIPLE ENDOCRINE NEOPLASIA TYPE 1	FAMILIAL HYPOCALCIURIC HYPERCALCEMIA	NEONATAL SEVERE PRIMARY HYPERPARATHYROIDISM
Inheritance	Not inherited	Autosomal dominant	Autosomal dominant	Autosomal recessive
Age at onset of hypercalcemia	55 yr	25 yr	Birth	Birth
Urinary calcium excretion	Normal to high	Normal to high	Low to normal	Low to normal
Serum parathyroid hormone concentration	High	High	Normal	Very high
Parathyroid glands				
No. abnormal	One	Multiple	Multiple	Multiple
Enlargement	20 times normal size	5 times normal size	Minimally enlarged	Very enlarged
Clonality	Monoclonal or oligoclonal	Monoclonal or oligoclonal	Polyclonal	Polyclonal
Effectiveness of parathyroidectomy	95% cured	90% cured, but many recur	Surgery not indicated	Total parathyroidectomy required
Pathophysiology	Stepwise acquired mutations of certain genes, such as *MEN1*, promote the emergence of a neoplastic clone in parathyroid gland	Sequential inactivation of both copies (first copy by inheritance) of the *MEN1* gene leads to the growth of one or more neoplastic clones in parathyroid glands	Monoallelic inherited inactivation of the calcium-sensing receptor gene decreases the sensing of serum calcium by parathyroid cells and by renal tubules	Biallelic inactivation of the calcium-sensing receptor gene impairs calcium sensing in parathyroid cells more than does monoallelic inactivation

*All entries are typical for that disorder. Ranges are broad, with overlap (not shown) among categories.

NEJM 2000; 343:1863-1875

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Ca^{++} = calcium; PO_4 = phosphate radical.

Am Fam Physician 2003;67:1959-66

Parathyroid Scan:

localization of parathyroid adenoma/hyperplasia

- Subtraction scan (dual-isotope)
  - $^{201}Tl/^{99m}TcO_4$
  - ^{99m}Tc sestamibi/^{123}I
  - ^{99m}Tc tertrofosmin/^{123}I

  Rationale: (Thyroid + parathyroid) – (thyroid) = parathyroid adenoma

Parathyroid Scan:

localization of parathyroid adenoma/hyperplasia

- Dual-phase scan (single isotope)

  ^{99m}Tc sestamibi (5-15' early vs. 2-5Hr late)

  Rationale: MIBI retained longer in parathyroid adenoma

Clinical relevance of Parathyroid scan

- Pre-op localization
  - Less extensive surgery
  - Identification of ectopic tumor
- Recurrent hyperPTH post surgery
- Autologous re-implantation

Management of hyperparathyroidism

Criteria for Surgery in Primary Hyperparathyroidism*

- Serum total calcium level > 12 mg per dL (3 mmol per L) at any time
- Hyperparathyroid crisis (discrete episode of life-threatening hypercalcemia)
- Marked hypercalciuria (urinary calcium excretion more than 400 mg per day)
- Nephrolithiasis
- Impaired renal function
- Osteitis fibrosa cystica
- Reduced cortical bone density (measure with dual x-ray absorptiometry or similar technique)
  - Bone mass more than two standard deviations below age-matched controls (Z score less than 2)
- Classic neuromuscular symptoms
  - Proximal muscle weakness and atrophy, hyperreflexia, and gait disturbance
- Age younger than 50

*—*Guidelines from the National Institutes of Health Consensus Development Conference.*

Information from NIH conference: diagnosis and management of asymptomatic primary hyperparathyroidism: consensus development conference statement. Ann Intern Med 1991;114:593-7.

Table 26–1. Indications for Surgery in Primary Hyperparathyroidism

1. Overt clinical manifestations of primary hyperparathyroidism
   a. Radiographic nephrolithiasis or otherwise documented kidney stone(s)
   b. Reduced creatinine clearance (not otherwise explained)
   c. Radiographically evident hyperparathyroid bone disease
   d. Classical hyperparathyroid neuromuscular disease
   e. Symptoms attributable to hypercalcemia per se
   f. Previous episode of life-threatening hypercalcemia
2. Serum calcium concentration greater than 12 mg/dL (2.99 mM)
3. Urinary calcium excretion greater than 400 mg/day (9.98 mmol/day)
4. Low or declining bone mineral density
   a. Less than 2 SDs below age/sex-matched controls (any site) *or*
   b. Vertebral osteopenia* *or*
   c. Declining vertebral bone density*
5. Age younger than 50 years
6. Uncertain prospect for successful medical monitoring
   a. Patient requests surgery
   b. Consistent follow-up seems unlikely
   c. Coexistent illness that may contribute to, or confound detection of, disease progression

*Not among original recommendations of NIH Consensus Conference.
SD, standard deviation.

Management of asymptomatic hyperparathyroidism

TABLE 332-2 Guidelines for Parathyroid Surgery in Asymptomatic Primary Hyperparathyroidism[a]

Measurement	Guidelines, 1990	Guidelines, 2002
Serum calcium (above upper limit of normal)	0.3-0.4 mmol/L (1-6 mg/dL)	0.3 mmol/L (1.0 mg/dL)
24-h urinary calcium	>400 mg	>400 mg
Creatinine clearance	Reduced by 30%	Reduced by 30%
Bone mineral density	Z-score < -2.0 (forearm)	T-score < -2.5 at any site
Age	<50	<50

[a] Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.

Source: From JP Bilezikian et al: J Clin Endocrinol Metab 87:5353, 2002.

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Follow-up of hyperparathyroidism

TABLE 332-3 Management Guidelines for Patients with Aymptomatic Primary Hyperparathyroidism Who Do Not Undergo Parathyroid Surgery

Measurement	Older Guidelines	New Guidelines
Serum calcium	Biannually	Biannually
24-h urinary calcium	Annually	Not recommended[a]
Creatinine clearance	Annually	Not recommended[a]
Serum creatinine	Annually	Annually[b]
Bone density	Annually (forearm)	Annually (lumbar spine, hip, forearm)
Abdominal x-ray (+/- ultrasound)	Annually	Not recommended[a]

[a] Except at the time of initial evaluation.

[b] If the serum creatinine concentration suggests a change in the creatinine clearance when the Cockroft-Gault equation is applied, further, more direct assessments of the creatinine clearance are recommended.

Source: From JP Bilezikian et al: J Clin Endocrinol Metab 87:5353, 2002.

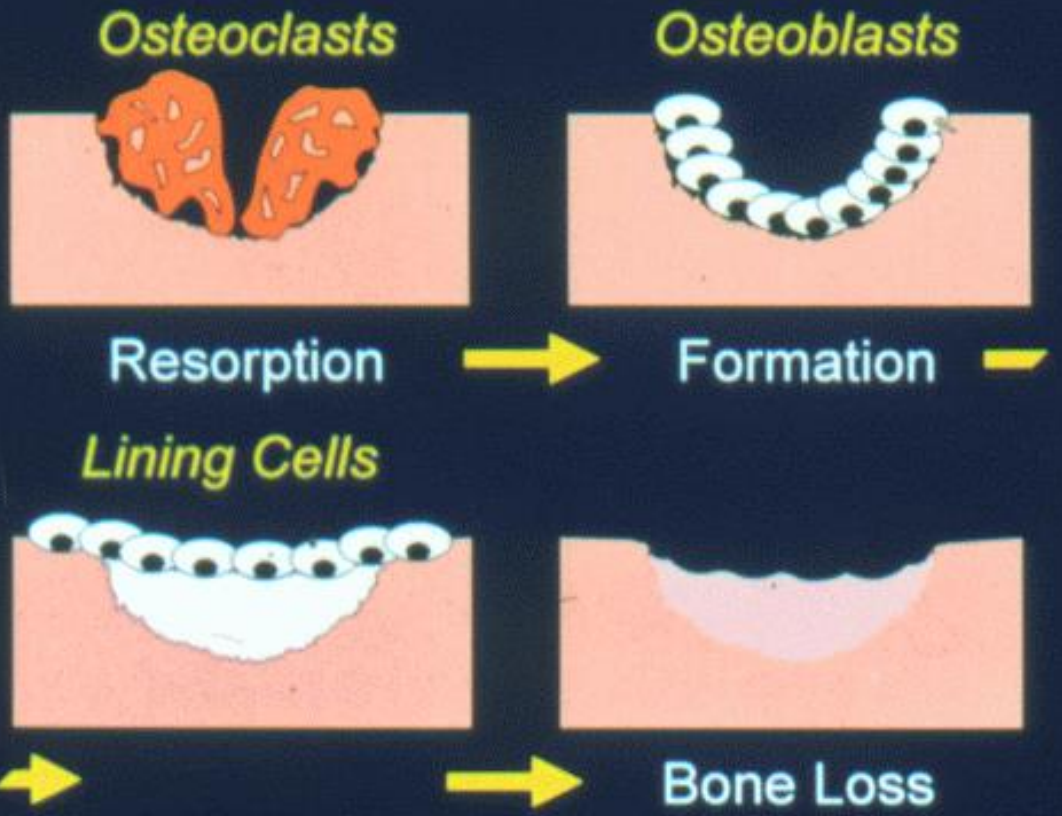
Management of hypercalcemia

TABLE 332-4 Therapies for Severe Hypercalcemia

Treatment	Onset of Action	Duration of Action	Advantages	Disadvantages
MOST USEFUL THERAPIES				
Hydration with saline Forced diuresis; saline plus loop diuretic	Hours Hours	During infusion During treatment	Rehydration invariably needed Rapid action	Volume overload, cardiac decompensation, intensive monitoring, electrolyte disturbance, inconvenience
Bisphosphonates 1st generation: etidronate	1-2 days	5-7 days in doses used	First available bisphosphonate; intermediate onset of action	Less effective than other bisphosphonates
2d generation: pamidronate	1-2 days	10-14 days to weeks	High potency; intermediate onset of action	Fever in 20% hypophosphatemia, hypocalcemia, hypomagnesemia
3d generation: zolendronate	1-2 days	>3 weeks	High potency; rapid infusion; prolonged duration of action	Minor; fever, rarely hypocalcemia or hypophosphatemia
Calcitonin	Hours	1-2 days	Rapid onset of action; useful as adjunct in severe hypercalcemia	Rapid tachyphylaxis

Bone metabolism

Bone Turnover in a Remodeling Unit in Adults



Trabecular Bone
20% of the skeletal mass
80% of the turnover

Cortical Bone
80% of the skeletal mass
20% of the turnover

Comparison of Osteoporosis and Osteomalacia

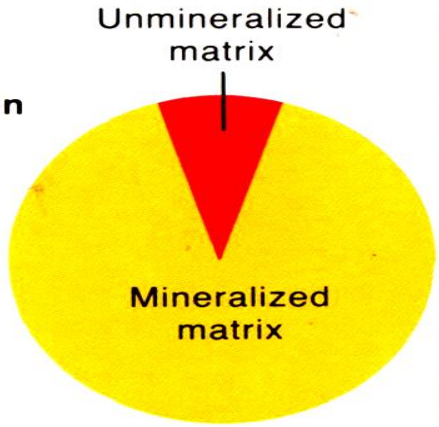
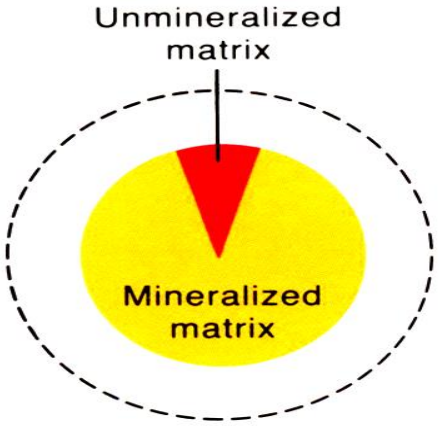
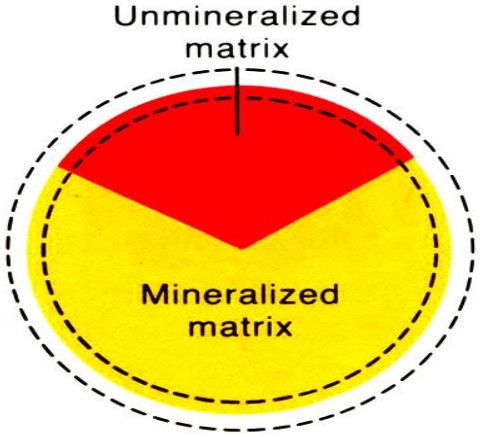
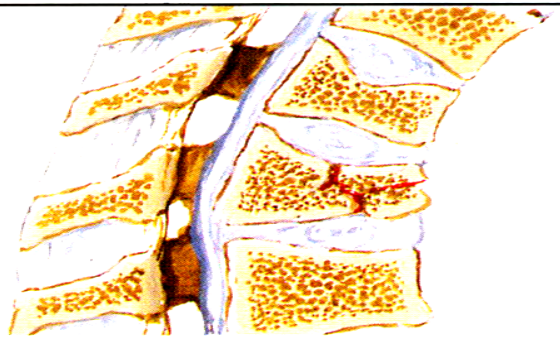
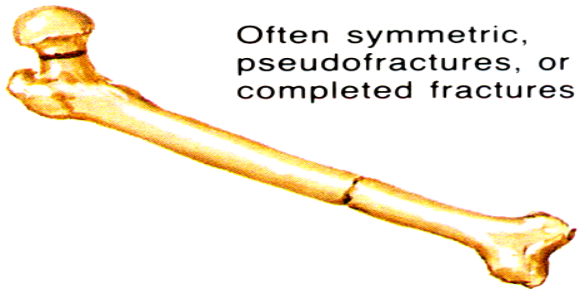
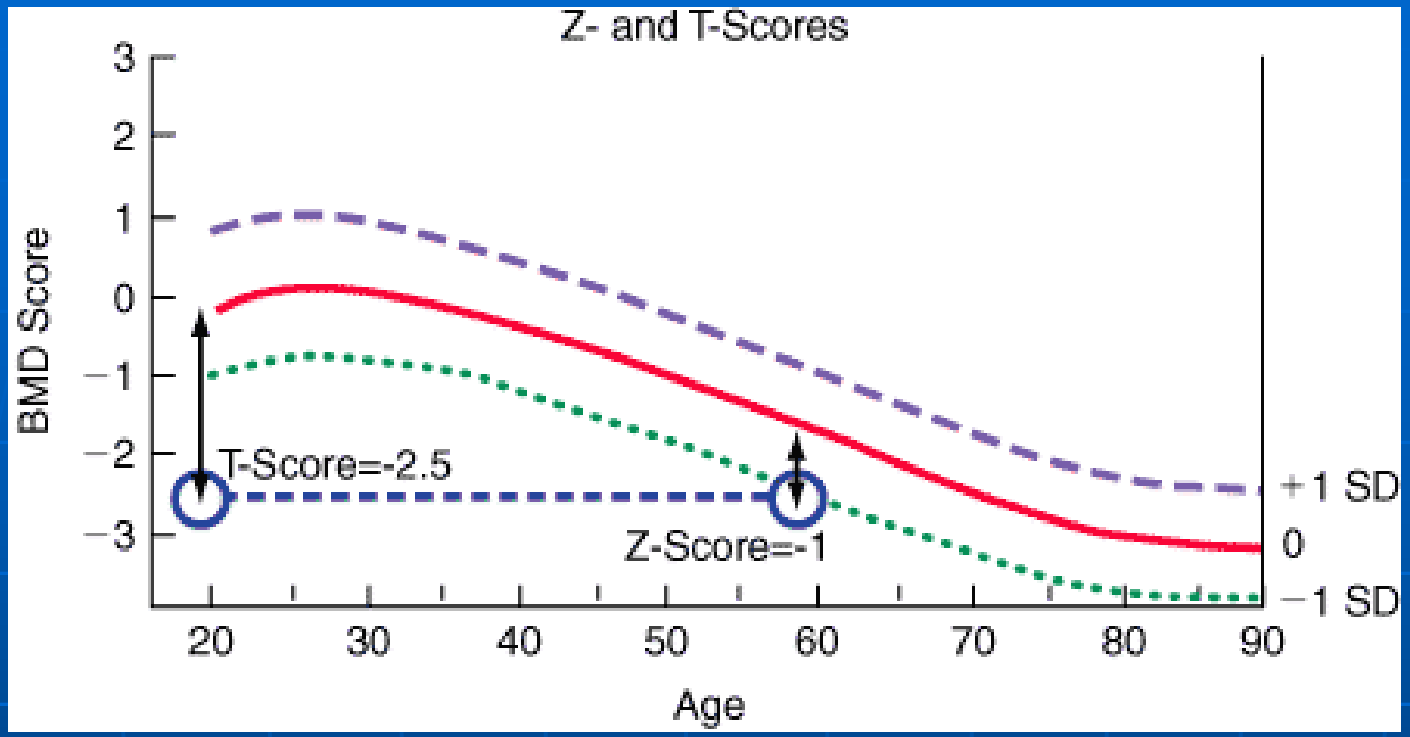
	Osteoporosis	Osteomalacia
Definition	 Normal	 Bone mass decreased, mineralization normal	 Bone mass variable, mineralization decreased
Radiographic features	 Axial predominance	 Often symmetric, pseudofractures, or completed fractures Appendicular predominance
Laboratory findings		
Serum Ca^{++}	Normal	Low or normal (high in hypophosphatasia)
Serum P_i	Normal $Ca^{++} \times P_i > 30$	Low or normal $Ca^{++} \times P_i < 30$ if albumin normal (high in renal osteodystrophy)
Alkaline phosphatase	Normal	Elevated, except in hypophosphatasia
Urinary Ca^{++}	High or normal	Normal or low (high in hypophosphatasia)
Bone biopsy	Tetracycline labels normal	Tetracycline labels abnormal

Fig. 333-6



- a 60-year-old woman with a Z-score of –1 (1 SD below mean for age) has a T-score of –2.5 (2.5 SD below mean for a young control group)
- T-score: reflects standard deviation from a young healthy adult population
- Z-score: 同年齢平均値

WHO Diagnostic Criteria for Women Without Fragility Fractures

Diagnosis	BMD Criteria (T- score)
Normal	Within 1 SD of the young adult man
Osteopenia	Between –1SD and –2.5SD below the young adult man
Osteoporosis	At least –2.5 SD below the young adult man

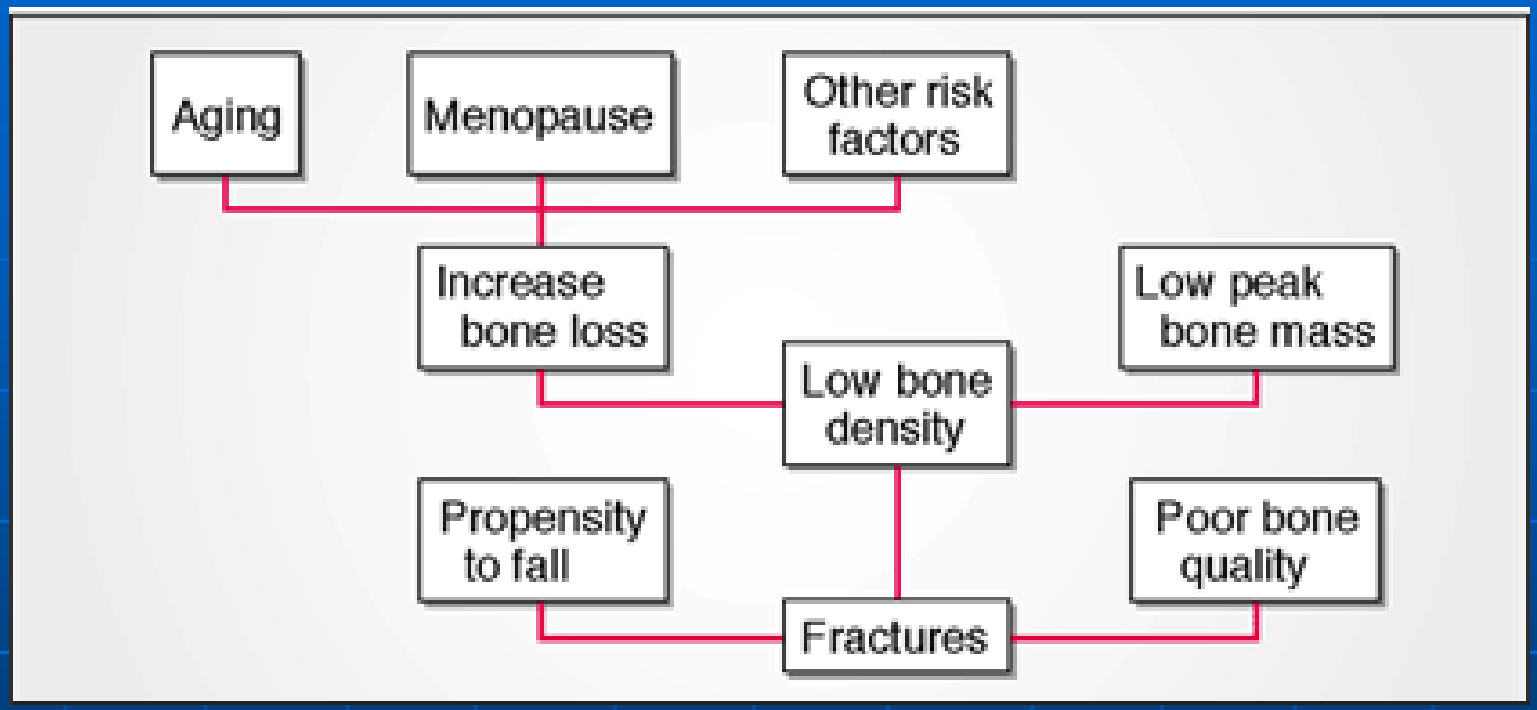


FIGURE 333-3 Factors leading to osteoporotic fractures.

Drug affects bone metabolism

- Cyclosporin – increase bone turnover
- Antiepileptics– interfere Vit D metabolism
- Heparin– decrease bone mass and BMD
- Thiazide diuretics – stimulate distal tubule reabsorption of calcium, BMD↑, fracture risk↓

Diagnostic tools

- Single-photon absorptionmetry
- Dual-photon absorptiomerty
- Dual x-ray absorptiometry (DEXA)
  - 雙能X光骨密度儀 一種非侵入性的放射性檢查，主要在量測第一到第四節腰椎與近端股骨的骨質狀態，使用的是QDR-4500 骨密度儀（Hologic, Waltham,MA），骨密度由每平方公分測得的重量決定，再個別以T-score表示
- Quantitative computed tomography
- Ultrasonography

Treatment

- Management of osteoporotic fractures
  - Hip fractures almost always require surgical repair
  - Other fractures are usually managed with only supportive care
- Management of the underlying disease
  - Risk factor reduction
  - Nutritional recommendations
    - Calcium, vitamin D, exercise

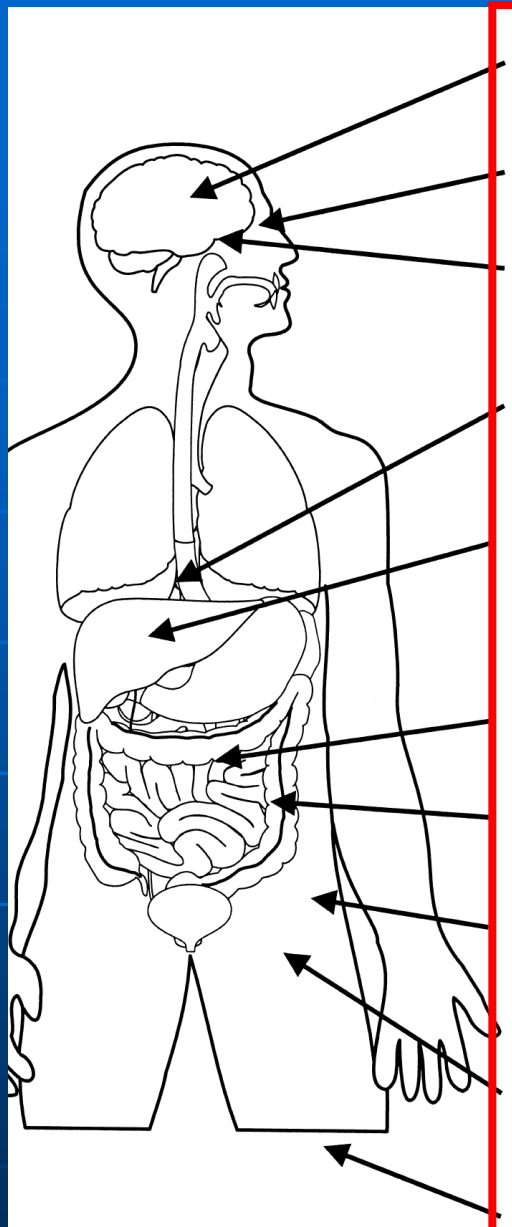
Treatment

- Pharmacologic therapies
  - Estrogens : reduce bone turnover, prevent bone loss
  - Progestins
  - Selective estrogen response modulators (SERMs)
    - Raloxifene : prevention and treatment of osteoporosis
    - Tamoxifen : prevention and treatment of breast cancer
  - Bisphosphonates : postmenopausal and steroid induced ostoporosis
    - Alendronate, risedronate : decrease bone turnover rate
  - Calcitonin : women > 5 years past menopause
  - Parathyroid hormone : a true increase in bone tissue
  - Fluoride : a potent stimulator of osteoprogenitor cells

Bisphosphonates

- Act directly on mature osteoclast, decrease bone resorption activity.
- Induce osteoclast apoptosis.
- Alendronate (Fosamax), Risedronate have the similar effects and adverse effects (GI).
- Reduce the vertebral fractures and minimizes their severity
- Long-term alendronate therapy may suppress bone turnover, resulting in increased susceptibility to and delayed healing of non-spinal fractures

Adrenal gland



Brain/CNS:
Depression
Psychosis

Eye:
Glaucoma

Endocrine system:
↓ LH, FSH release
↓ TSH release
↓ GH secretion

GI tract:
Peptic ulcerations

Carbohydrate/lipid metabolism:
↑ hepatic glycogen deposition
↑ peripheral insulin resistance
↑ gluconeogenesis
↑ free fatty acid production
Overall diabetogenic effect

Adipose tissue distribution:
Promotes visceral obesity

Cardiovascular/Renal:
Salt and water retention
Hypertension

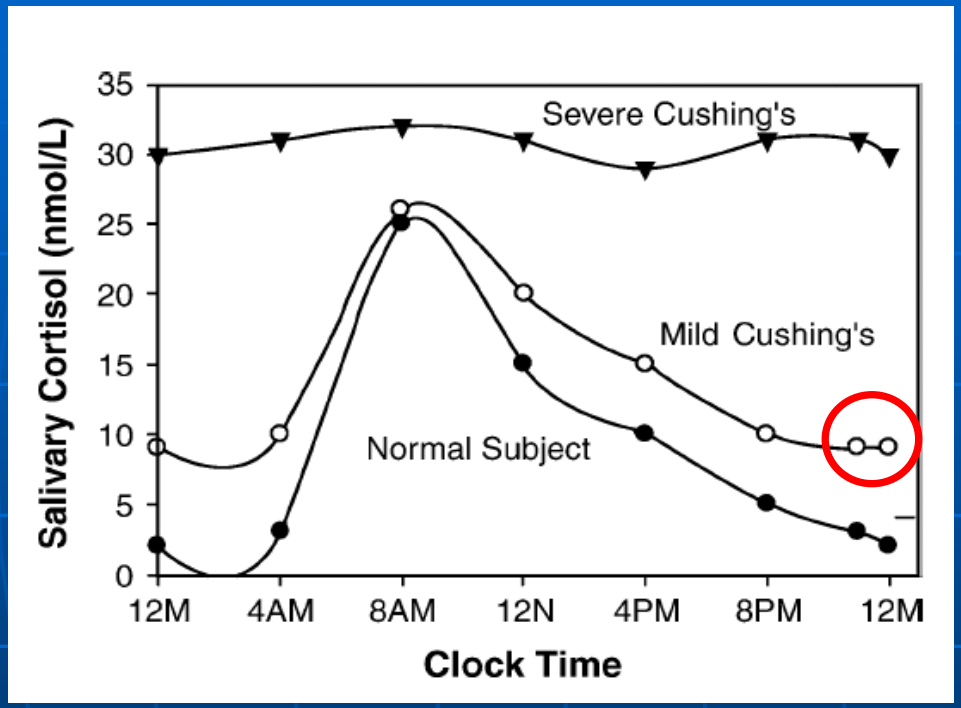
Skin/muscle/connective tissue:
Protein catabolism/collagen breakdown
Skin thinning
Muscular atrophy

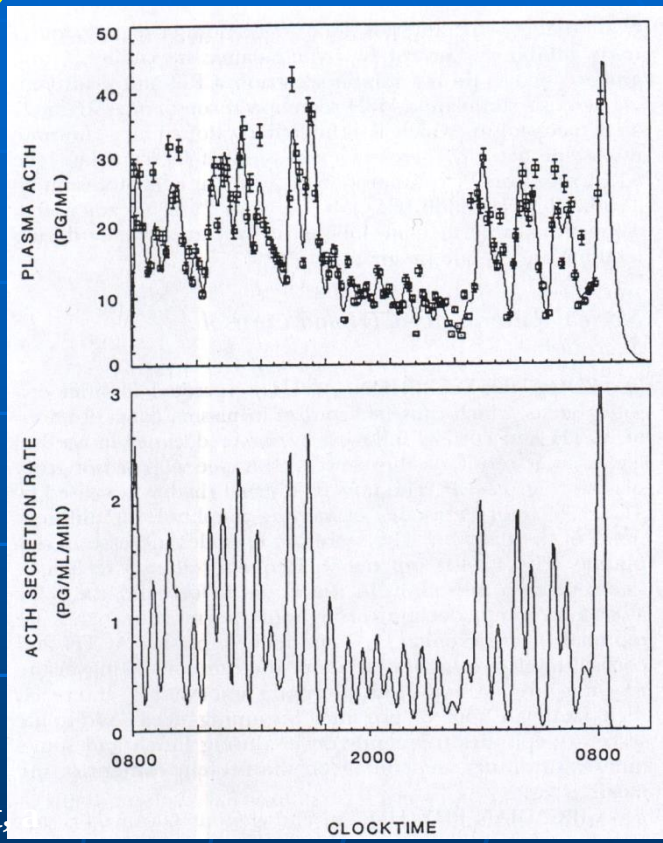
Bone and calcium metabolism:
↓ bone formation
↓ bone mass and osteoporosis

Growth and Development:
↓ linear growth

Immune system:
Anti-inflammatory action
Immunosuppression

Cortisol Circadian *VS* Cushing's Syndrome

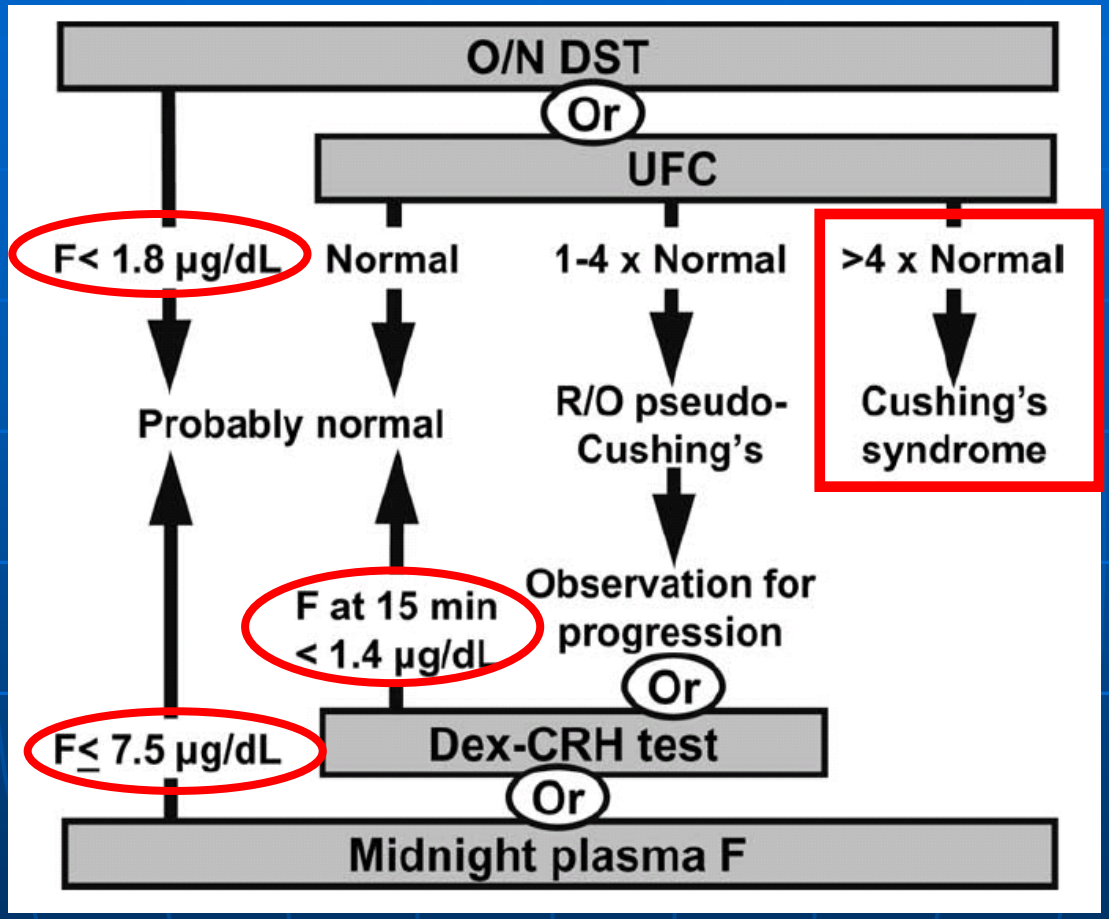




Theoretical salivary cortisol levels during a typical day in a normal subject, patient who has mild Cushing's disease, and a patient who has severe Cushing's syndrome. Note that the 11 PM-3 AM time period is the best to discriminate between mild Cushing's disease and normal subjects. For diagnostic purposes, salivary cortisol is usually sampled at 11 PM. (Reprinted from Raff H. Role of salivary cortisol determinations in the diagnosis of Cushing's syndrome.

Endocrinol Metab Clin N Am 2005; 34:

Establishing the Diagnosis of Cushing's Syndrome (CS)



An algorithm for establishing the diagnosis of Cushing's syndrome. To calculate values in SI units (nmol/L) multiply by 27.59. O/N DST = overnight 1-mg dexamethasone suppression test; UFC = urinary free cortisol; F = cortisol; R/O = rule out; Dex-CRH = dexamethasone-corticotropin-releasing hormone test.

Am J Med 2005; 118: 1340-

Screening & Confirmatory Tests for Cushing's Syndrome

Type of evaluation	Protocol	Interpretation	Sensitivity%	Specificity%	Remarks
Screening UFC	24-hour urine	Normal cortisol secretion usually <90 µg/24hr	95-100	98	Test of choice;>250-300 µg/d diagnostic
1-mg DST	1mg p.o. at 11PM	Normal < 5 µg/dL	98	70-80	The low specificity is problematic
Confirmatory UFC	24-hour urine	See above	95-100	98	Test of choice;>250-300 µg/d diagnostic
LDD/CRH test	DEX, 0.5mg/6h x 2 d; 2h later,CRH 1 µg/kg IV(8AM)	Normal < 1.4 µg/dL	100	100	Useful in borderline UFC, pseudo-Cushing
Low-dose DST	DEX, 0.5mg/ 6h x 2 d	UFC>36 µg/dL or 17 HS>4mg/d	56-69	74-100	Historical gold standard of limited usefulness

Atlas of clinical endocrinology,1999,vol 4,163

Table 14–10. Classification of Causes of Cushing's Syndrome

ACTH-Dependent

Cushing's disease (pituitary-dependent)
Ectopic ACTH syndrome
Ectopic CRH syndrome
Macronodular adrenal hyperplasia
Iatrogenic (treatment with ACTH 1–24)

ACTH-Independent

Adrenal adenoma and carcinoma
Primary pigmented nodular adrenal hyperplasia and Carney's syndrome.
McCune-Albright syndrome
Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1β).
Iatrogenic (e.g., pharmacologic doses of prednisolone, dexamethasone)

Pseudo-Cushing's Syndromes

Alcoholism
Depression
Obesity

ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone.

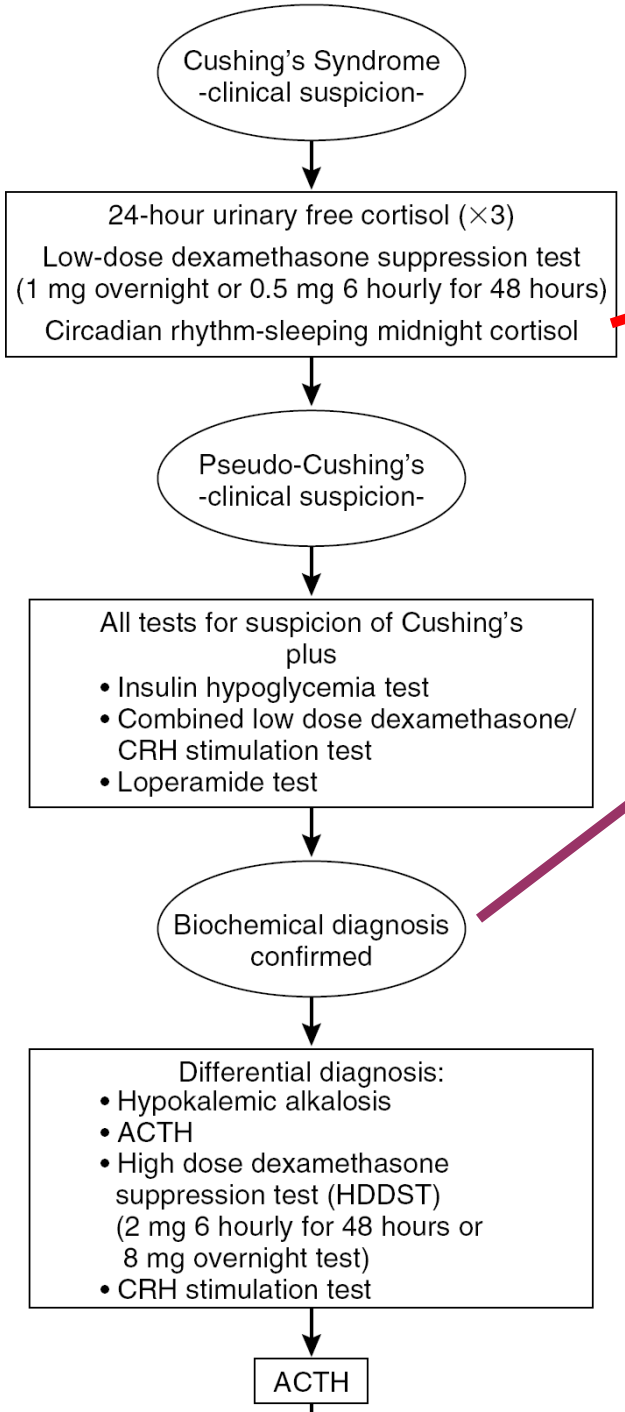
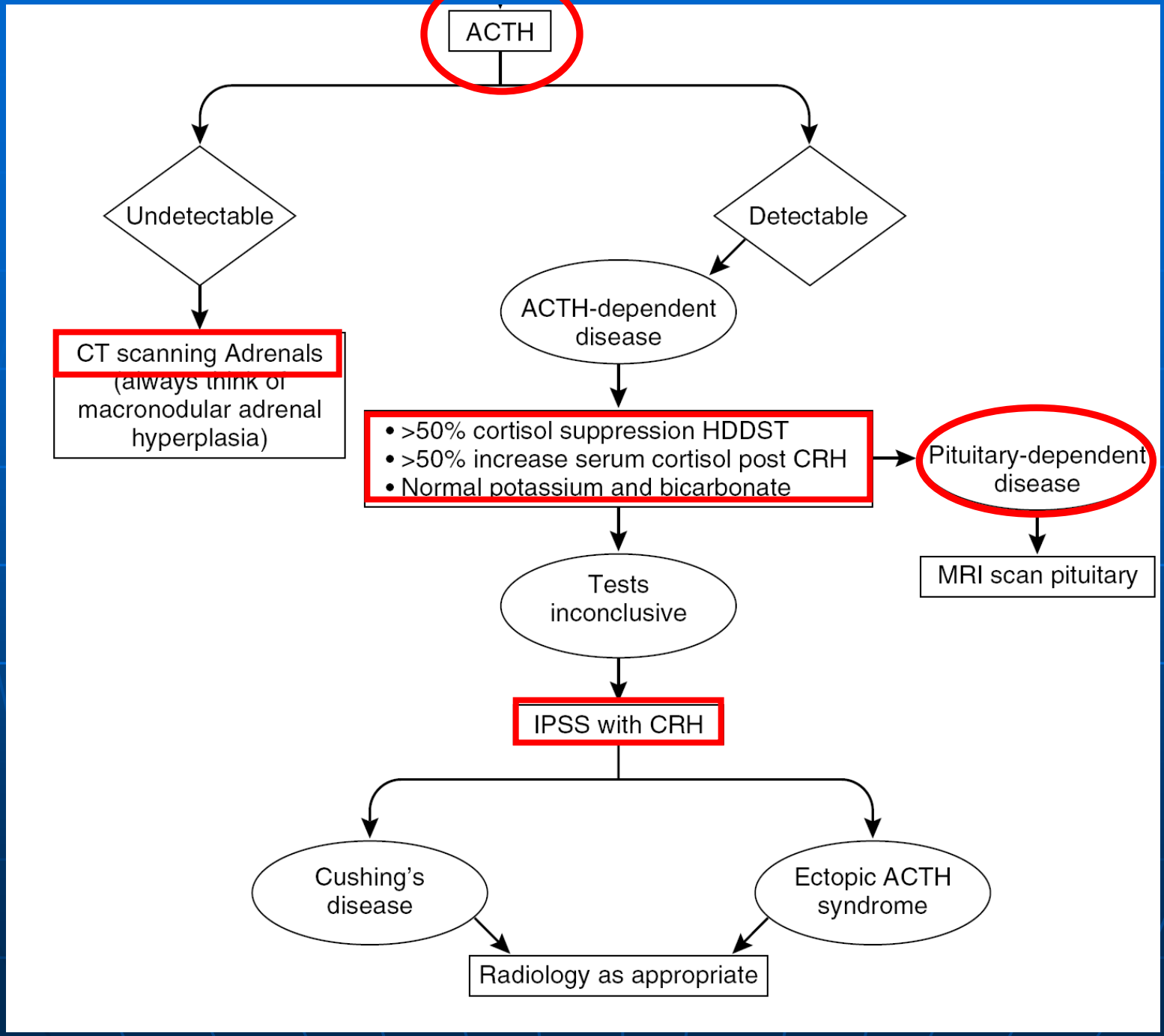


Table 14–15. *Tests Used in the Diagnosis and Differential Diagnosis of Cushing's Syndrome*

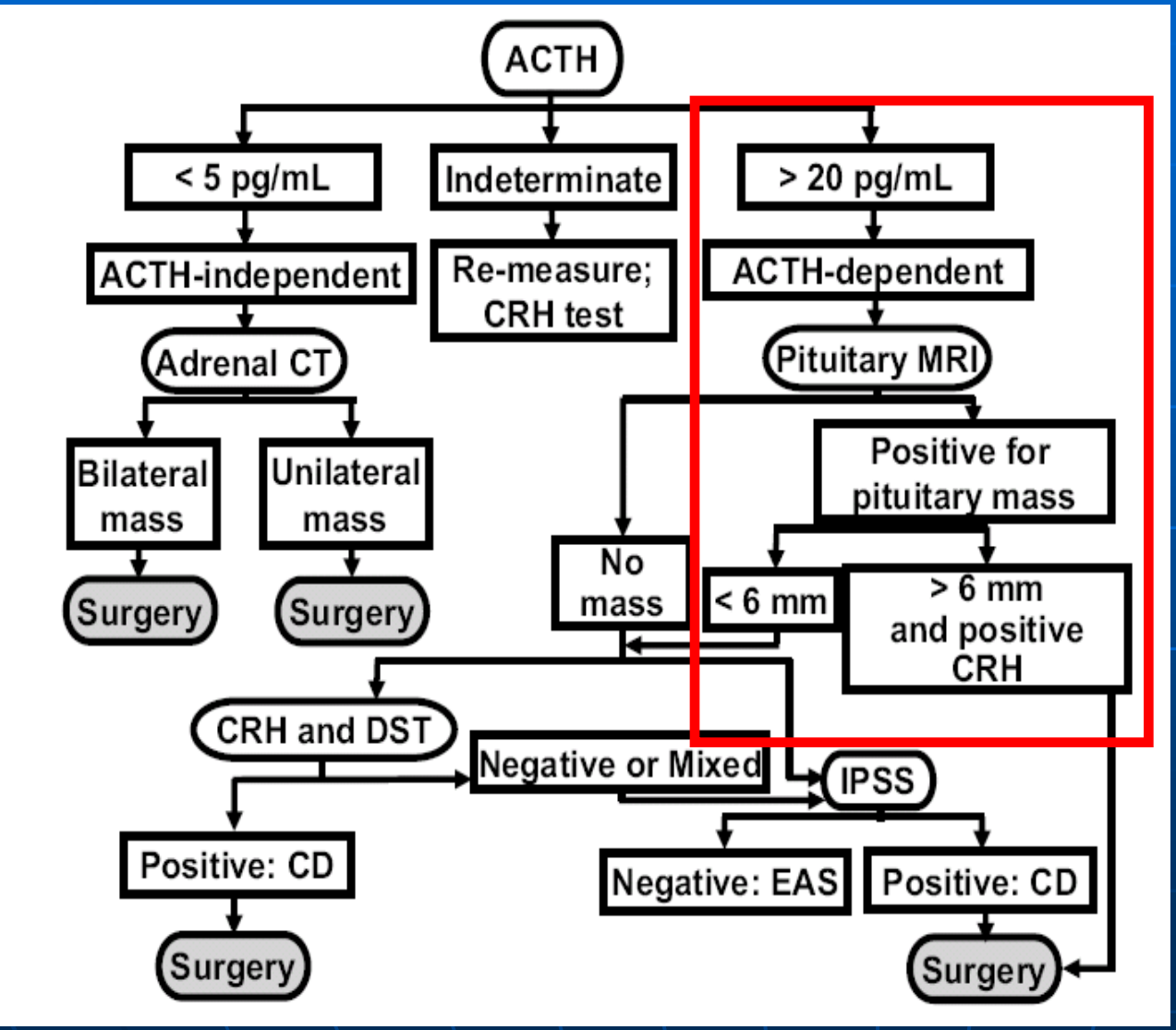
Diagnosis
Does the patient have Cushing's syndrome?
Circadian rhythm of plasma cortisol
Urinary free cortisol excretion*
Low-dose dexamethasone suppression test*
Differential Diagnosis
What is the cause of the Cushing's syndrome?
Plasma ACTH
Plasma potassium, bicarbonate
High-dose dexamethasone suppression test
Metyrapone test
Corticotropin-releasing hormone
Inferior petrosal sinus sampling
CT, MRI scanning of pituitary, adrenals
Scintigraphy
Tumor markers

*Valuable outpatient screening tests (see text).

ACTH, adrenocorticotropic hormone; CT, computed tomography; MRI, magnetic resonance imaging.


ACTH
Undetectable
Detectable
CT scanning Adrenals
(always think of
macronodular adrenal
hyperplasia)
ACTH-dependent
disease
• >50% cortisol suppression HDDST
• >50% increase serum cortisol post CRH
• Normal potassium and bicarbonate
Pituitary-dependent
disease
MRI scan pituitary
Tests
inconclusive
IPSS with CRH
Cushing's
disease
Ectopic ACTH
syndrome
Radiology as appropriate

Differential Diagnosis of Cushing's Syndrome



An algorithm for the differential diagnosis of Cushing's syndrome. ACHT= corticotrophin; CT= computed tomography; CRH= corticotrophin-releasing hormone; MRI= magnetic resonance imaging; NP-59= [131I]-6-iodomethyI norcholesterol scintigraphy; DST=8-mg dexamethasone suppression test ; IPSS= bilateral inferior petrosal sampling; CD=Cushing's disease; EAS=ectopic ACTH secretion.

Am J Med 2005; 118: 1340-1346

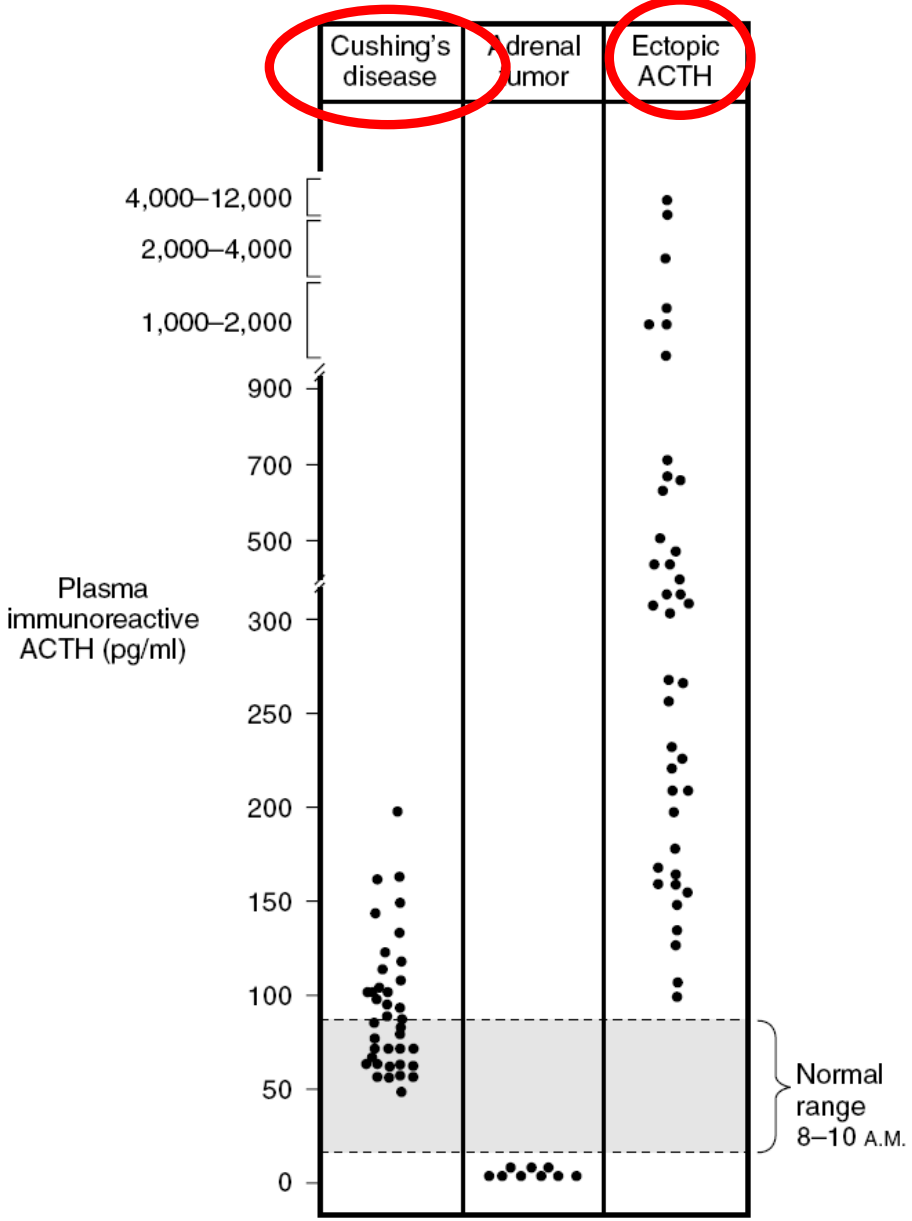


Figure 14–20. Plasma adrenocorticotropic hormone (ACTH) concentrations in patients with Cushing's disease and Cushing's syndrome associated with adrenocortical tumors and ectopic ACTH syndrome. To convert values to pmol/L, multiply by 0.2202. (From Besser GM, Edwards CRW. Cushing's syndrome. Clin Endocrinol Metab 1972; 1: 451–490.)

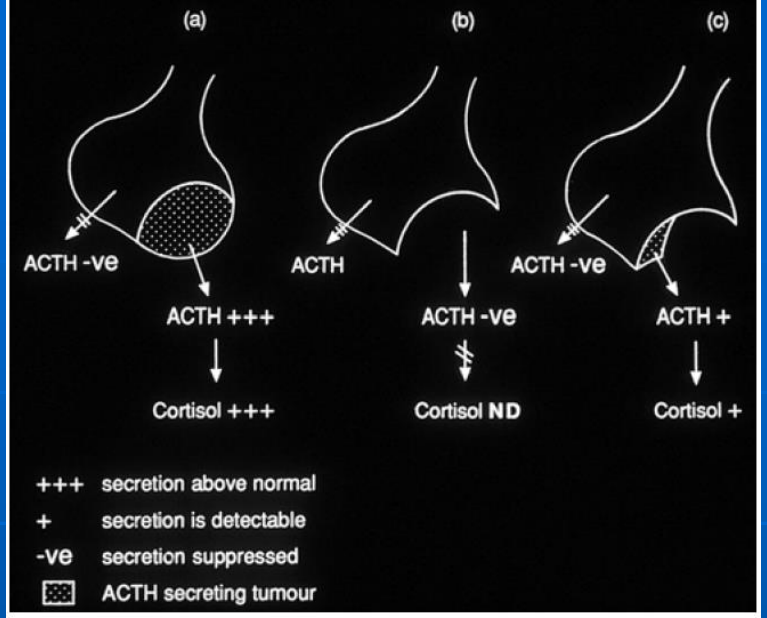


Figure 14–28. Selective removal of a microadenoma and its effect on the hypothalamic-pituitary-adrenal axis. Because the surrounding normal pituitary corticotrophs are suppressed in a patient with an adrenocorticotropic hormone (ACTH)–secreting pituitary adenoma, successful removal of the tumor results in ACTH and hence adrenocortical deficiency with an undetectable (<50 nmol/L [2 μg/dL]) plasma cortisol level. A plasma cortisol level higher than 50 nmol/L (2 μg/dL) postoperatively implies that the patient is not cured. (Courtesy of Dr.

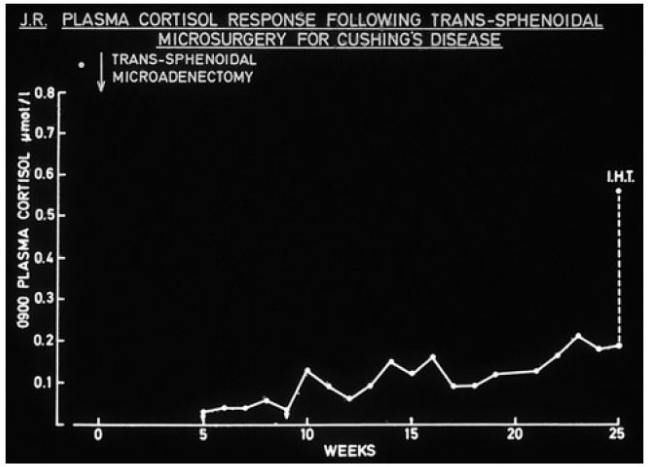


Figure 14–29. Gradual recovery of function of the hypothalamic-pituitary-adrenal axis after removal of a pituitary adrenocorticotropic hormone–secreting microadenoma. The insulin hypoglycemia test (I.H.T.) eventually demonstrated the return of a normal stress response.

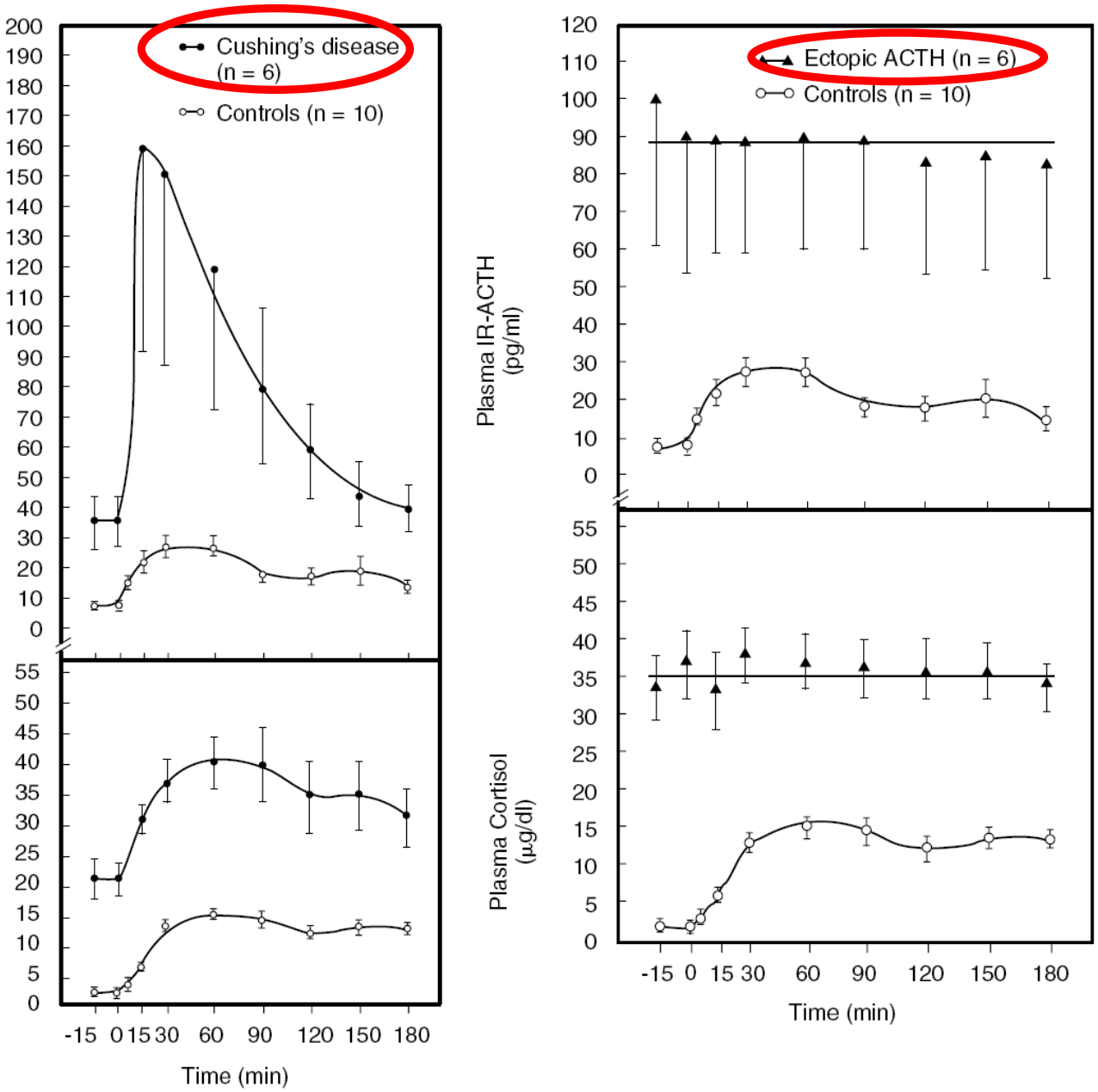


Figure 14–21. Comparison of the cortisol and adrenocorticotropic hormone (ACTH) responses to an intravenous injection of ovine corticotropin-releasing hormone (1 μg/kg) in normal subjects, patients with Cushing's disease, and patients with ectopic ACTH. (From Chrousos GP, Schulte HM, Oldfield EH, et al. The corticotropin-releasing factor stimulation test: an aid in the evaluation of patients with Cushing's syndrome. N Engl J Med 1984; 310:622–626.)

Print Graphic Presentatio

- Adrenal insufficiency

Table 14–22. Treatment of Chronic Primary Adrenal Insufficiency

Maintenance Therapy

Glucocorticoid Replacement

- Hydrocortisone 15–20 mg on awakening and 5–10 mg in early afternoon.
- Monitor clinical symptoms and morning plasma ACTH.

Mineralocorticoid Replacement

- Fludrocortisone 0.1 (0.05–0.2) mg orally.
- Liberal salt intake.
- Monitor lying and standing blood pressure and pulse, edema, serum potassium, and plasma renin activity.
- Educate patient about the disease, how to manage minor illnesses and major stresses, and how to inject steroid intramuscularly.
- Obtain Medic Alert bracelet/necklace, Emergency Medical Information Card.

Treatment of Minor Febrile Illness or Stress

- Increase glucocorticoid dose twofold to threefold for the few days of illness; do not change mineralocorticoid dose.
- Contact physician if illness worsens or persists for more than 3 days or if vomiting develops.
- No extra supplementation is needed for most uncomplicated, outpatient dental procedures under local anesthesia. General anesthesia or intravenous sedation should not be used in the office.

Emergency Treatment of Severe Stress or Trauma

- Inject contents of prefilled dexamethasone (4-mg) syringe intramuscularly.
- Get to physician as quickly as possible.

Steroid Coverage for illness or Surgery in Hospital

- For moderate illness give hydrocortisone 50 mg twice a day orally or intravenously. Taper rapidly to maintenance dose as patient recovers.
- For severe illness give hydrocortisone 100 mg intravenously every 8 hr. Taper dose to maintenance level by decreasing by half every day. Adjust dose according to course of illness.
- For minor procedures under local anesthesia and most radiologic studies, no extra supplementation is needed.
- For moderately stressful procedures, such as barium enema, endoscopy, or arteriography, give a single 100 mg intravenous dose of hydrocortisone just before the procedure.
- For major surgery, give hydrocortisone 100 mg intravenously just before induction of anesthesia and continue every 8 hr for first 24 hr. Taper dose rapidly, decreasing by half per day, to maintenance level.

各種情況下之糖皮素置換劑量

Table 14–16. Etiology of Adrenocortical Insufficiency (Excluding CAH)

Primary: Addison's Disease
Autoimmune
Sporadic
Autoimmune polyendocrine syndrome type I (Addison's disease, chronic mucocutaneous candidiasis, hypoparathyroidism, dental enamel hypoplasia, alopecia, primary gonadal failure, see Chapter 37)
Autoimmune polyendocrine syndrome type II (Schmidt's syndrome) (Addison's disease, primary hypothyroidism, primary hypogonadism, insulin-dependent diabetes, pernicious anaemia, vitiligo, Chapter 37)
Infections
Tuberculosis
Fungal infections
Cytomegalovirus
HIV
Metastatic tumor
Infiltrations
Amyloid
Hemochromatosis
Intra-adrenal haemorrhage (Waterhouse-Friderichsen syndrome) after meningococcal septicemia
Adrenoleukodystrophies
Congenital adrenal hypoplasia
DAX-1 mutations
SF-1 mutations
ACTH resistance syndromes
Mutations in *MC2-R*
Triple A syndrome
Bilateral adrenalectomy

Secondary
Exogenous glucocorticoid therapy
Hypopituitarism
Selective removal of ACTH-secreting pituitary adenoma
Pituitary tumors and pituitary surgery, craniopharyngiomas
Pituitary apoplexy
Granulomatous disease (tuberculosis, sarcoid, eosinophilic granuloma)
Secondary tumor deposits (breast, bronchus)
Postpartum pituitary infarction (Sheehan's syndrome)
Pituitary irradiation (effect usually delayed for several years)
Isolated ACTH deficiency
Idiopathic
Lymphocytic hypophysitis
POMC processing defect
POMC gene mutations

ACTH, adrenocorticotropic hormone; HIV, human immunodeficiency virus; POMC, pro-opiomelanocortin.

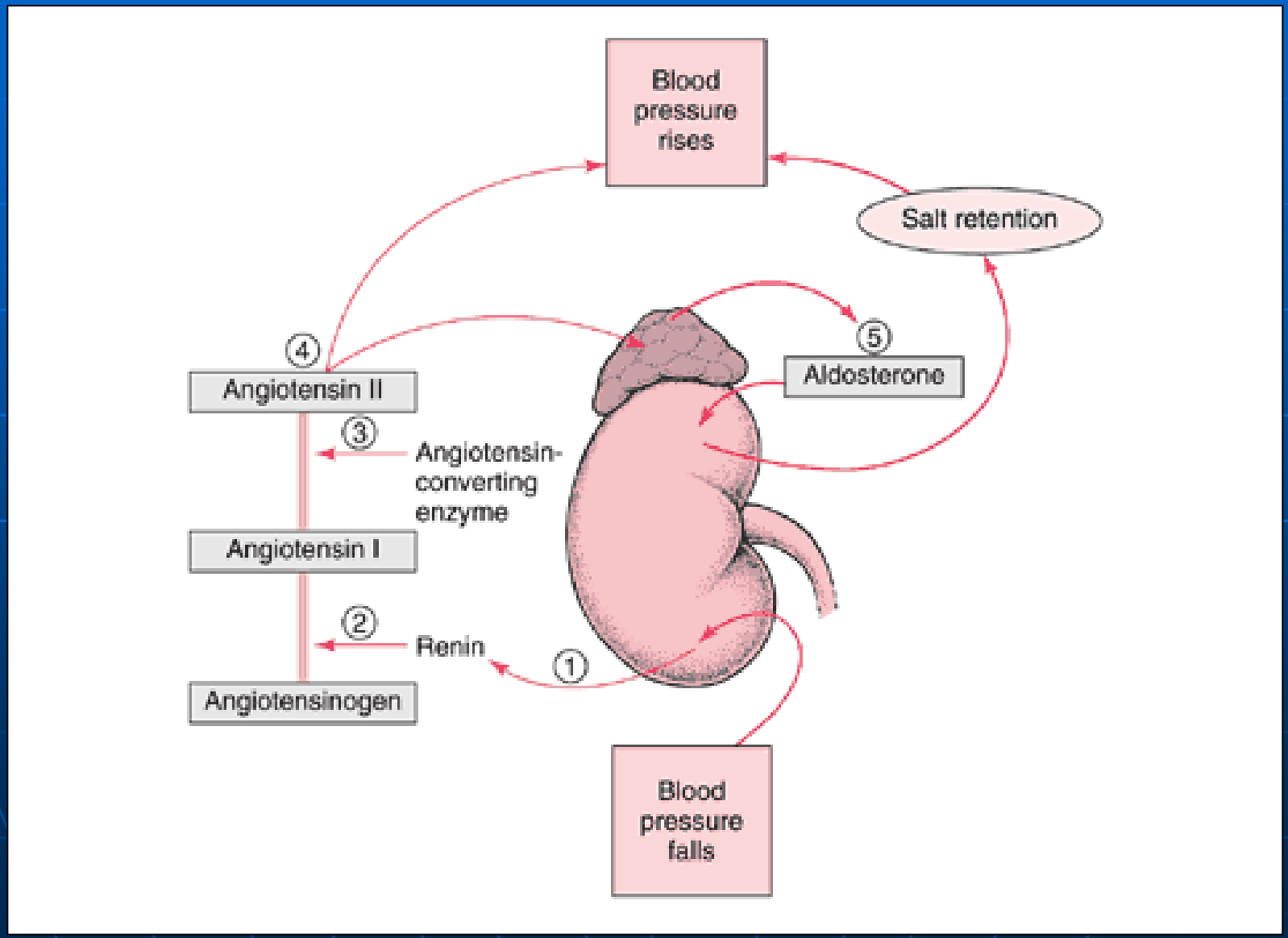
Table 14–19. Clinical Features of Primary Adrenal Insufficiency

Symptom, Sign, or Laboratory Finding	Frequency (%)
Symptom	
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	6–13
Sign	
Weight loss	100
Hyperpigmentation	94
Hypotension (<110 mm Hg systolic)	88–94
Vitiligo	10–20
Auricular calcification	5
Laboratory Finding	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

Table 14–7. Relative Biologic Potencies of Synthetic Steroids in Bioassay Systems

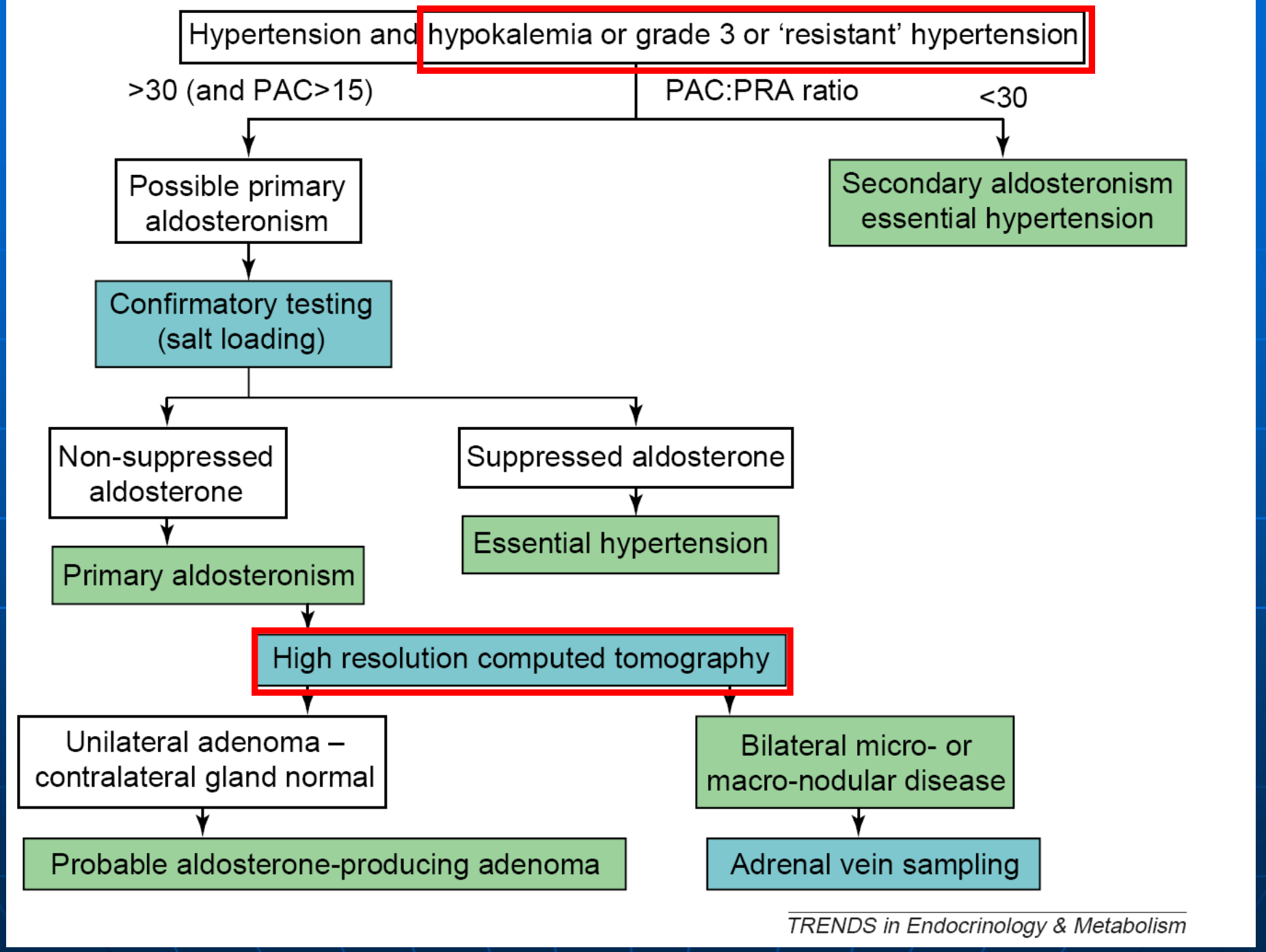
Steroid	Anti-inflammatory Action	Hypothalamic-Pituitary-Adrenal Suppression	Salt Retention
Cortisol	1	1	1
Prednisolone	3	4	0.75
Methylprednisolone	6.2	4	0.5
Fludrocortisone	12	12	125
Δ^1 Fludrocortisone	14		225
Triamcinolone	5	4	0
Dexamethasone	26	17	0

Regulation of Aldosterone Secretion



Etiology of Primary Aldosteronism

- Aldosterone-producing adenoma (Conn's syndrome): 60%
- Idiopathic hyperaldosteronism (IHA) with bilateral micronodular hyperplasia (40%)
- Glucocorticoid remediable hyperaldosteronism
  - Rare familial disease (autosomal dominant)
  - Bilateral adrenal hyperplasia (BAH)
  - Glucocorticoid treatable
    - Dex 0.5mg po q6h, 4 days, plasma aldosterone < 4ng/dl
- Aldosterone-producing carcinoma: rare



TRENDS in Endocrinology & Metabolism

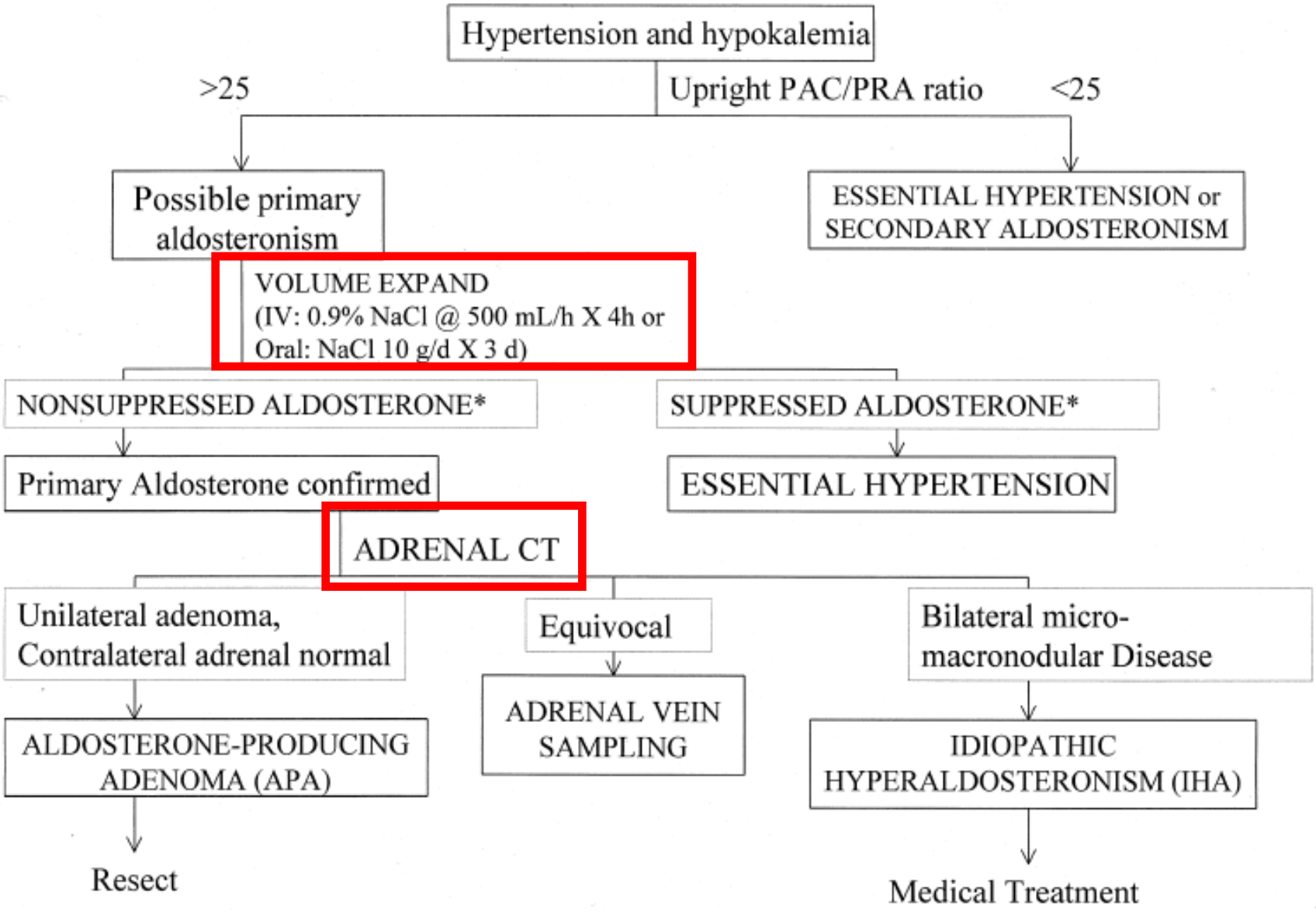
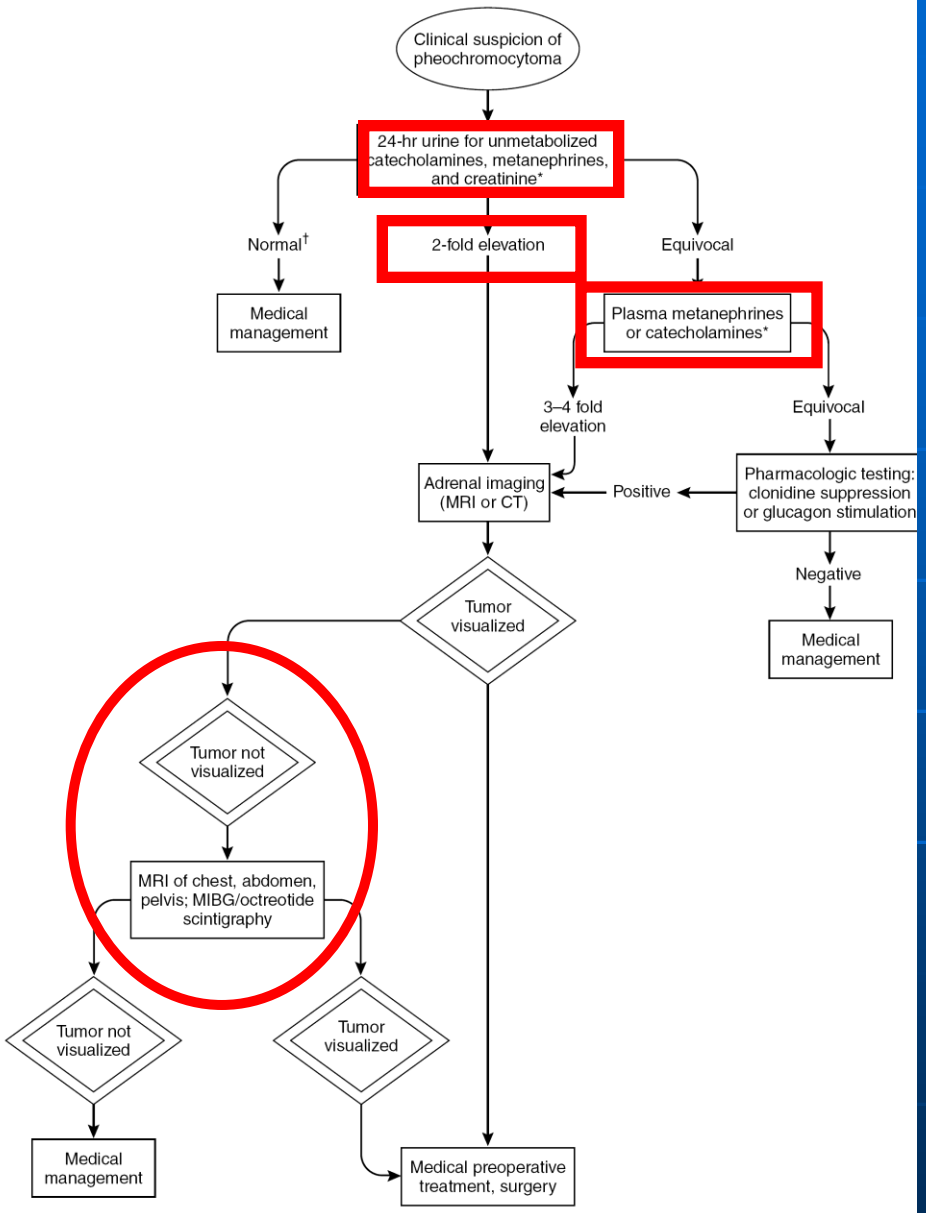

Hypertension and hypokalemia
Upright PAC/PRA ratio
>25
<25
Possible primary aldosteronism
ESSENTIAL HYPERTENSION or SECONDARY ALDOSTERONISM
VOLUME EXPAND
(IV: 0.9% NaCl @ 500 mL/h X 4h or
Oral: NaCl 10 g/d X 3 d)
NONSUPPRESSED ALDOSTERONE*
SUPPRESSED ALDOSTERONE*
Primary Aldosterone confirmed
ESSENTIAL HYPERTENSION
ADRENAL CT
Unilateral adenoma, Contralateral adrenal normal
Equivocal
Bilateral micro-macronodular Disease
ALDOSTERONE-PRODUCING ADENOMA (APA)
ADRENAL VEIN SAMPLING
IDIOPATHIC HYPERALDOSTERONISM (IHA)
Resect
Medical Treatment

Table: Test protocols of confirmatory tests used in primary aldosteronism **Part I**

Test	Protocol	Threshold value for primary aldosteronism	Reference
Fludrocortisone suppression test	0.1 mg fludrocortisone/6 hourly and sodium supplementation (slow release natrium 30 mmol/day) over 4 days	Upright plasma Aldosterone at day 5 at 10am >6 ng/dl	Stowasser et al 2001
Saline infusion test	2000 ml 0.9% saline i.v. over 4 hours; beginning between 8am and 10am	Plasma aldosterone after saline infusion >5 ng/dl	Kem et al and Holland et al 1984
Oral sodium loading	3 days of oral sodium loading (urinary sodium >200 mEq/day), collection of 24 hours urine	Urinary aldosterone after sodium loading >12 mg/day	Young 2002

Best Practice & Research Clinical Endocrinology & Metabolism 2006; 20: 369-84

Pheochromocytoma



* In some institutions, plasma metanephrines are being used for the initial screening, especially in patients with hereditary syndromes. See text for details.

† Repeat 24-hour urine collection may be indicated during a hypertensive crisis or a paroxysm in a patient with episodic symptomatology.

- When **α**-blockade is established, **β**-blockade may be initiated if the patient is tachycardic or has arrhythmias.
- Phenoxybenzamine blocks catecholamine binding to receptors, it minimizes the risk of a hypertensive crisis during intubation, anesthesia, or exploration and tumor manipulation.

- Calcium channel blockers, particular dihydropyridine class, improve intraoperative systemic vascular resistance by blunting catecholamine-mediated arterial vasoconstriction.
- The selective α_1 inhibitor doxazosin has been effective in preoperative management without causing tachycardia or other serious side effects.
- The oral formulation of labetalol, with an α/β-blocking ratio of 1:3, may not be ideal for preparation for surgery

Table 1
Comparison of sensitivity and specificity of tests commonly used for the evaluation of patients with suspected pheochromocytoma

Test	Sensitivity (%)	95% Confidence interval	Specificity (%)	95% Confidence interval
Plasma free metanephrines	99	96–100	89	87–92
Urinary fractionated metanephrines	97	92–99	69	64–72
Plasma catecholamines	84	78–89	81	78–84
Urinary catecholamines	86	80–91	88	85–91
Urinary total metanephrines	77	68–85	93	89–97
Urinary vanillylmandelic acid	64	55–71	95	93–97

	Frequency
Headache	60–90%
Palpitations	50–70%
Sweating	55–75%
Pallor	40–45%
Nausea	20–40%
Flushing	10–20%
Weight loss	20–40%
Tiredness	25–40%
Psychological symptoms (anxiety, panic)	20–40%
Sustained hypertension	50–60%
Paroxysmal hypertension	30%
Orthostatic hypotension	10–50%
Hyperglycaemia	40%

Table adapted from references 17, 20, and 21. *Frequency in patients tested because of signs and symptoms.

Table 1: **Frequency of signs and symptoms (%) of phaeochromocytoma***

LANCET

Panel 1: Differential diagnosis of phaeochromocytoma

Endocrine

Hyperthyroidism
Carcinoid
Hypoglycaemia
Medullary thyroid carcinoma
Mastocytosis
Menopausal syndrome

Cardiovascular

Heart failure
Arrhythmias
Ischaemic heart disease
Baroreflex failure

Neurological

Migraine
Stroke
Diencephalic epilepsia
Meningioma
Postural orthostatic tachycardia syndrome (POTS)

Miscellaneous

Porphyria
Panic disorder or anxiety
Factitious disorders (eg, from use of sympathomimetic drugs such as ephedrine)
Drug treatment (eg, monoamine oxidase inhibitors, sympathomimetic drugs, withdrawal of clonidine)
Illegal drugs (eg, cocaine)

1 Gene mutations associated with familial phaeochromocytoma[3-5]

RET gene mutation !

Gene	Syndrome	Other manifestations	Lifetime risk of tumour (%)
RET	Multiple endocrine neoplasia type 2A	Medullary thyroid carcinoma, hyperparathyroidism	40%
RET	Multiple endocrine neoplasia type 2B	Medullary thyroid carcinoma, mucosal (oral) neuromas, intestinal ganglioneuromas, marfanoid habitus	40%
VHL	Von Hippel–Lindau disease	Multiple infratentorial haemangioblastomas and retinal angiomas, renal cell (clear cell) carcinoma, renal and pancreatic cysts, papillary cystadenomas of the reproductive tract and ear	10%–20%
NF1	Neurofibromatosis type 1	Peripheral neurofibromas, café-au-lait spots, intertriginous freckling, Lisch nodules, optic gliomas, bony abnormalities, other CNS tumours	< 5%
SDHD	Familial phaeochromocytoma/	None identified	Unknown

Table 1. Symptoms and Signs Suggestive of Adrenal Hyperfunction or Malignant Disease.

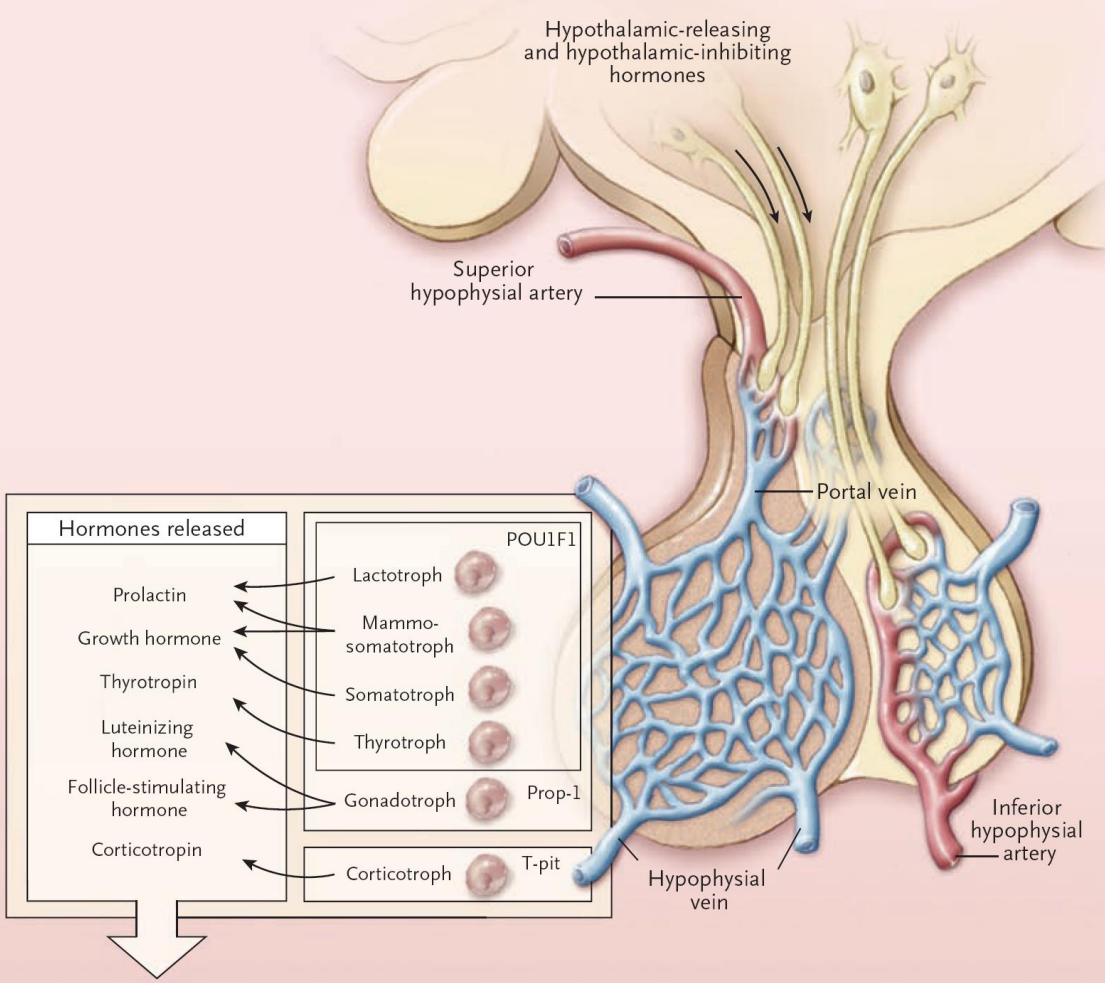
Disorder	Symptoms	Signs
Cushing's syndrome	Patient may be asymptomatic if disease is subclinical; symptoms may include weight gain with central obesity, facial rounding and plethora, supraclavicular and dorsocervical fat pads, easy bruising, thin skin, poor wound healing, purple striae, proximal muscle weakness, emotional and cognitive changes (e.g., irritability, spontaneous tearfulness, depression, and restlessness), opportunistic and fungal infections, altered reproductive function, acne, and hirsutism	Hypertension, osteopenia, osteoporosis, fasting hyperglycemia, diabetes mellitus, hypokalemia, hyperlipidemia, and leukocytosis with relative lymphopenia
Pheochromocytoma	Patient may be asymptomatic; episodic symptoms may occur in spells (paroxysms) that can be extremely variable in presentation but typically include forceful heartbeat, pallor, tremor, headache, and diaphoresis; spells may be either spontaneous or precipitated by postural change, anxiety, medications (e.g., metoclopramide, anesthetic agents), and maneuvers that increase intraabdominal pressure (e.g., change in position, lifting, defecation, exercise, colonoscopy, pregnancy, and trauma)	Hypertension (paroxysmal or sustained), orthostatic hypotension, pallor, retinopathy grades 1 to 4, tremor, and fever
Primary aldosteronism	If hypokalemia is present, nocturia, polyuria, muscle cramps, and palpitations may be present	Hypertension, mild or severe; possibly hypokalemia and mild hypernatremia
Adrenocortical carcinoma	Symptoms may include mass effect (e.g., abdominal pain) and symptoms related to adrenal hypersecretion of cortisol (Cushing's syndrome), androgens (hirsutism, acne, amenorrhea or oligomenorrhea, oily skin, and increased libido), estrogens (gynecomastia), or aldosterone (hypokalemia-related symptoms)	Hypertension, osteopenia, osteoporosis, fasting hyperglycemia, diabetes mellitus, hypokalemia, hyperlipidemia, and leukocytosis with relative lymphopenia
Metastatic cancer	History of an extraadrenal cancer	Cancer-specific signs

Table 2. Laboratory Evaluation of the Patient with Adrenal Incidentaloma.

Possible Diagnosis	Screening Test	Causes of False Positive Results	Confirmatory Tests
Subclinical Cushing's syndrome	Overnight dexamethasone (1 mg) suppression test; abnormal result: serum cortisol, >5 μg per deciliter (138 nmol per liter); some clinicians use a higher dose of dexamethasone (e.g., 3 mg instead of the standard 1 mg) to reduce the possibility of a false positive result without a change in sensitivity	Medications that accelerate hepatic metabolism of dexamethasone (e.g., anticonvulsants); noncompliance with dexamethasone regimen	Consider the following tests: serum corticotropin, cortisol in a blood specimen and 24-hr urine specimen, midnight salivary measurement of cortisol, and a formal 2-day high-dose dexamethasone suppression test (the result is considered abnormal when the cortisol level in the 24-hr urine specimen is greater than the lower limit of the normal range for the local laboratory)
Pheochromocytoma	Measurement of fractionated metanephrines and catecholamines in a 24-hr urinary specimen; imaging phenotype may also suggest pheochromocytoma	Any situation (e.g., illness requiring hospitalization) or medication (e.g., tricyclic antidepressant) that increases endogenous production of catecholamines[7]	Consider iodine-123 metaiodobenzylguanidine scintigraphy, MRI, subspecialty consultation, and surgery
Primary aldosteronism	Morning measurement of the plasma aldosterone concentration and plasma renin activity,* which can be performed while the patient is receiving any antihypertensive drug except spironolactone (Aldactone, Searle), eplerenone (Inspra, Pfizer), or high-dose amiloride (Midamor, Merck); the plasma aldosterone concentration and plasma renin activity ratio of ≥20 and a plasma aldosterone concentration of ≥15 ng per deciliter are positive results (but the cutoff for a positive result is laboratory-dependent)	Assay and biologic variability	To confirm the diagnosis of primary aldosteronism: aldosterone suppression testing with either a saline infusion test or 24-hour urinary aldosterone excretion test while the patient maintains a high-sodium diet[8] To confirm that the adrenal mass (and not bilateral adrenal hyperplasia) is the source of aldosterone excess in patients with documented primary aldosteronism, adrenal venous sampling should be considered[8]

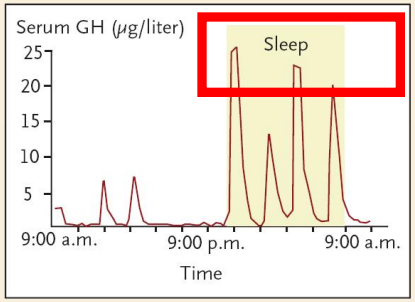
* In this test, values for the plasma aldosterone concentration are in nanograms per deciliter, and values for plasma renin activity are in nanograms per milliliter per hour.

Pituitary gland



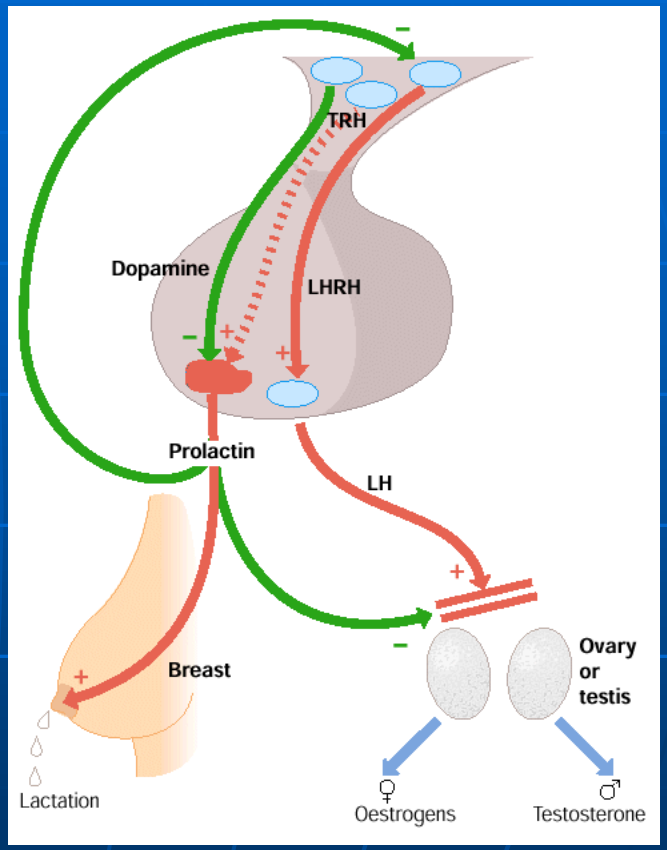
GH 191-amino-acid polypeptide

Chromosomal gene locus	17q
Stimulators	GHRH, GHS
Inhibitors	SRIF, IGF-I, activins
Target	Liver, skeleton, other tissue
Trophic effects	IGF-I production Growth induction Insulin antagonism
Normal daytime circulating levels	<0.5 μg/liter



Prolactinomas

- PRL different control to all other anterior pituitary hormones
  - Tonic release of DA inhibits PRL release
- Many drugs interfere with DA and PRL secretion
- Features of PRL excess (hypogonadism)
  - Infertility - Oligoamenorrhoea
  - Amenorrhoea - Galactorrhoea
  - Reduced libido - Impotence
- Treatment - dopamine agonists - bromocriptine, cabergoline (not surgery)



Clinical presentation

- Children

  Delayed puberty, primary amenorrhea and galactorrhea
- Premenopausal women
  - Amenorrhea(90%), infertility and galactorrhea (80%)
  - Reduce vertebral bone mineral density (both sex)
  - Decreased libido, weight gain, and mild hirsutism
- Men
  - Impotence, infertility, and decreased libido
  - Galactorrhea and gynecomastia are uncommon

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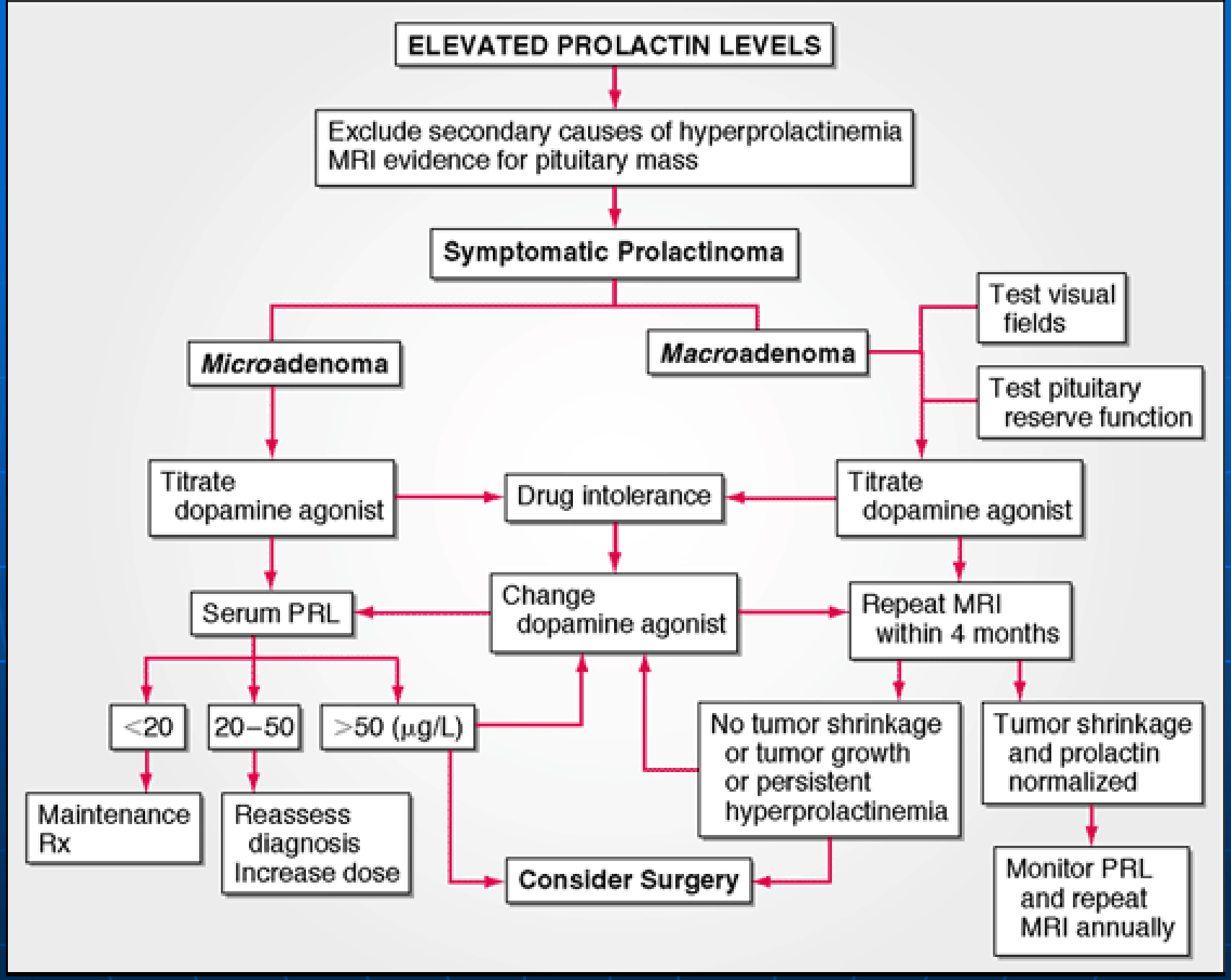
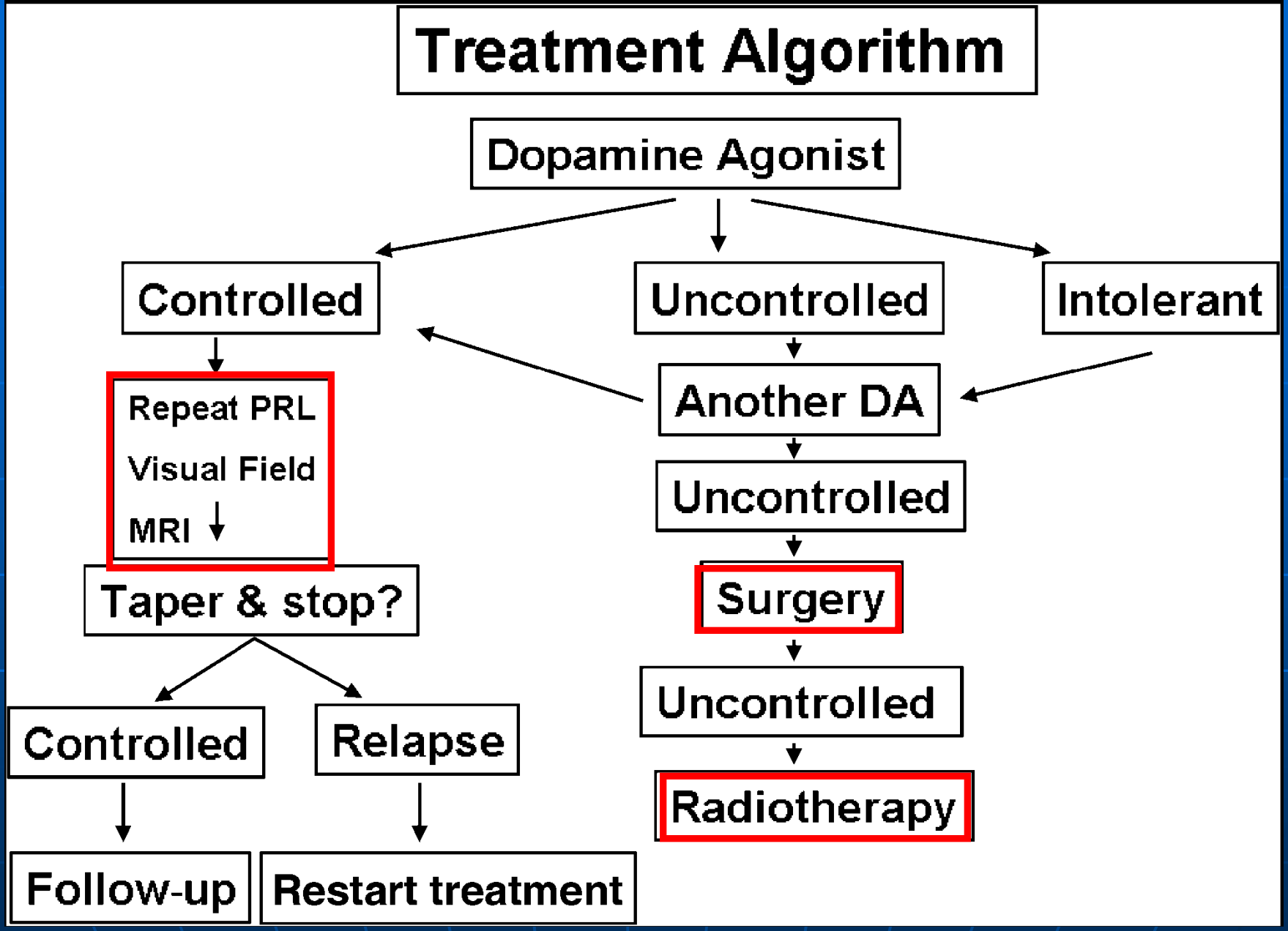


Harrison 16th edi Figure 318-6



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Etiology of Hyperprolactinemia

Prolactin ≦100 ng/mL

- Altered metabolism
  - -Liver failure
  - -Renal failure
- Ectopic production
  - - Bronchogenic
  - - Gonadoblastoma
  - - Hypopharynx
  - - Ovarian dermoid cyst
  - - Renal cell carcinoma
  - - Teratoma
- Breastfeeding

- Breast stimulation
- Hypothyroidism
- Medications
  - - Oral contraceptive pills
  - - Antipsychotics
  - - Antidepressants
  - - Antihypertensives
  - - H2 blockers
  - - Opiates, cocaine

Prolactin >100 ng/mL

- Empty sella syndrome
- Pituitary adenoma

Am Fam Physician 2006;73:1374-82

Table 8–24. Presentation of Acromegaly*

Presenting Chief Complaint	Frequency (%)
Menstrual disturbance	13
Change in appearance, acral growth	11
Headaches	8
Paresthesias, carpal tunnel syndrome	6
Diabetes mellitus, impaired glucose tolerance	5
Heart disease	3
Visual impairment	3
Decreased libido, impotence	3
Arthopathy	3
Thyroid disorder	2
Hypertension	1
Gigantism	1
Fatigue	0.3
Hyperhidrosis	0.3
Somnolence	0.3
Other	5
Chance (detected by unrelated physical or dental examination or radiograph)	40
Total	100
Causes of Death	
Cardiovascular	60
Respiratory	25
Malignancy	15

*From Molitch ME. Clinical manifestations of acromegaly. Endocrinol Metab Clin North Am 1992; 21:597–614, based on 310 patients.

Data integrated from Holdaway, 1998; Wright, 1969; Alexander, 1980; Nabarro, 1987; Bengtsson, 1988; Bates, 1993; Extabe, 1993; Rajasoorya, 1994.

Table 1. Clinical Features of Acromegaly.

Local tumor effects	**Visceromegaly**
Pituitary enlargement	Tongue
Visual-field defects	Thyroid gland
Cranial-nerve palsy	Salivary glands
Headache	Liver
Somatic systems	Spleen
Acral enlargement, including thickness of soft tissue of hands and feet	Kidney
Musculoskeletal system	Prostate
Gigantism	**Endocrine and metabolic systems**
Prognathism	Reproduction
Jaw malocclusion	Menstrual abnormalities
Arthralgias and arthritis	Galactorrhea
Carpal tunnel syndrome	Decreased libido, impotence, low levels of sex hormone–binding globulin
Acroparesthesia	Multiple endocrine neoplasia type 1
Proximal myopathy	Hyperparathyroidism
Hypertrophy of frontal bones	Pancreatic islet-cell tumors
Skin and gastrointestinal system	Carbohydrate
Hyperhidrosis	Impaired glucose tolerance
Oily texture	Insulin resistance and hyperinsulinemia
Skin tags	Diabetes mellitus
Colon polyps	Lipid
Cardiovascular system	Hypertriglyceridemia
Left ventricular hypertrophy	Mineral
Asymmetric septal hypertrophy	Hypercalciuria, increased levels of 25-hydroxyvitamin D_3
Cardiomyopathy	Urinary hydroxyproline
Hypertension	Electrolyte
Congestive heart failure	Low renin levels
Pulmonary system	Increased aldosterone levels
Sleep disturbances	Thyroid
Sleep apnea (central and obstructive)	Low thyroxine-binding–globulin levels
Narcolepsy	Goiter

Table 8–29. Treatment Options for Acromegaly

Surgery	Somatostatin Analogue	Radiotherapy	Dopamine Agonists (High Dose)	Growth Hormone-Receptor Antagonist
Efficacy				
80% of microadenomas: GH controlled	GH controlled in ~65% of patients	GH <5 μg/L in 90% of patients in 18 yr	GH <5 μg/L in 15%	Elevated bioinactive GH
<50% of macroadenomas: GH controlled	Normal IGF-I in ~70%	Normal IGF-I in <7 yr 24%, >10 yr 54%	Normal IGF-I in ~10%	Normal IGF-I in >90%
IGF-I normalized in ~50%				
Advantages				
Rapid onset	No hypopituitarism	Permanent	Oral administration	Rapid onset
One-time cost	Rapid onset	One-time cost	Low cost	No hypopituitarism
Maybe permanent control	Sustained long-term efficacy	Good compliance by patients	No hypopituitarism	Sustained efficacy
Disadvantages				
New hypopituitarism (10%)	Cost of drug and monitoring	Ineffective and slow onset	Relatively ineffective	Long-term safety unknown
Diabetes insipidus (2–3%)	Asymptomatic gallstones (25%)	Hypopituitarism (70%)	Adverse events (~30%)	
Local complications (~6%)	Injections required	Visual and CNS dysfunction (~2%)	High dose required	Not yet approved (2002)
Cranial nerve or CNS damage (~1%)		Cost of interim medical therapy		
Tumor persistence				

CNS, central nervous system; GH, growth hormone; IGF-I, insulin-like growth factor I.

Adapted from Melmed S, Jackson I, Kleinberg D, Klibanski A. Current treatment guidelines for acromegaly. J Clin Endocrinol Metab 1998; 83:2646–2652.