Endocrine Disease and the Heart

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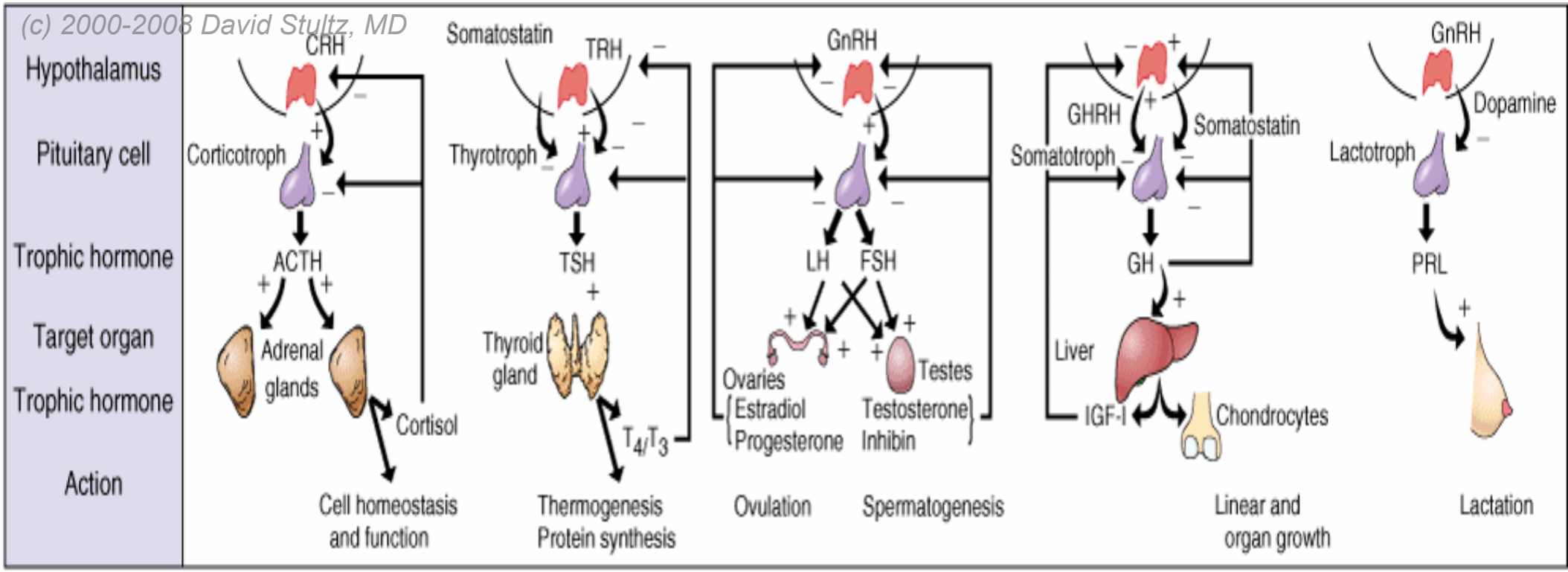
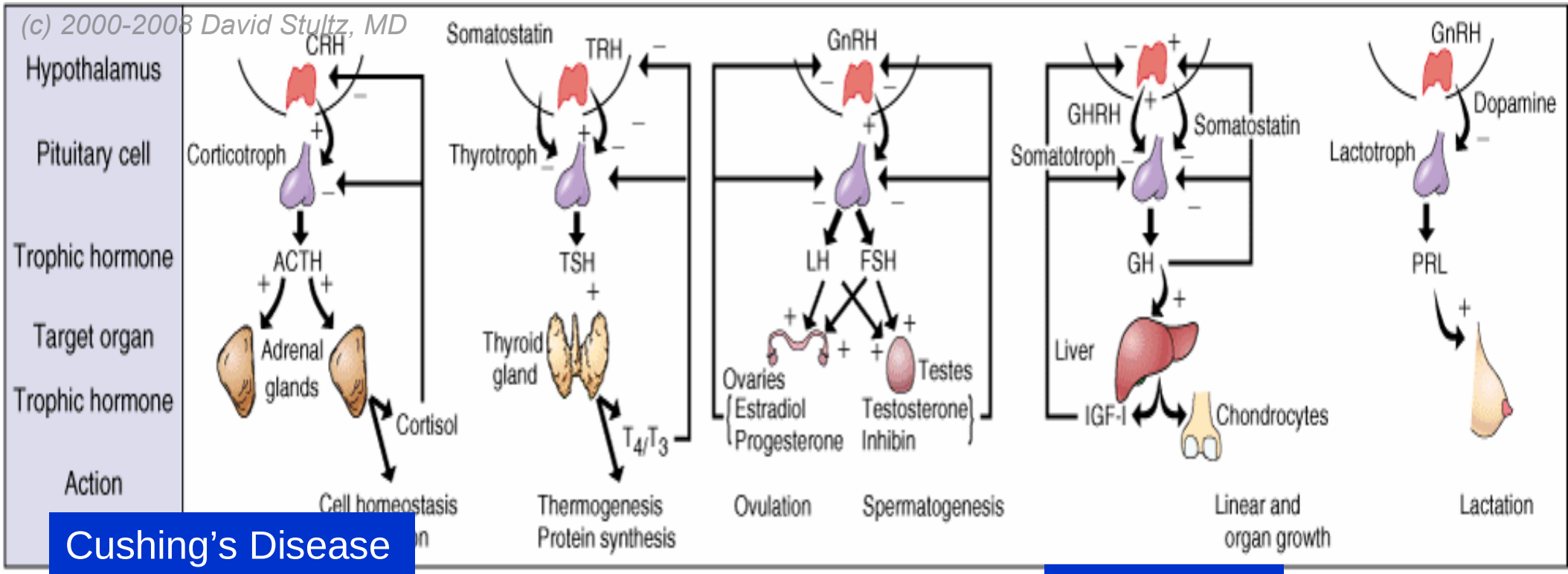
Topics to be covered

- Pituitary axis
- Acromegaly (GH)
- Cushing's (ACTH, cortisol)
- Conn's syndrome (hyper-aldosteronism)
- Addison's disease (hypo-aldosteronism)
- Hyperparathyroidism (Ca^{2+})
- Hypocalcemia
- Pheochromocytoma
- Hyperthyroidism
- Hypothyroidism
- Amiodarone effects on thyroid function



Source: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, Isselbacher KJ: *Harrison's Principles of Internal Medicine*, 16th Edition: http://www.accessmedicine.com

- Hypothalamic hormones regulate anterior pituitary trophic hormones that, in turn, determine target gland secretion. Peripheral hormones feed back to regulate hypothalamic and pituitary hormones.



Cushing's Disease
Cushing Syndrome

Acromegaly

- Hypothalamic hormones regulate anterior pituitary trophic hormones that, in turn, determine target gland secretion. Peripheral hormones feed back to regulate hypothalamic and pituitary hormones.

Acromegaly

- Approximately 900 new cases in the US each year
- Excessive production of Human Growth Hormone (hGH) which subsequently increases levels of Insulin-like growth factor type 1 (IGF-1)
- hGH also has target receptors on heart, muscle, liver, kidney and fat cells

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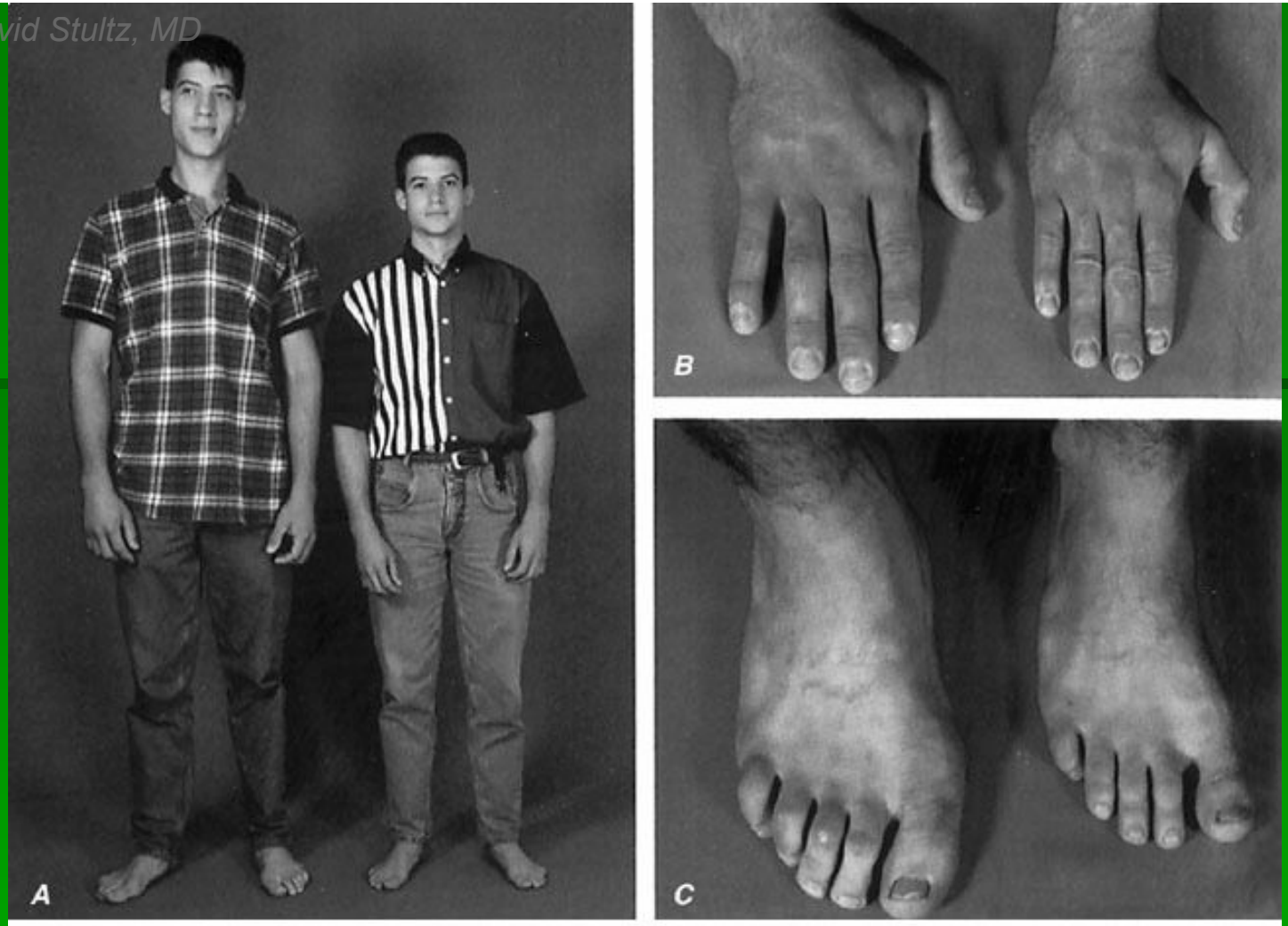

- Features of acromegaly/gigantism. A 22-year-old man with gigantism due to excess growth hormone is shown to the left of his identical twin. The increased height and prognathism (*A*) and enlarged hand (*B*) and foot (*C*) of the affected twin are apparent. Their clinical features began to diverge at the age of approximately 13 years.

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Cardiac changes in Acromegaly

- Increased cardiac mass
- Increased cardiac output/index
- Increased stroke volume/index
- Left ventricular hypertrophy

- Hypertension, Diabetes, Hyperlipidemia are common in patients with acromegaly

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Diagnosis and Treatment of Acromegaly

- Serum growth hormone >5ng/dL and serum IGF-1 >300μIU/mL measured 1 hour after 100g oral glucose load
- MRI of pituitary usually shows macroadenoma (>10mm)
- Transsphenoid resection of the pituitary is treatment of choice (in most patients)
- Octreotide can be used to lower hGH
- Pegvisomant (hGH receptor antagonist) can be used in octreotide resistant patients (normalizes IGF-1 levels)
- ACE inhibitors can paradoxically elevate blood pressure
- Treatment of Acromegaly can improve hypertension

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ACTH

- Anterior pituitary produces proteins including ACTH
- ACTH binds to target cells in adrenal gland
- ACTH regulates cortisol secretion from zona fasciculata and zona reticularis of the adrenal gland

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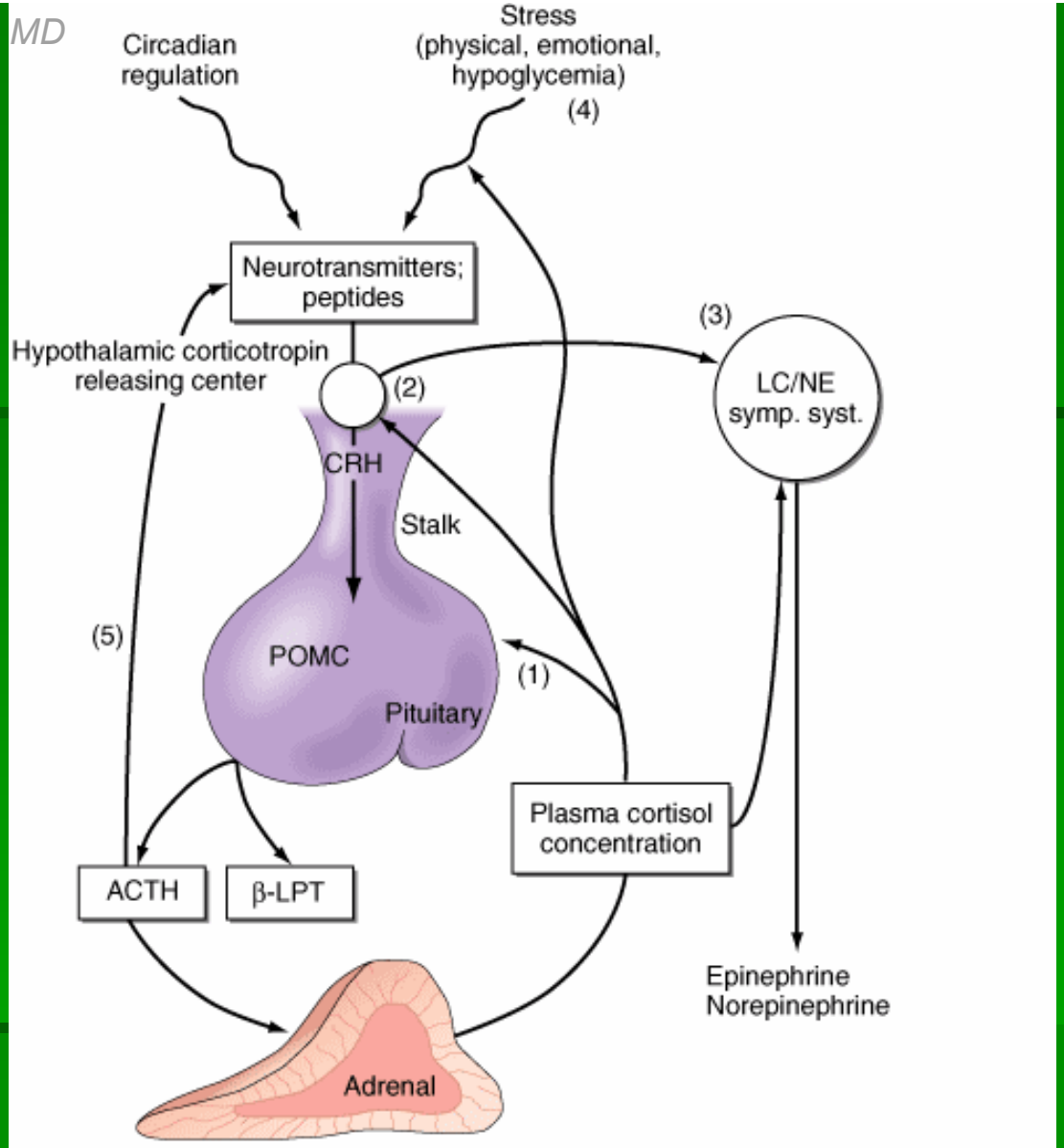

The hypothalamic-pituitary-adrenal axis. The main sites for feedback control by plasma cortisol are the pituitary gland (1) and the hypothalamic corticotropin-releasing center (2). Feedback control by plasma cortisol also occurs at the locus coeruleus/sympathetic system (3) and may involve higher nerve centers (4) as well. There may also be a short feedback loop involving inhibition of corticotropin-releasing hormone (CRH) by adrenocorticotropic hormone (ACTH) (5). Hypothalamic neurotransmitters influence CRH release; serotoninergic and cholinergic systems stimulate the secretion of CRH and ACTH; -adrenergic agonists and -aminobutyric acid (GABA) probably inhibit CRH release. The opioid peptides -endorphin and enkephalin inhibit, and vasopressin and angiotensin II augment, the secretion of CRH and ACTH. -LPT, -lipotropin; POMC, pro-opiomelanocortin; LC, locus coeruleus; NE, norepinephrine.

Cushing's Disease Excess ACTH and Cortisol

- Cushing's Disease
  - Excess ACTH production from pituitary
  - Results in excess cortisol secretion from adrenal zona fasciculata
- Cushing syndrome
  - Excess cortisol secretion from adrenal tumor
- Ectopic ACTH can also be produced by carcinoid tumors, lung and thyroid tumors

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Excess Cortisol and the Heart

- Accelerated Atherosclerosis
- Also Cerebral and peripheral vascular disease
- Mainly due to hypertension and hyperlipidemia
- Carney complex
  - Cushing syndrome
  - Cardiac myxoma
  - Variety of pigmented dermal lesions (not café-au-lait)
  - Monogenic autosomal dominant trait on chromosome 17q2

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Diagnosis of Cushing's Disease/Syndrome

- Increased 24 hour urinary free cortisol
- ACTH measurement
- MRI localization

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Treatment of Excess ACTH

- Cushing's Disease
  - Transsphenoidal hypophysectomy
- Cushing's Syndrome
  - Removal of one or both adrenal glands
    - Must replace cortisol and fludrocortisone to prevent adrenal crisis
  - Ketoconazole inhibits adrenal enzymes and can be used in inoperable patients

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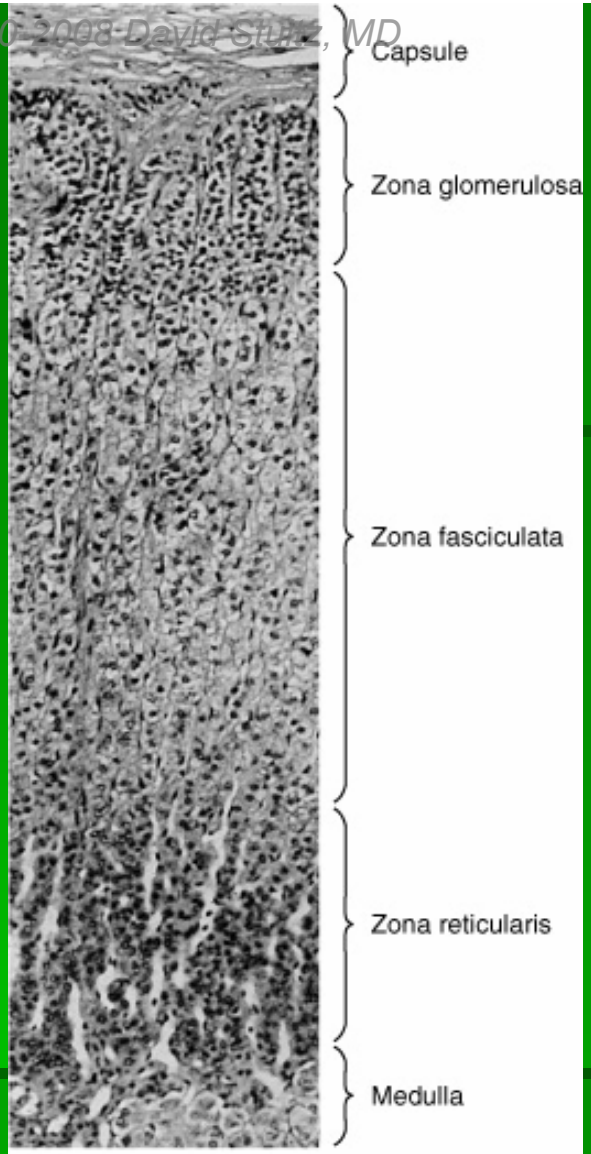
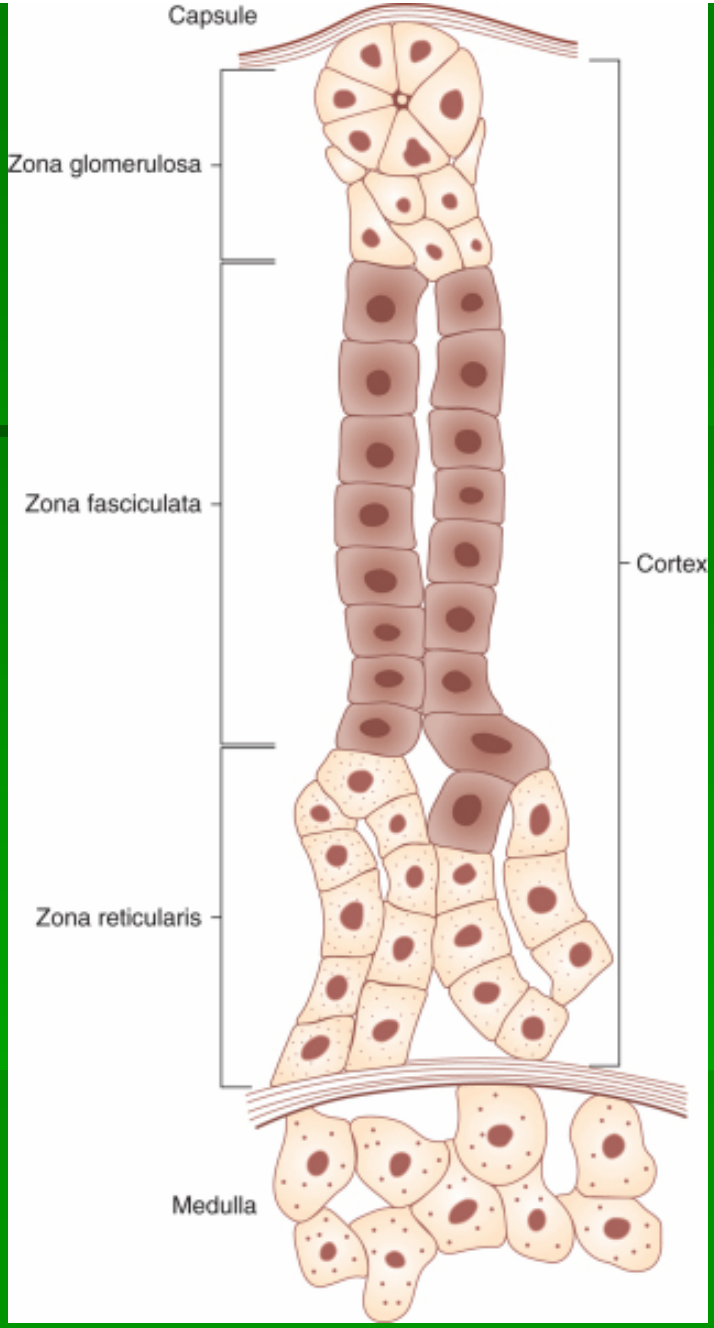


Histologic section through a normal adult adrenal gland showing the progression, outside in, of the zona glomerulosa, zona fasciculata, and zona reticularis.



Schematic diagram of the structure of the human adrenal cortex, depicting the outer zona glomerulosa and inner zona fasciculata and zona reticularis

Cecil Textbook of Medicine
Kronenberg: Williams Textbook of Endocrinology, 11th ed.

Aldosterone

- Produced by zona glomerulosa
- Aldosterone release stimulated by angiotensin II binding to angiotensin II type 1 receptors

- Aldosterone effect is protein synthesis
- Augments development of left ventricular hypertrophy

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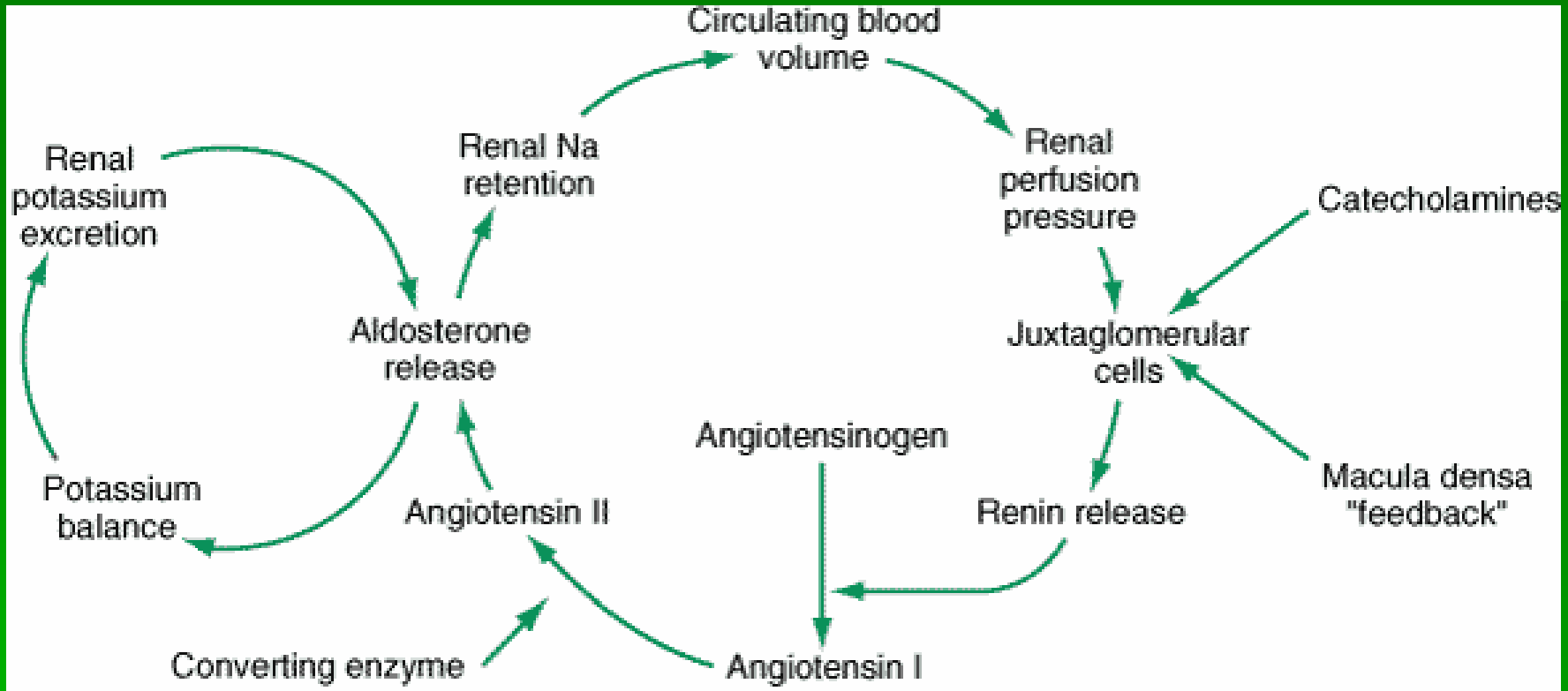

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The interrelationship of the volume and potassium feedback loops on aldosterone secretion. Integration of signals from each loop determines the level of aldosterone secretion.

Hyperaldosteronism

- Conn syndrome
  - Benign adrenal adenoma produces excess aldosterone
  - Diagnosed by low renin:aldosterone ratio
  - Treatment by surgical resection
- Sodium retention
- Hypertension
- Loss of Magnesium and Potassium
- Increased systemic vascular resistance
- Left ventricular hypertrophy beyond degree expected from hypertension alone

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Addison's Disease (JFK)

Diagnosed with Addison's disease at age 30

http://jfkspeeches.podomatic.com/jfkspeeches-1193066137.jpg

Addison's Disease Hypoaldosteronism

- Primary adrenal insufficiency
  - Loss of bilateral adrenal function due to
    - Autoimmune
    - Hemorrhage
    - Malignancy
- Secondary adrenal insufficiency
  - Due to lack of ACTH from pituitary
  - Usually aldosterone levels are ok (glucocorticoids low)

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Signs of Addison's Disease

- Noncardiac signs
  - Pigmentation
  - Abdominal pain
  - Nausea and vomiting
  - Weight loss
- Addisonian Crisis
  - Hypovolemia
  - Hypotension
  - Hyperkalemia
  - Sodium wasting

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Cardiac Manifestations of Addison's Disease

- Peaked T waves on EKG (hyperkalemia)
- Small cardiac dimensions
- Cardiac atrophy seen in extreme cases

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Diagnosis of Addison's Disease

- Clinical setting
  - Acute adrenal insufficiency can occur in patient with acute stress, infection or trauma
  - Adrenal hemorrhage can occur with severe infection or diffuse intravascular coagulation
  - Secondary adrenal insufficiency usually chronic
    - Acute changes can occur with pituitary inflammation or hemorrhage
  - Withdrawal after long term steroid use can cause acute crisis
- Laboratory studies
  - AM cortisol less than 8mg/dL
  - 30 minute cortisol level after 0.25mg IV cosyntropin less than 20mg/dL

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Treatment of Addison's Disease

- Addisonian crisis
  - Hydrocorisone 100mg IV every 8 hours for 24 hours
  - Taper dose for subsequent 72-96 hours
  - Large volume of normal saline with 5% dextrose
  - Identify and treat precipitating cause
- Chronic treatment
  - Corticosteroid and mineralocorticoid
  - Fludrocortisone 0.1mg daily

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Hyperparathyroidism

- Typically solitary parathyroid adenoma
- Increases serum calcium
- Hypercalcemia
  - Enhanced cardiac contractility
  - EKG changes
    - Short QT
    - Short PR
    - Flat T wave
  - Chronically calcium deposits in myocardial interstitium, valve annulus and cups
  - Increased blood pressure (although PTH is a vasodilator)

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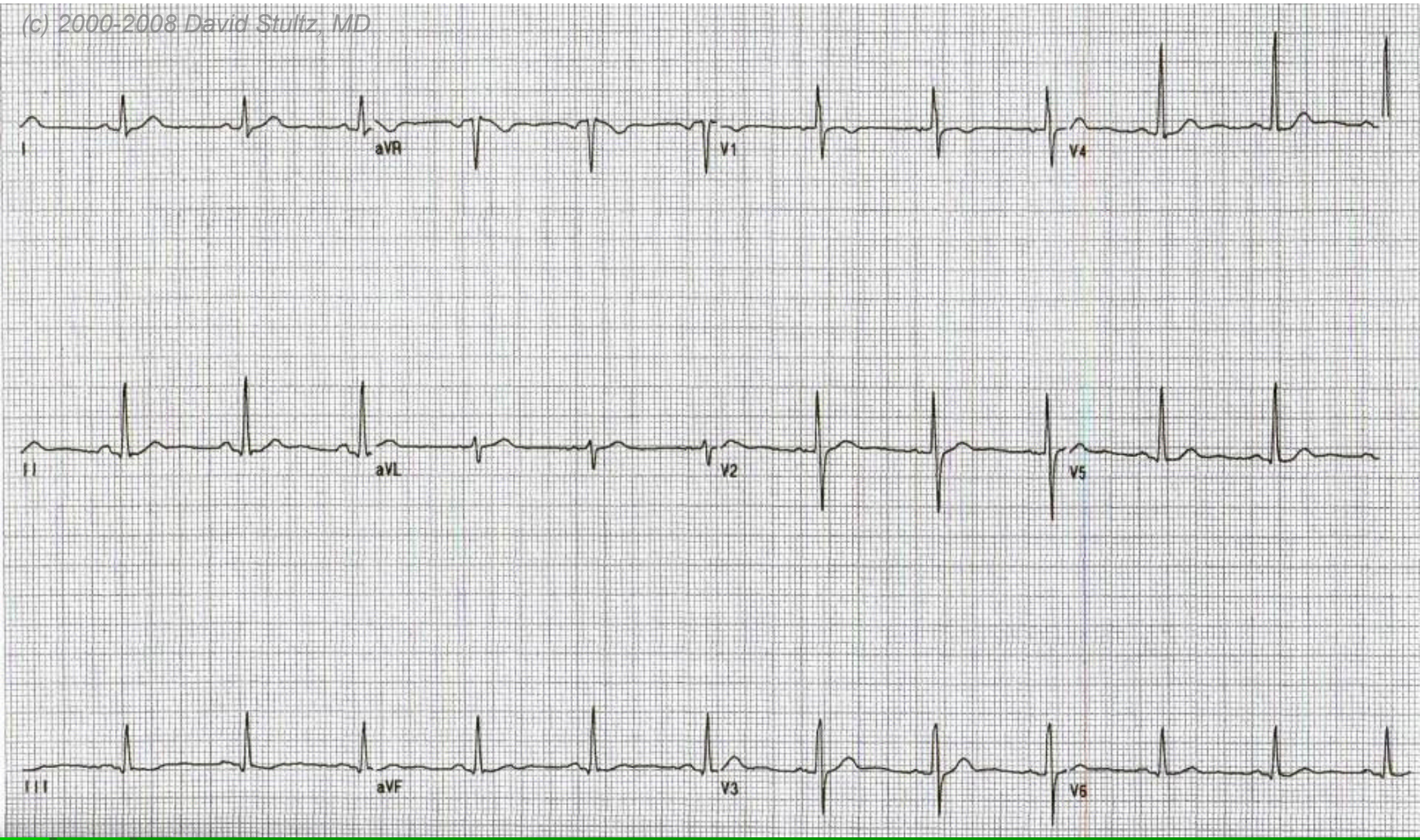

Hypocalcemia
Short PR interval
Short QT interval

O'Keefe

Diagnosis and Treatment Hyperparathyroidism

- Primary
  - Increase serum intact PTH
  - Elevated serum calcium
  - Treated by surgical removal of parathyroid adenoma
- Secondary (malignancy, sarcoidosis)
  - Increased PTH-related peptide
  - Increased 1,25-dihydroxyvitamin D3

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Hypocalcemia

- Can impair cardiac contractility
- Prolonged QT interval on EKG
- Primary hypoparathyroidism
  - due to Surgical resection, DiGeorge syndrome
- Low calcium commonly occurs in renal failure
- High PTH levels
  - Left ventricular hypertrophy
  - Low systemic vascular resistance

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Pheochromocytoma

- "Benign" tumor of neuroendocrine chromaffin cells
  - Adrenal medulla
  - Or anywhere else (primarily abdominal)
- Incidence less than 1 in 2000 for patients with diastolic hypertension
- 10% familial
  - More commonly bilateral adrenal or extra-adrenal
- Multiple Endocrine Neoplasia type-2
  - Medullary thyroid carcinoma
  - Hyperparathyroidism
- Releases norepinephrine and epinephrine
  - Dopamine release may indicate malignant transformation

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Clinical Features of Pheochromocytoma

- Headache
- Palpitations
- Sweating
- Tremors
- Chest pain
- Weight loss
- Hypertension usually constant
- Orthostatic hypotension may occur in morning

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Cardiac Effects of Pheochromocytoma

- Hypertension
- Left ventricular hypertrophy
- Tachycardia induced cardiomyopathy

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Diagnosing Pheochromocytoma

- Screening
  - 24 hour urine metanephrines
  - Plasma catecholamines
- Functional
  - Clonidine will not suppress plasma catecholamines >50%
- Localizing
  - CT
  - MRI
  - I^{131} metaiodobenzylguanidine (MIBG)

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Treatment of Pheochromocytoma

- α blockade 1-2 weeks before surgery
  - Prazosin
  - Phenoxybenzamine
- Avoid Beta blockers before alpha blockade
  - β_1 selective (atenolol) preferred
- Phentolamine or nipride used for intraoperative hypertension
- Resection is main treatment
- Metyrosine can be used to decrease catecholamine synthesis in non-operative patients

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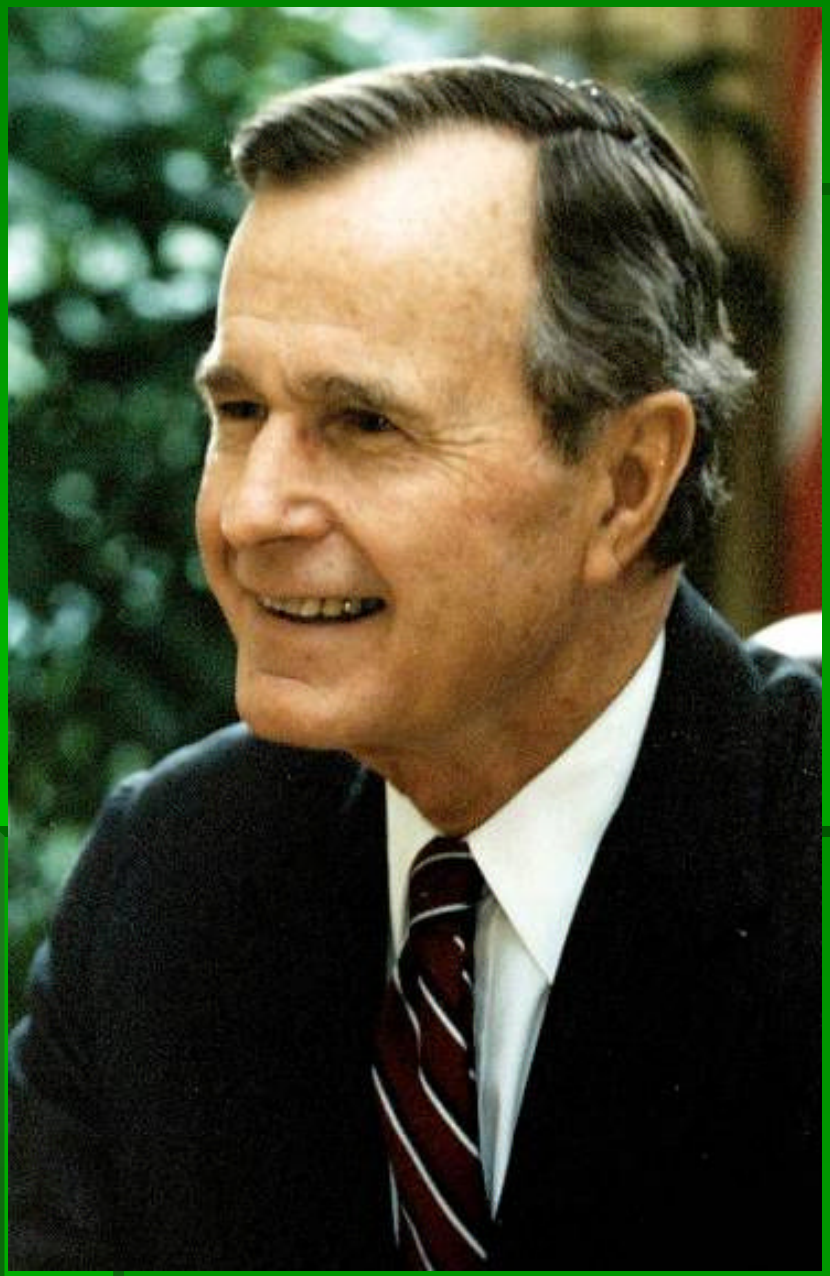
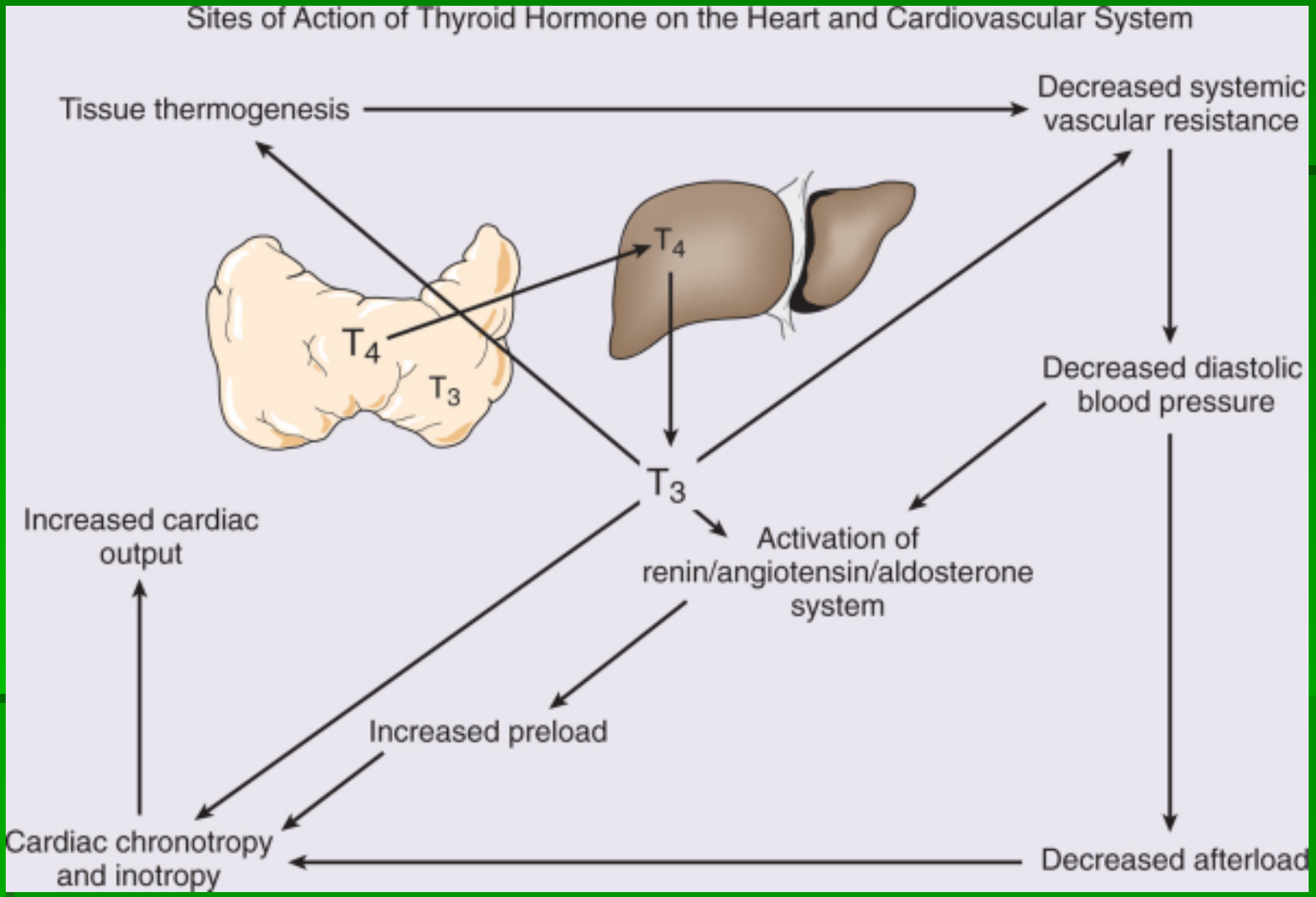
George H. W. Bush



- Developed palpitations while jogging 1991
- Atrial fibrillation with heart rate around 150
- Medically treated
- Ultimately diagnosed with hyperthyroidism due to Grave's Disease
- Received radioactive iodine ablation

http://www.af.mil/shared/media/photodb/photos/071009-F-2911S-010.jpg
http://www.doctorzebra.com/prez/g41.htm

Thyroid Function



Schematic representation of thyroid hormone metabolism and the effects of triiodothyronine (T3) on the heart and systemic vasculature. T4 = tetraiodothyronine.

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Overview of Thyroid Function

- Thyroid gland produces
  - T_4(85%)
  - T_3(15%)
- T_4 to T_3 conversion in kidney and liver
- T_3 mostly responsible for thyroid effects

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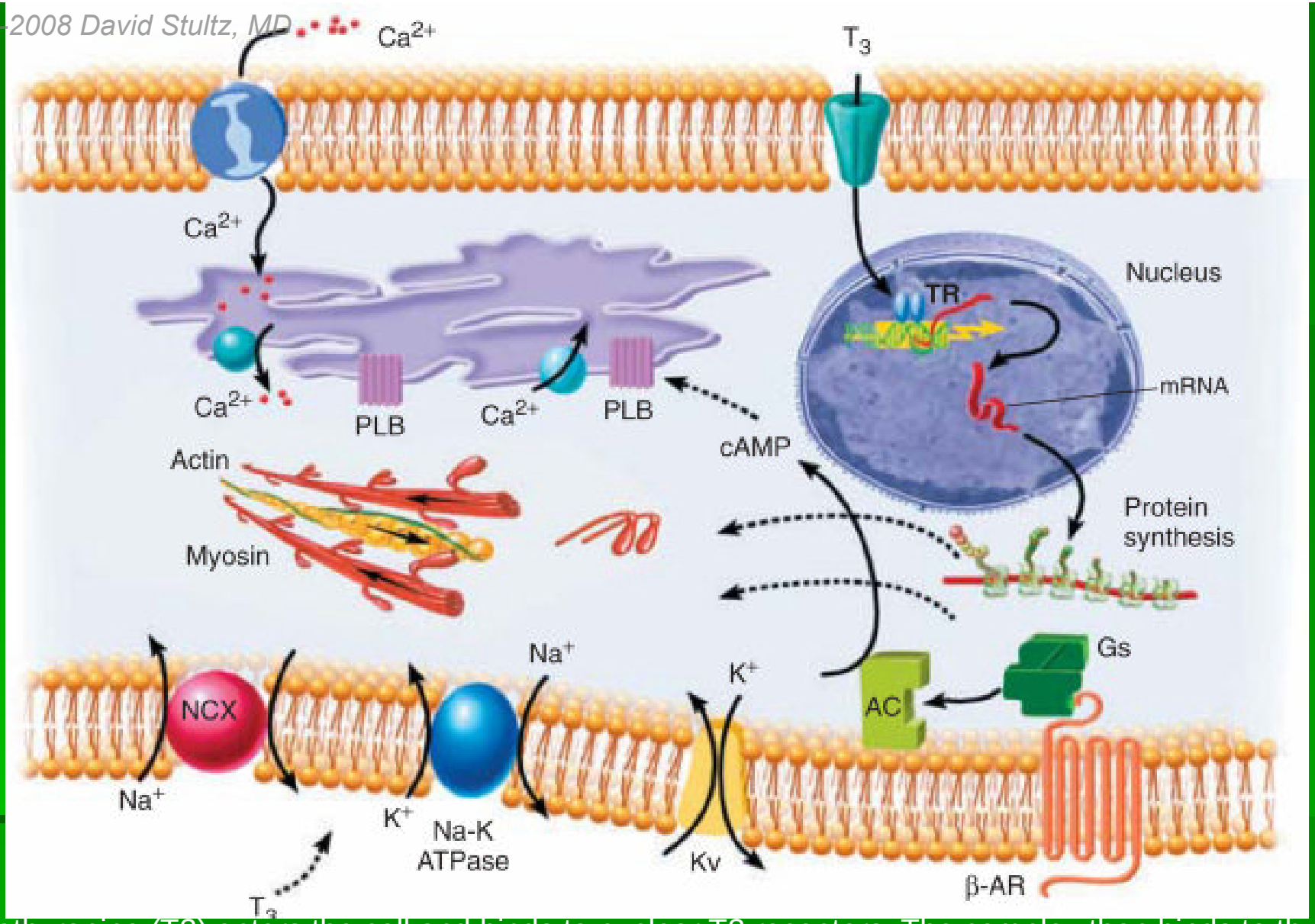

Triiodothyronine (T3) enters the cell and binds to nuclear T3 receptors. The complex then binds to thyroid hormone response elements and regulates transcription of specific genes. Nonnuclear T3 actions on ion channels for sodium (Na+), potassium (K+), and calcium (Ca2+) ions are indicated. AC = adenylyl cyclase; ATPase = adenosine triphosphatase; b-AR = beta adrenergic receptor; cAMP = cyclic adenosine monophosphate; Gs = guanine nucleotide binding protein subunit; Kv = voltage-gated potassium channel; mRNA = messenger RNA; NCX = sodium channel; PLB = phospholamban; TR = T3 receptor protein.

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Thyroid Effects on the Heart

- T_3 receptors in cardiac myocytes
  - Affects protein synthesis
- Cardiac contractility affected by regulation of calcium cycling through the SERCA-phospholamban system
- Elevated thyroid levels enhance cardiac response to catecholamines

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Cardiac Response to T_3

Positively Regulated	Negatively Regulated
Alpha-myosin heavy chain	Beta-myosin heavy chain
Sarcoplasmic reticulum Ca^{2+} -ATPase	Phospholamban
Na^+, K^+ -ATPase	Na^+/Ca^{2+} exchanger
Voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3)	Thyroid hormone receptor alpha1
Atrial and brain natriuretic peptide	Adenylyl cyclase (AC) types V, VI
Malic enzyme	Guanine nucleotide–binding protein G_i
Beta-adrenergic receptor	
Guanine nucleotide–binding protein G_s	
Adenine nucleotide transporter 1	

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Assessing Thyroid Function

- Thyroid stimulating hormone
  - Decreased in primary hyperthyroidism
  - Increased in primary hypothyroidism
- T_4 measurement useful when thyroxine-binding globulin levels are low
  - Nutritional deficiency
  - Hepatic disease
- Antithyroid peroxidase (anti-TPO), antithyroglobulin antibodies useful to diagnose autoimmune thyroid disease

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Hemodynamic Effects

- Elevated thyroid levels
  - Decrease systemic vascular resistance
  - Increase heart rate
  - Increase cardiac output
  - Increased blood volume
    - Erythropoeisis mediated by thyroid hormone
    - Increased sodium retention due to lower SVR

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Symptoms of Hyperthyroidism

- Palpitations
- Increased heart rate
- Dyspnea
- Exercise intolerance
- Angina

- Pulmonary Hypertension

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Atrial Fibrillation and Hyperthyroidism

- Less than 1% of new onset atrial fibrillation is caused by hyperthyroidism
- In patients with hyperthyroidism, 2-20% have atrial fibrillation

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Treatment of Hyperthyroid Atrial Fibrillation

- Beta Blockers preferred
- Digoxin can be used
- Anticoagulation based on stroke risk
- Antithyroid medications or radioactive iodine
- Should only try cardioversion when euthyroid state has been restored

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"High Output Heart Failure"

- Increased cardiac contractility and output
- Fatigue usually caused due to skeletal muscle weakness
- Increased volume due to renal sodium reabsorption
- Symptoms of right heart failure due to pulmonary hypertension

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Tachycardia Induced Cardiomypothy

- Longstanding hyperthyroidism
- Atrial fibrillation or sinus tachycardia
- Left ventricular dilitation and dysfunction
- Mitral regurgitation
- Control of heart rate can improve cardiac function

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Hypothyroidism

- Increased LDL
  - Decreases number of LDL receptors
- Accelerated atherosclerosis?
- Pericardial effusion
  - Decreased lymphatic clearance
  - Improves with thyroid replacement

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EKG in Hypothyroidism

- Low voltage
- Bradycardia
- Long QT

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Treating Patients with Coronary Atherosclerosis and Hypothyroidism

- Is revascularization required before starting thyroid replacement?
- If CAD is stable, start low dose thyroid replacement, titrate slowly every 6-8 weeks
- Patients with risk factors for CAD should be monitored while titrating dose

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Screening for Hypothyroidism

- Hypertension
- Hyperlipidemia
- Hypertriglyceridemia
- Coronary atherosclerosis
- Peripheral vascular disease
- Pleural or pericardial effusions
- Myalgias/myositis

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Subclinical hypothyoidism

- Mild elevation of TSH
- Cardiac effects
  - Prolonged QT interval
  - Increased risk of heart failure
  - Systolic and diastolic dysfunction
- Vascular effects
  - Increased cholesterol and LDL-c
  - Lower HDL-c
  - Increased peripheral vascular resistance
  - Elevated C-reactive protein
  - Risk of peripheral arterial disease (females)
  - Increased carotid media thickness

Subclinical Hypothyroidism

- Treatment to normalize TSH has been shown to
  - Improve lipids
  - Lower systemic vascular resistance
  - Improve cardiac contractility
  - Improve diastolic function

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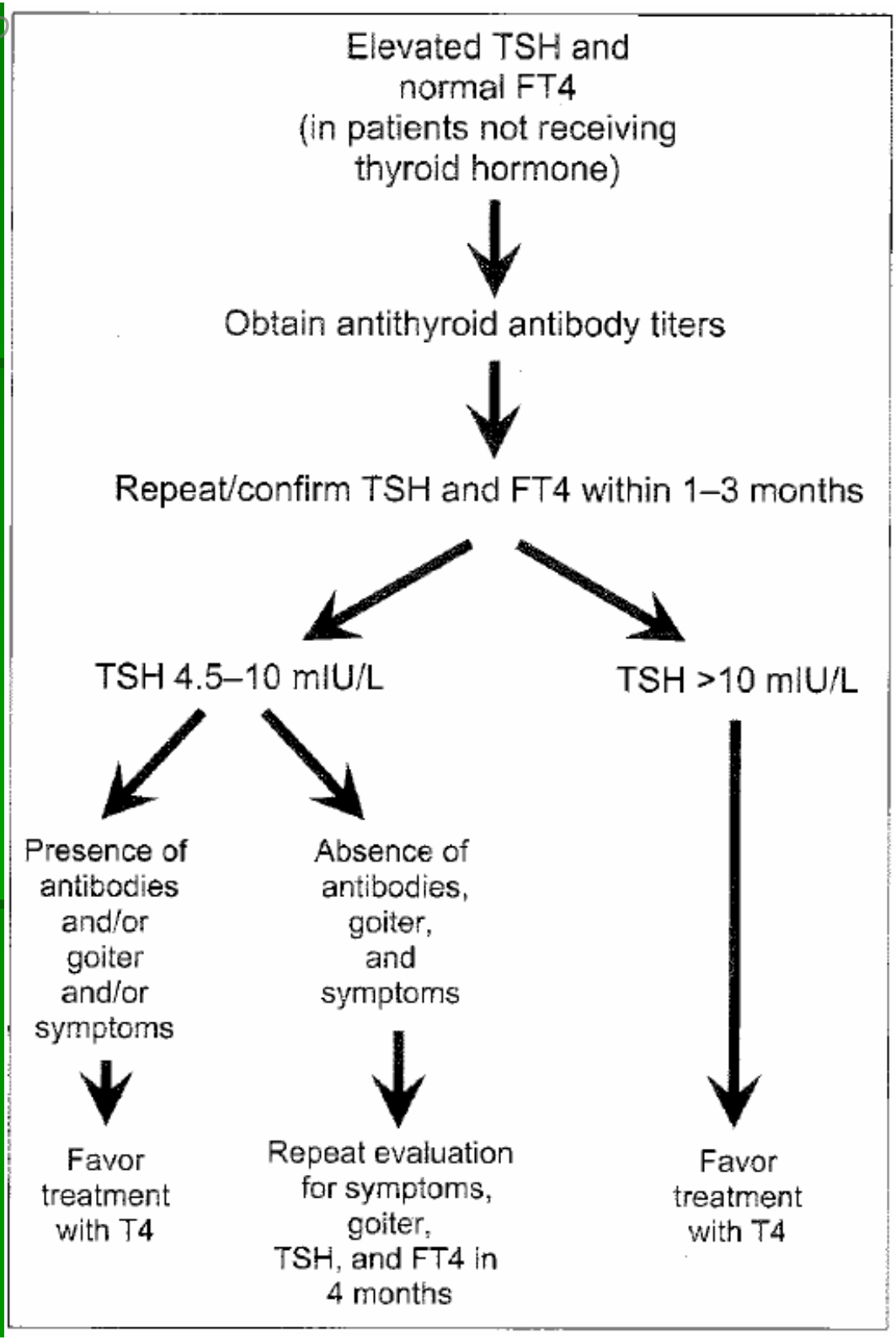

Duggal J

Subclinical hyperthyroidism

- Low TSH without overt symptoms
- Increased heart rate
- Increased left ventricular mass and hypertrophy
- Diastolic dysfunction
- Atrial arrhythmias
  - Especially atrial fibrillation

Subclinical Hyperthyroidism

- Increases risk of developing atrial fibrillation
- Overall two times mortality risk compared to euthyroid control
  - Increased cardiovascular mortality
- Treatment? Not well defined
  - Reduce thyroid replacement dose
  - Methimazole

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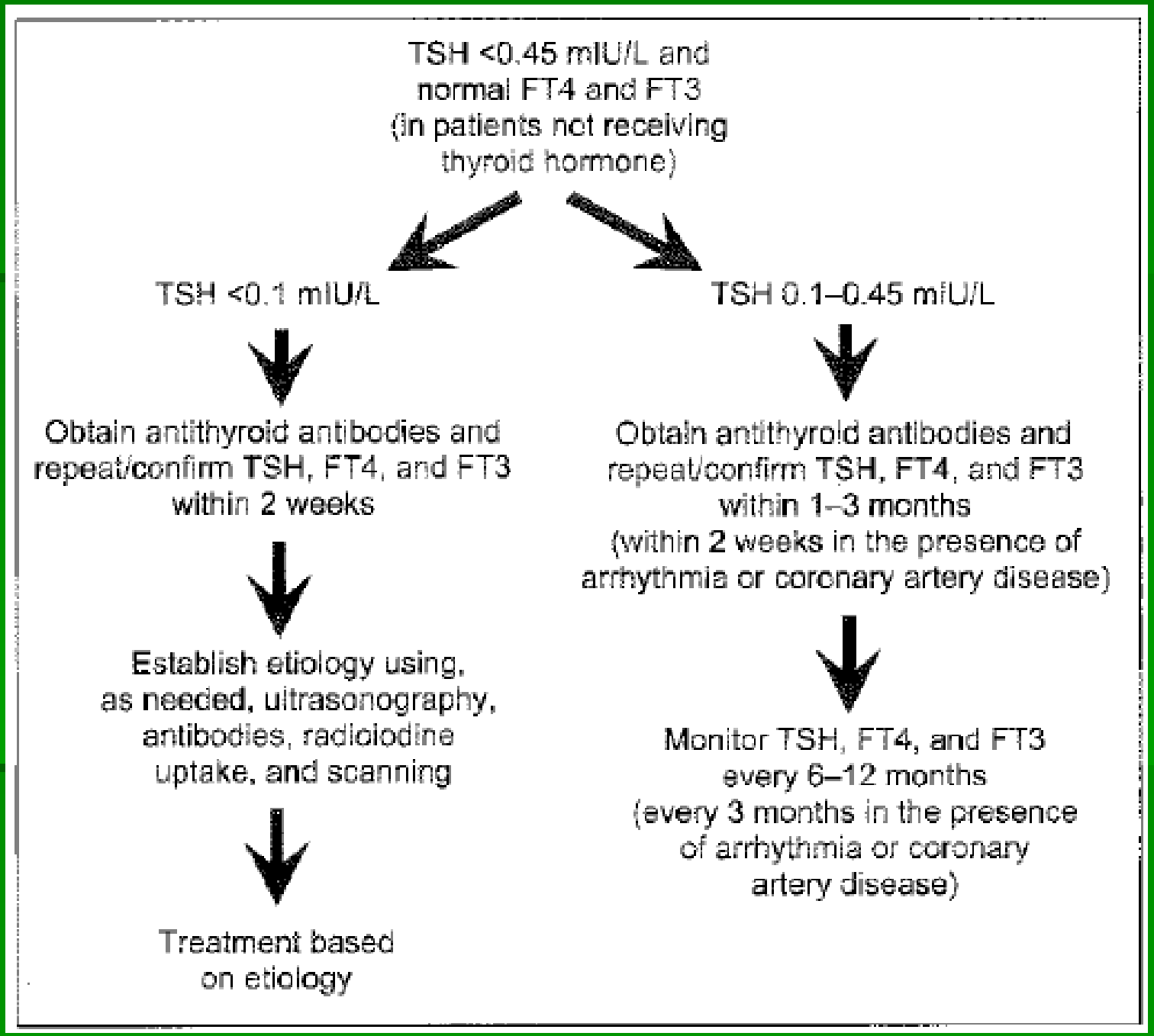

Amiodarone

- Antiarrhythmic drug used in variety of settings
  - Atrial fibrillation
  - Ventricular tachycardia
- 30% iodine by weight

- Dronedarone similar in effect without iodine content

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Acute Amiodarone Effects

- High iodine content inhibits conversion of T_4 to T_3
- T_4 metabolism is decreased in liver
- Serum T_4 increased relative to T_3
- TSH remains stable

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Amiodarone Induced Hypothyroidism

- Total body iodine content increases
- T_4 production in thyroid gland is inhibited
- TSH rises
- Hypothyroidism occurs in 15-20% of patients on chronic amiodarone therapy
- Does not depend on dose
- Can occur at any time during therapy
- Treatment with thyroid replacement
- Consider amiodarone cessation

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Amiodarone Induced Hyperthyroidism

- Less common
  - 10% in iodine-poor regions
- Type 1
  - Pre-existing thyroid disease, iodine poor diet
  - Mimics autoimmune thyroid disease
- Type 2
  - Thyroiditis
  - Mediated by cytokines (IL-6)
  - Release of thyroglobulin
- Significant overlap between types

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Treatment of Amiodarone Induced Hyperthyroidism

- Iodine-131 not effective (high iodine state)
- Prednisone 20-40mg daily
- Methimazole
- Beta blockers
- Thyroidectomy!

- Amiodarone cessation not helpful

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Summary

- Acromegaly (GH)
- Cushing's (increased ACTH, cortisol)
- Conn's syndrome (hyper-aldosteronism)
- Addison's disease (hypo-aldosteronism)
- Hyperparathyroidism (increased Ca^{2+})
- Hypocalcemia
- Pheochromocytoma (norepinephrine, epinephrine)
- Hyperthyroidism
- Hypothyroidism
- Subclinical hypothyroidism and hyperthyroidism
- Amiodarone effects on thyroid function

References

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