	RAIU	Cms	Lab	Rx
Grave≪s disease	^ or nl (1)	Diffuse, soft, symmetric goiter in 70%. Triad: 1) Painless, diffuse symmetric gland (70%) with bruit. 2) Ophthalmopathy lid lag, lid retraction, exopthalmos (irreversible) 3) Pre-tibial myxedema (peau d≪Orange). (2) **Apathetic hyperthyroidism**: Elderly, apathetic, CHF, A. Fib, v WT, syncope, confusion or depression. Can be **post partum** . Often AD (mothers-daughters). v TSH and nl T4 >> AF & osteoporosis. Autoimmune correlates (3).	TSH low, Free T4 hi. TSH receptor Abs(= thyroid stimulating immune globulins)(90%). Some specificity for Graves. (**Obtain if pregnant; TSIGs can cause neonatal thyroiditis).** Anti-thyroid peroxidase Abs. ^ alk phos,^ Ca, V Hgb, V platelets.^thyrogl≪n	**Young & no C-P Dis**: I121 (steroids to block ophthalmopathy) **OR** methimazole +_ beta blocker, then surgery. **Older or C-P Dis**: Methimazole, then stop 1 week then I121 (with steroids) (4)(14) **Mild thyrotoxicosis**: Drugs alone up to 2 yrs
Multinodular goiter	^	Multinodular goiter. (Hot nodule)	TSH low, Free T4 hi.	Surgery or I121
Thyroiditis factitia	V	Medical workers. Gland small & painless.	vTSH,^T4, v thyroglobulin	
Painless thyroiditis= chronic lymphocytic thyroidits	V	Thyroid is non-tender, firm and slightly enlarged (in 75%). 2 - 4 mo≪s of transient hyperthyroidism (in 5%) or euthyroid followed by hypothyroidism (20%) before returning to a euthyroid state. May recur. Possible apathetic hyperthyroidism.	^ thyroglobulin (released from thyroid gland due to inflammation.). TSH, T4, T3 are hi, lo, or nl.	
Post partum thyroiditis (in up to 15% of women)	V	Occurs 1-4 mo≪s post partum. Normal size thyroid (unlike Graves), painless gland. Hyperthyroid for 3 mo, then hypothyroid for 3 mo, then euthyroid. See (4b)	Anti-thyroid peroxidase Abs. ^ thyroglobulin No Anti-thyroid receptor Abs in hyperthyroid phase	Observation with or without beta blocker (Caution: secreted into breast milk)
Subacute (or Acute) thyroiditis = Giant Cell = Granulomatous = de Quervain	V	Post URI (**viral**) or pharyngitis, a painful thyroid (often radiating to the ear), and a tender, nodular, asymmetrically enlarged thyroid gland. Early, mild hyperthyroidism, then hypothyroid x several months, then euthyroid.	^^^ESR ^Thyroglobulin Abs to thyroglobulin and TSH receptors in 15%.	ASA or steroids.
Hashimoto≪s thyroidits (most common cause of hypothyroidism)	V	Firm, multinodular asymmetric goiter. **Sometimes hyperthyroidism**, but usually euthyroid, then often becoming **hypothyroidism (most comon cause)**. Often AD (women & daughters), autoimmune correlates(3)	Anti-thyroid peroxidase Abs (5) & thyroglobulin. Subclinical hypothyroid= NL T4 & ^TSH. T & B Lymphs invade thyroid.	Levothyroxin(9)(11) Dose is ^ in pregnancy. Rx of nl T4 & ^ TSH will v sx≪s, v cholest., & ^ contractility.
Radiation thyroiditis	V	7 to 10 days post I 131 RX. (Transient)	RAIU is low, v T4, ^TSH	
Amiodarone	V	Hyperthyroidism or hypothyroidism. (6)	v Thyrd RAIU. IDs locale.	
Struma ovarii	V	thyroid tissue in an ovarian teratoma.	(RAIU is low)	

(1) **RAIU (RADIOIODINE UPTAKE**) gives a **NUMBER** and distinguishes Graves or hot nodules versus thyroiditis or amiodarone. **THYROID SCAN OR SCINTISCAN OR RADIONUCLIDE SCAN** gives a **PICTURE** of the gland and a) distinguishes hot (rarely malignant) versus cold nodule and b) localizes the nodule. **NO RAIU OR SCANS DURING PREGNANCY OR NURSING !!!!!!!**

(2) Common Sx≪s: v WT, heat intol, sweating, insomia, ^HR,Palpitations, hyperdefecation. Less Common: Menstrual irregularities, infertility, gynecomastia, n-v-abd pn, ^ LFTs, ≙ADD≙. Also, hyperthyroidism can cause ^ Ca (hypercalcemia) with v PTH.

(3) Graves & Hashimoto≪s thyroiditis occur with Addison≪s dis, DM I, Premature ovarian failure, myasthenia gravis, & celiac sprue. V Thyroid<>myalgias.

(4) PTU & methimazole can give rash, arthralgias, agranulocytosis and hepatitis. Methimazole and I121 contraind. in pregnancy. Give I131 if severe hyperthyroidism, goiter 4X normal size, or T3/T4 > 20. For methimazole therapy, get CBC baseline; instruct patient to call if T ^ or ST. Monitor thyroid function Q5 weeks until euthyroid. D/C after 1 - 1.5 years. (NEJM 2005;352:905.) PTU blocks T4 & T3 synthesis and blocks T4 to T3 peripherally. For thyroid ablation, if the patient is elderly or has multiple comorbidities, give anti-thyroid drug until 3 days before ablation. Resume the drug 3 days later and continue for 3 months, then tapered.

(5) Anti-peroxidase Abs, previously ≙Anti-microsomal Abs≙, are obtained when patient has borderline TSH & T4 and may be heading to hypothyroid state.

(6) Hyperthyroidism occurs if there is underlying autoimmunity. Hypothyroidism from I2 load, x in T3 to T4, and competitive of T3 on cells.

(7) During pregnancy, TSH decreases to .1-.5 in 1st trimester, but free T4 remains normal, while thyroglobulin & total T4 is elevated. Also, hyperemesis gravidarum can give low TSH & high T4 due to very high HCG, while patient is metabolically euthyroid. Mothers with Grave≪s disease and **TSIGs 5X normal** are at risk of delivering hyperthyroid infant with ^ HR, advanced bone age, craniosynostosis, and goiter.
(8) Euthyroid sick syndrome (e.g., ICU) has ≙adaptively≙ reduced TSH and/or low, normal or increased free T4, low total T3, or low free T3. Reverse T3 is high in this but low in pituitary hypothyrodism. After recovery from non-thyroidal illness, TSH can transiently increase to 15uU/ml before normalizing.
(9) Calcium, iron, & aluminum antacids block levothyroxin absorption; phenytoin, phenobarb & sertraline increase metabolic clearance.
(10) Goiter of pregnancy. HCG mimics TSH causing goiter but T4 is nl or slightly ^ & may be associated with hyperemesis gravidarum (Q11,MKSAP13).
(11) T3/mcg=4x T4/mcg. 1 grain of dessicated thyroid is 39 mcg T4 and 9 mcg T3=74 mcg T4. Human ratio is 14:1 T4:T3.
(14) When using methimazole or PTU warn the patient about agranulocytosis.
There is an entity called T3 toxicosis: normal T4, elevated T3. When T4 is elevated, do thyroid uptake. If it is low, and thyroglobulin is decreased, this represents exogenous hormone. If increased, it is thyroiditis. If thyroid uptake is high, it is either Graves (diffuse) or toxic multinodular goiter or toxic adenoma. (15) for controlling symptoms, give propranolol SR 80-120mg HS.

Screening for thyroid dysfunction (for inpatients interpreting TSH and T4 is problematic:

>Serum TSH is normal >>> no further testing performed.
>Serum TSH high >>> add free T4 to determine the degree of hypothyroidism
>Serum TSH low >> add free T4 and total T3 to determine degree of hyperthyroidism
>If pituitary or hypothalamic disease is suspected, measure serum TSH and free T4.
>Serum TSH is normal but patient has sx≪s of hyper or hypothyroidism: add free T4

Gharib H et al. J Clinical Endocrin & Metab 2005; 90:581-5. Consensus statement of endocrinologists:
After change in thyroid dose, check TSH in 6 to 8 weeks.
1) Treat subclinical hyperthyrodism (TSH lo, free T4 & T3 nl) if the TSH is <0.1mU/L; monitor if TSH is 0.1-0.4.
2) Treat subclinical hypothyroidism (TSH hi, free T4 and T3 are nl) if the TSH is >10. If the TSH is 4.5 - 10 mU/L, then it is up to the clinician.
3) Screen adult patients routinely for subclinical thyroid dysfunction, particularly in the pregnant and in those contemplating pregnancy.
The average dose for complete hypothyroid state is 1.5 mcg/kg or about 100 to 124 mcg.
In pregnancy, T4 requirements increase by 50% beginning weeks 8 thru 16. Keep TSH in low nl range. T4 requirements may also increase with estrogen use.
For multinodulare goiter, bipsy cold nodules greater than 1cm (MKSAP 14).
The TSH will come down more quickly than it will go up.
Case
Asymptomatic, nl T4 and sl ^ TSH, ^ cholesterol
Progression to sx≪s is 4%/year... Higher if thyroid peroxide antibody positive.
Management: Treat with T4. (Progression likely. Q104, MKSAP 12).

Treatment of hypothyroidism and monitoring levothyroxine therapy: Bottom line: measure and treat the TSH. Free T4 is insensitive to overtreatment: E.G.: T4 is 40% too high, with free T4 normal and Low TSH. Only follow free T4 in secondary hypothyroidism. Replacement dose is 1.6 mcg/kg

Treatment of hyperthyroidism early in the course of therapy: Bottom line: Measure and treat the free T4 and free T3. TSH measurements are useful for the **diagnosis** of hyperthyroidism, but they are unable to distinguish the degree of hyperthyroidism **since TSH suppression occurs in the early stages of the disease (even when free T4 and T3 are corrected). TSH may remain subnormal for several weeks and rarely for several months**. One must therefore rely upon serum free T4 and T3 measurements when assessing the efficacy of antithyroid drugs, radioiodine, or surgery [11,21]. **Once steady-state conditions are assured, measurement of serum TSH is required to assess the efficacy of therapy.**
The lag time of TSH is about 3 weeks from hyper or hypothyrodism and free T4 will be more accurate.

Treatment of thyroid storm or pre-op hyyperthyroidsm:
1. Steroids (blocks T4 to T3 conversion) +PTU first.
2. After 1 hour, Inorganic Iodine.
3. Then Beta blockers.
NO RAI treatment acutely.

For papillary thyroid ca, rx is surgery (near total thyroidectomy), RAI ablation, and T4 suppression. For poor prognosis, use all three.

Case

27 y.o. woman 12 weeks pregnant. Feels well. Small Goiter.
TSH 0.3 micro Units/ml. T4 is 16 mcg/dL (5-12)
Dx: ^ HCG mimics TSH causing goiter and ^ T4. Free T4 is normal or slightly elevated.
Hyperemesis gravidarum is associated with ^^ HCG.

Case (Q12, MKSAP 13)
41 y.o. Hispanic male. Normal Hx and PE.
Free T4 15 (12-31). Total T4 17 (5-12). Total T3 115 (70-195). TSH 0.8 (0.5 - 5.0)
Dx: Familial dysalbuminemic hyperthyroxinemia. More common in Hispanic males. (In familial TBG excess, T3 is also elevated.)
Iodine induced thyrotoxicosis occurs when a patient comes from a low iodine region to the U.S. where there is much more iodine in the diet. This can result in a low RAIU.
Hypothyroidism can rarely cause hypertrophy of pituitary gland (from TSH secreting cells ≐ thyrotrophs) as well as mild elevation in prolactin. Treat the hypothyroidism and hold off on the surgery (Med study question 28 in endocrinology).

FACTORS EFFECTING PITUITARY HORMONES September 15, 2004

Hormone	Increasing or Facilitating	Decreasing or blocking
GnRH >> GH >> IGF 1	Dopamine	Hypoglycemia >> A 3 hour GTT is used to confirm acromegaly. Somatostatin (released from hypothalamus) Octreotide, a somatostatin analogue, or cabergoline (paradoxical) (Both are used to treat acromegaly if surgery is ineffective.)
PRH >> Prolactin	**Hypothyroidism causes hyper-prolactinemia due to ^TRH & ^TSH.** MOAIs Amitryptiline. Phenothiazines Metoclopramide (1) SSRIS Spinal cord & chest wall lesions Liver & Kidney failure	Dopamine (released from hypothalamus & used medicinally) Bromocriptine Carbergoline Pergolide Thyroid hormone
GnRH >> FSH, LH >> Estrogen, Testosterone	HCG stimulates estrogen and testosterone release. ACTH stimulates zona fasciculata in feamels causing increased androgen secretion.	**Prolactin via suppression of GnRH.** Estradiol Testosterone
TRH >> TSH >> T4 (some T3)		T4, T3 Somatostatin Dopamine Steroids Bexarotine (vit A analogue
CRH >> ACTH >> Cortisol	Cosyntropin (used diagnostically) Serotonin Stress	Cortisol
ADH	^ Osmolality v Glucose Age ^ Calcium Decreased volume Angiotensin II Lithium Pregnancy Menses	V Osmolality V K ^ Volume Hypertension Cortisol (allows secretion of free water) Demeclocycline

	Chlorpropamide Clofibrate Carbamazepine	

(1) Estrogens, Methyldopa, Verapamil, Cocaine, & Opioids are rare causes of galactorrhea.

*Bromocryptine can start to shrink a prolactinoma in days (thoughit usually takes longer).
*A pituitary mass effect can decrease secretion of dopamine (and hence increase prolactin secretion), TSH, and ACTH.
*Case
28 y.o. woman depression, weight loss, mild hypotension (98/54, pulse 98).
Ddx: bulemia, Addison≪s disease, hyperthyroidism.

TESTING FOR PITUITARY HORMONE September 15, 2004

Hormone	Hyposecretion	Hypersecretion
Growth Hormone	Insulin tolerance test	IGF-1 (random measurement) If elevated, do a 3 hr GTT and measure Growth Hormone. If normal and acromegaly is strongly suspected, do a 3 hr GTT and measure Growth Hormone anyway (more sensitive than the random 1, which depends on liver synthesis).
Prolactin	Not Tested	Prolactin Level
FSH, LH	Postmen: FSH levels. Pre-men: FSH, LH & estradiol In men: FSH, LH, Testosterone.	Postmen: FSH levels. Pre-men: FSH, LH & estradiol In men: FSH, LH, Testosterone.
TSH	Level	Level
ACTH	1. AM Cortisol (nl 8-20 mcg/dL) 2. Rapid (1 hr) cosyntropin (Synthetic ACTH) stimulation test and measure cortisol at 1 hour (NL > 18mcg/dL)	24 hr urine free cortisol (nl < 100 mcg) OR Evening (11PM) salivary cortisol (normally nadir). OR 1 mg over night dexamethasone suppression test.

CAUSES OF INCREASED UTERINE BLEEDING
Structural: Poyps, hyperplasia, **ca**, fibroids, IUD, uterine AVM
Pregnancy related: Pregnancy, ectopic, spontaneous abortion.
Hormonal: PCO, ovarian cyst, ovarian tumor, perimenopause, hypothyroidism
Hematologic: von Willebrand≪s, hemophilia, thrombocytopenia, liver disease, hematologic malignancies

SECRETORY ENDOCRINE DIARRHEAS

Carcinoid syndrome	Flushing, right sided heart murmur, hypo or hypertension.	5 HIAA (5 hydroxy indole acetic acid) in urine. Treat receptor antagonists (adansetron) and octreotide.
VIP oma	Severe dehydration	v K, ^HCO3. Stool osmolal gap <35* ^ VIPser CT: Pancreatic mass ± liver mets.

Gastrinoma	diarrhea, PUD	Secretin > ^ gastrin (paradoxical)
Pheo	hypertension, Cushings, or hypercalcemia (MEN 2) @	Plasma free metanephrines. VIP if diarrhea.

2(stool Na + stool K) - stool measured osmolality

@A pheo can have unexplained hypotension with surgery and hypercalcemia from ectopic PTH-related protein.

SOME CLINICAL MANIFESTATIONS & SOME DIAGNOSES September 22, 2004

Obesity	Empty Sella syndrome*	
	PCOD, Cushings, etc.	
Impotence, ED	Prolactinoma or prolactinemia	via v GnRH causing v FSH & LH
	Acromegaly	
	DM	
	Aortic/vascular insufficiency (Leriche syndrome)	
	Nerve Dysfunction	
	Obesity (> ^ insulin > v Sex Hormone Binding Globulin and v rate of testosterone production.)	See Q 7, p 107, MKSAP 13)
Precocious puberty	Estrogen secreting tumor.	Lo LH, FSH, GnRH,, 17 ketosteroids & C
Galactorrhea	Prolactinoma	
	Hypothyroidism	
	Drugs: MOAIs, Amitryptiline, Phenothiazines, Metoclopramide, SSRIS, estrogens.	
Hyperglycemia	Acromegaly, Cushings, hyperthyroidism	
Carpal Tunnel Syndr.	DM	
	Acromegaly	
	Hypothyroidism	
	Hemachromatosis	
Hypercholesterolemia	Hypothyroidism	
	DM	
	Acromegaly	
	Drugs: steroids & some anti-BP meds	
	Obstructive liver disease	
	Nephrotic sydrome	
Acanthosis nigricans	**In Young**: suggests autoimmune disease. **In old**: suggests malignancy.	
	DM Type II	
	Acromegaly	
	Cushings	

	Hyper or Hypo thyroidism	
	Excessive niacin use	

*Empty sella syndrome can be created by multiple pregnancies, with increase in pituitary size and blood flow, pushing on and stretching the diaphragm of the sella above the pituitary. After pregnancy, the diaphragm remains stretched and the weight of the CSF fluid pushes the diaphragm down against the pituitary, displacing it and creating the picture of an empty sella.

	Hirsute	fsh[2]		Other CMS	Lab
ovary			**Pregnancy**		^ Beta hCG, ^ estradiol. ^LH(artifactual)
ovary	Y	V	**PCOD** (diagnosis of exclusion)	obese, large ovaries, ^glucose, acanthosis nigricans. Indolent.	LH/FSH > 3, Testosterone 76-200. ^ DHEA. ^ Estrone, NL estradiol.
ovary		^	**Premature ovarian failure**(autoimmune polyglandular def.)	Autosomal recessive (1/10). **vitiligo**, DM, Graves dis, PA, etc.	^ FSH, ^ LH. Bleeds with progesterone withdrawal(3), but **only** after estrogen priming.
ovary	YY	NL, v	ovarian tumors: sertoli-leydig(arrhe-	noblastomas),granulosa theca(stromal),hilus tumors	^^^ **Testosterone**(>200);NL DHEA. Bleeds with test (3)
ovary		NL, ^	**Ovarian dysfnctn (Estrogen def.)**	No response to test (3). Bleeds after 2 months of OCPs.	Give OCPs (with progesterone) to prevent osteoporosis (& uterine CA).
Endo mtrm		NL ^	**Endometrial failure.**	No bleeding after test (3) or OCPs for 2 months.	(E.G., Asherman≪s syndrome, occurring after vigorous D&C.)
Adrnl	YY	nl, v	Adrenal CA		nl Testosterone, ^^^ **DHEA**
	Y, N		Cushing≪s Synd	Cushingoid	^ 24hr urine free cortisol
	Y	v	CAH, 21 hydroxylase def (6)	AR. Young women: no ^K. Childhood: usually ^K. Bleeds with test (3)	^ Testosterone, ^ ACTH ^ 17 OH progresterone. ± v aldosterone
	Y	v	CAH, 11 hydroxylase def	AR. ^ BP. Cliteromegaly.	v K. Modestly incr Testosterone, ^ 11deoxycortisol. ^pH.
Pitui-tary		V	**Hypothalamic Amenorrhea**	Stress, anorexia, bulemia, excess exercise, can develop osteoporosis!!	via v GnRH > v LH & FSH. Nl prolactin. GnRH induces menses & pregnancy. Bleeds with test (3). Treat with OCPs.
	Y	V	**Hyperprolactin-emia** (4),(5)	Galactorrhea. +_ hypothyroid	via vGnRH & hence vLH & v FSH. Bleeds with test (2). Do TSH & MRI. (7)
		V	Adrenal insuffic.	Tired,pale,n,v,abd pn,vBP	1 mcg cosyntropin:crtsl<18mcg/dL; vACTH
			Acromegaly	acral^, coarse, prognathism	^insulin like growth factor 1
Thrd	Y	V	**Hypothyroidism**(5)	± galactorrhea	^TSH, ^ prolactin. Bleeds with test(3)

(1) Most common causes are **Pregnancy, hypothyroidism, hyper-prolactinemia, and drugs**. Also, **rule out cancer**. By H&P, is the patient pregnant, hirsute, obese, Cushingoid, hyper-glycemic or agromegalic. If not, this goes against pregnancy, PCOD, cushings, ovarian or adrenal cancers, and acromegaly.

(2) Do FSH test first, per MKSAP 13. If this is low, rule out prolactinemia, hypothyroidism, & androgen hyper-secretion from ovarian cancer, adrenal cancer, CAH 12, and CAH 11. So, get prolactin, TSH, testosterone, DHEA & LH. Menometrorrhagia may occur from unopposed estrogen, endometrial hyperplasia, and cancer. Give medroxyprogestrone withdrawal trial. After there is withdrawal bleeding, rule out endometrial cancer with intra-uterine US (Q86,MKSAP12).

(3) Progesterone trial: Give 10mg medroxyprogresterone QD x 10days, then withdraw. Bleeding within one week of withdrawal implies the presence of estrogen.

(4) Via a prolactinoma (e.g., prolactin > 200 ng/ml) Or Via blockage of dopamine (e.g., prolactin 20-200 ng/ml) by mass, empty sella, bleeding (pituitary apoplexy), infarction(Sheehan≪s syndrome post partum), auto-immune causes, infiltration (sarcoid, hemachoromatosis, etc), chronic renal failure, cirrhosis, chest lesions, spinal cord lesions, or drugs (e.g., anti-psychotics: phenothiazines and newer anti-psychotics and metoclopramide).

(5) Hyperprolactinemia & hypothyroidism are the two most common causes of amenorrhea. Causes include ^TSH, empty sulla syndrome, large non-function adenoma, and a functioning adenoma. The pituitary is ~1 cm diameter; a very large non-functioning pituitary adenoma (3.g., 2.4cm) blocks dopamine, permitting modest increases in prolactin; a 2.4 cm functioning adenoma should make more than 200 ng/ml. The former is treated surgically, the latter with dopaminergics.

Drugs causing hirsutism: Phenytoin, penicillamine, diazoxide, streptomycin, cyclosproine, anabolic steroids.

(6) CAH 21 hydroxylase deficiency occurs in as many as 1% of young women.

(7)Rx=Cabergoline for 4-9 years, then withdrawn; recurrence of 1/3 but with lower prolactins and lesser sx≪s (Colao, 2003)

Y = Hirsute. YY=Hirsutism with Virilization: male balding, clitoromegaly, male muscle mass, voice deepening.;

PRIMARY AMENORRHEA (1)	Features	RX
Physiologic Delay		
Hymen, vaginal, or uterine atresia	May have nl secondary sex characteristics.	
All causes of 2ndary amenorrhea	**Particularly see CAH 21 hydroxylase def.**	
Turner≪s Syndrome	Short stature, wide-spaced nipples, no breast development, short 4th metacarpals, XO karyoype, webbed neck in 2/3, low set ears, epicanthal folds, coarc of aorta, aortic stenosis, gonadoblastomas.	Gonadectomy at young age.
Androgen resistance =Testicular feminization = insensitivity to testosterone in a genetic male (XY).	Absent uterus and shallow vagina, no axillary or pubic hair. Otherwise normal body habitus. Increased testosterone. (2)	
Aromatase deficiency	Pseudo-hermaphroditism, tall. vv Estrogens, ^^ testosterone & androstenedione. ^^ FSH & LH. Ovarian cysts.	
Idiopathic hypogonadal hypogonadism	^ fsh	

(1) In all patients, check for uterus, normal vagina, HCG, FSH, TSH and prolactin.
(2) In testicular feminization (XY genotype) there is wide variation from phenotypic females to nearly normal males with minor defects in masculinization or infertility.

POLY CYSTIC OVARY SYNDROME (STEIN LEVENTHAL) November 12, 2005

DX: see above. **Pathogenesis**: Excess Androgen from ovaries + obesity >>> increased fat production of estrogen >>hyperandrogenism >>>> increased LH (positive effect) and decrease FSH >> LH/FSH greater than 2 and anovulation.

Rx: (Table below is adapted from NEJM 2005; 352: 1231.)

Agent	mechanism of action	Advantages, Disadvantages	E.G.	v hirsute, acne	For ameno rrhea	To induce ovulation	Lower insulin
Estrogen + Progestin	^SHBG, v LH, vFSH, v androgen prod≪n and effect.	Possible ^ risk of DVT and PE.	Orthocyclen Orthocept Yasmin	x	x		
Glucorti-coid	Supresses corticotropin & thus adrenal androgens	Long term risk of glucose intolerance, insulin resistance, ostopenia, and weight gain.	Prednisone, Dexametha-sone	x	x	x	x
Biguanide (or glitazones)	v hepatic glucose > v Insulin. ? v ovarian steroid genesis	Very effective to v insulin, androgens. Modest weight gain.		x	x	x	x

Causes of hirsuitism in females:

Idiopathic
Ovarian Tumor
Adrenal tumor
Cushings
CAH 21 or 11 hydorxylase deficiencies.
Drugs: Phenytoin, minodxidil, cyclosporine.
PCOS

HYPOGONADISM (ANOTHER WAY OF LOOKING AT THINGS)

Primary hypogonadism: High FSH and LH.

Congenital: Turner≪s syndrome, Klinefelter≪s syndrome.

Acquired: Autoimmune, infectious, chemotherapy, surgery.

Secondary hypogonadism: Decreased or normal FSH and LH.

Congenital: Isolated GnRH defieciency: Without anosmia, with anosmia, and with mental retardation: Laurence-Moon-Biedl or Prader Willi Syndrome.

Acquired: Tumors, Metabolic (drugs, hypothyroidism, hyperprolactinemia, malnutrition), infiltrative: (hemochromatosis, trauma, pituitary apoplexy).

Klinefelters: Gynecomastia, small firm testes, Increased length of legs relative to arms, poor judgement, DM, impaired linguistics. XXY karyotype. ^ FSH & LH, v testosterone.

Case:

A 33-year-old woman, HA, N, constipation, cold intolerance, hoarse, amenorrheic, and galactorrheic. Thyroidectomy 3 years ago for a solitary thyroid nodule, which was benign.

PE: palpable, dry and scaly skin, and bilateral nonpitting edema.

Labs: creatine kinase of 800 U/L (26-140), free T4 of 0.4 ng/dL (0.7-1.5), TSH 75, and prolactin 100 ng/mL (0-20). Pregnancy test negative; CT with and without contrast: diffuse pituitary enlargement.

Dx: Hypothyroidism causing hyperprolactinemia without a pituitary tumor

Rx: T4.

Causes of erectile dysfunction include antihypertensive agents, the thiazide diuretics and beta blockers, calcium channel blockers and angiotensin converting-enzyme inhibitors.

Sildenafil inhibits cyclic GMP specific phosphodiesterase type V, which metabolizes cyclic GMP in the corpus cavernosum, which relaxes smooth muscle. Sildenafil has no effect on libido or sexual performance. Side effects: HA, flushing, dyspepsia, nasal congestionn, transient visual blue halo effect. Contraindications: nitroglycerin, erythromycin, cimetidine, antifungals, protease inhibitors (ritonavir).

OCPs: Contraindications: H/O DVT or PE, liver disease, breast cancer, abnormal vaginal bleeding of unknown cause, suspected pregnancy, smokers over age 35, patients on anti-leptics (may block effect of OCP). Patients on antiepileptic medicines (phenobarbital, phenytoin, carbamazepine, and paramethadione) should have 50 mcg of ethyinylestradiol rather than 35.

Steroid treatment: Both inhaled and topical steroids may effect bone metabolism. Alternate-day use of steroids does not prevent steroid induced bone loss (though it may prevent suppression of pituitary adrenal axis. Patients need calcium, vitamin D, and possibly a bisphosphonate.

Precocious puberty causes

Premature activation of GnRH release

Adrenal or ovarian oversecretion of estrogen:

>Idiopathic (the majority)

>McCune Albright syndrome (poly-ostotic fibrous dysplasia) with constitutive activation of the GnRH receptor

>Granulose theca tumors of the ovary >> increased secretion of estrogen.

Case

7 y.o. girl, vaginal bleeding for 2 months, tall, Tanner stage III breast dev≪t, no axillary or pubic hair.

Bone age: 10 years Urinary 17-ketosteroids normal. Urinary gonadotropins: undetectable.

CT: Tumor.

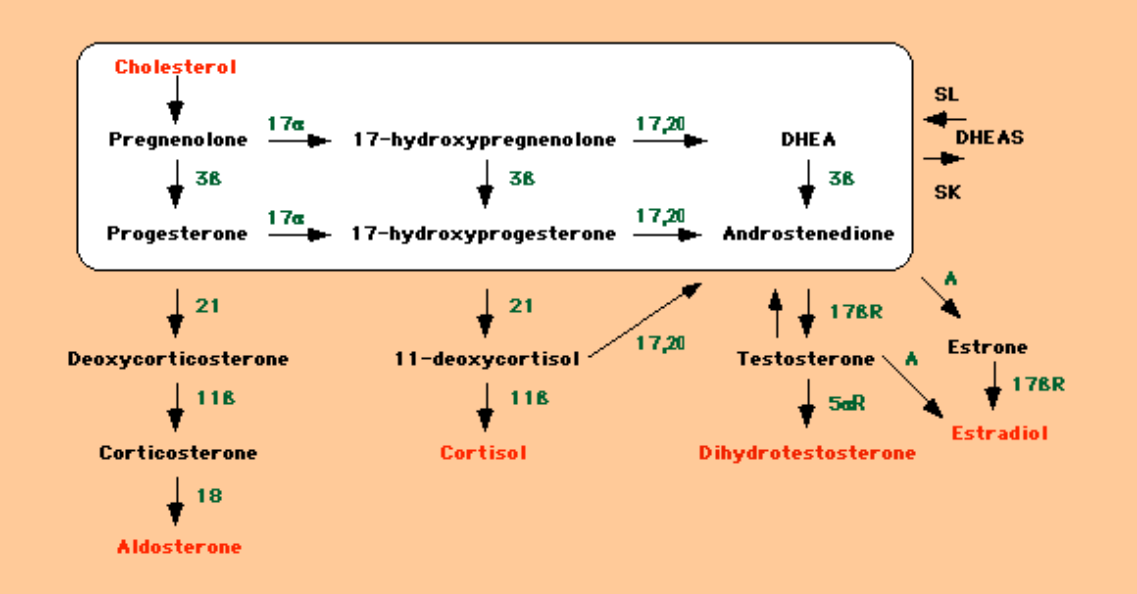
Dx: estrogen-secreting tumor. Ddx: precocious puberty has pubertal nocturnal surge in FSH & LH.

Case

52 man with erectile dysfunction (ED)

Obese: BMI 37. Type 2 DM for 13 years, acanthosis nigricans (implies insulin resistance).

Total testosterone is 230 ng/dL (300-1200)



Synthetic pathways for adrenal steroid synthesis The first step in adrenal steroid synthesis is the combination of acetyl CoA and squalene to form cholesterol, which is then converted into pregnenolone. The enclosed area contains the core steroidogenic pathway utilized by the adrenal glands and gonads. The numbers at the arrows refer to specific enzymes: 17α = 17α-hydroxylase (CYP17, P450c17); 17,20 = 17,20 lyase (also mediated by CYP17); 3ß = 3ß-hydroxysteroid dehydrogenase; 21 = 21-hydroxylase (CYP21A2, P450c21); 11ß = 11ß-hydroxylase; (CYP11B1, P450c11); 18 refers to the two-step process of aldosterone synthase (CYP11B2, P450c11as), resulting in the addition of an hydroxyl group that is then oxidized to an aldehyde group at the 18-carbon position; 17ßR = 17ß-reductase; 5αR = 5α-reductase; DHEA = dehydroepiandrostenedione; DHEAS= DHEA sulfate; and A = aromatase (CYP19).

LSH and LH are 5.5 and 4.5 mU/ml (3-15).
Dx: Decreased sex hormone binding globulin is due to suppression of production by insulin.

Hirsutism in Females: Male pattern hair growth ± Male balding

entity	Cm≪s	Lab	Other
Idiopathic	+ FH	Normal	? spironolactone
Drugs	Phenytoin, minoxidil, cyclosporin		
PCOS	menstrual irregularities, obese, ^glucose, acanthosis	LH/FSH>3; testosterone 76-200. ^DHEA.	spironolactone, metformin, OCPs,

	nigricans	Exclude causes of amenorrhea	steroids
ovarian tumor (e.g., arrhenoblastoma)	menstrual irregularities	^^ Testosterone. NL DHEA, bleeds with (1)	
Adrenal Tumor	ditto	Nl testosterone, ^^ DHEA, ^ urinary 17KS	
Cushings Syndrome	Cushingoid	^24 hr urine free cortisol	
CAH, 21 Hydroxylase def	Addisonian crisis	^ testoserone, ^ ACTH, ^17OH progesterone. ^ K	
CAH, 11 Hydroxylase def	^BP	v K, ^pH, sl ^ testosterone, ^11 deoxycortisol, v cortisol	

(1) give 10 mg medroxyprogesterone QDx5days, then withdraw. Bleeding within 1 week implies presence of estrogen.
GYNECOMASTIA: Rubbery firm tissue beneath the nipple. Rule out breast ca and pseudogynecomastia.
Persistent pubertal gynecomastia (25%). ?? Etiology.
Idiopathic (25%).
Drugs (15%): spironolactone, cimetidine, marijuana, opioids, psychoactive drugs, phenytoin, finasteride, ketoconazole, methotrexate, ACEIs, CCBs, hormones.
Cirrhosis or malnutrition (8%). v breakdown of estrogens.
Primary hypogonadism (8%). Infiltrative: Hemochromatosis. **Infection**. Mumps. **E.G. Klinefelter≪s syndrome**. Small firm testes, tall, long-limbed (armspan>height)(late epiphyseal closure due to v androgens with normal estrogens), centripetal obesity, leg ulcers, varicose veins, poor school performance, increased risk for non-seminoma germ cell tumor. Increased GnRH, FSH & LH; decreased androgens. Azospermia, XXYon buccal smear.
Obesity. Increased aromatization of androgens to estrogens.
Tumors: Adrenal (nl testosterone but ^ in DHEA) **or testicular tumors: germ cell or Leydig cell ca (3%)**. (Testicular mass. ^HCG>>^estradiol, LH and ^estradiol, respectively).
Secondary hypogonadism (2%)
Hyperthyroidism (1.5%). ^ testosterone to estrogen. ^ SHBG >> ^ binding of testosterol and v free testosterone.
Hypothyroidism. ^TRH & ^ TSH >>> ^ prolactin >>> v FSH, LH >>> v testosterone.
Renal insufficiency (1%). v Leydig cell function >> v testosterone.
Prolactionoma
Androgen insensitivity.

ADULT MALE HYPOGONADISM
High FSH, LH:
>Autoimmune (polyglandular syndromes)
> Infection (mumps)
>Drugs: cyclophosphamide (direct damage), ketoconazole (block of synthesis), spironolactone (block of action), steroids (block of pituitary axis).
>Klinefelter≪s syndrome: see above.
>Idiopathic subvertility: small testes (Q21, MKSAP 13), v sperm count.
Low FSH, LH:
>Prolactinoma (see above). Cabergoline normalizes sperm counts in most men (Colao, 2004).
>Other secondary causes: tumors, metabolic (malnutrition, hypothyroidism, hemochromatosis), pituitary apoplexy, drugs.
>CAH 21 hydroxylase deficiency or 11 beta hydroxylase deficiency.

DELAYED PUBERTY IN MALES

FSH,LH	Entity	Cms	Lab
High	Klinefelter≪s syndrome	see above	see above
Low or nl	Constitutionally delayed puberty	Short. Absent secondary sex ch≪cs	Delayed GnrH and adrenarche
Low or nl	Cryptorchidism	undescended testis	

Low or nl	Hypogonadotrophic hypogonadism, tumor, e.g., craniopharyngioma.	Evidence of total pituitary failure. Short, hypogonadal	v Testosterone, FSH, LH, cortisol, T4, TSH, GH, prolactin. Positive MRI
Low or nl	IHH (Idiopathic hypogonadal hypogonadism)≒ v GnRH release	Delayed puberty, short stature, small testes, may have nl pubic hair, no beard or deepening of voice, or cryptorchidism(1) (2) (3). M/F: 5/1	v GnRH, FSH, LH. Nl DHEA and low androgens & estrogens with nl adrenarche, FSH & LH increases with GnRH.
Low or nl	Hypogonadotrophic hypogonadism, GnRH receptor mutation	Similar to above (but Gn RH receptor mutation)	Similar to above but normal GnRH and no response to GnRH
Various	Adult male hypogonadism table	see above	see above

(1) Also, patients may have cleft palate or renal agenesis. With anosmia, it is Kalman≪s syndrome. If accompanied by mental retardation, it is either Laurence-Moon-Biedl or Prader Willi syndrome.
(2) Delayed closure of epipheses due to hopgonadism in puberty.
(3) There is both decreased estrogens and androgens causing short stature and no gynecomastia, unlike Klinefelters which has normal estrogens in males.

DIABETES INSIPIDUS... WORK UP September 11, 2004
Water deprivation test:

First rule out hyperglycemia, hypokalemia, and hypercalcemia as causes of polyuria (Q69, MKSAP 12). Then...

TAKE A HISTORY: Suggestive of primary polydipsia (loss of concentrating gradient in the kidney): gradual onset, polydipsia in an anxious middle aged woman, use of phenothiazine (associated with psychiatric abnormalities but also with the sensation of a dry mouth, or sarcoid (stimulates thirst center).
Causes: **Central DI**: infiltration (histiocytosis, sarcoid), tumor, AD inheritance.
Causes: Nephrogenic DI: ^Ca, vK, lithium, foscarnet, cidovir, ofloxacin, orlistat, amphoptericin, infiltration (SS disease, Sjogren≪s, amyloidosis) and X-lined inheritance.

LOOK AT THE SODIUM: A dilute sodium (Na < 137 mg/L) suggests primary polydipsia. High or high normal sodium suggests central or nephrogenic DI.

WATER DEPRIVATION TEST (May exclude steps 1 & 2 if patient is already dehydrated and hyperosmolar.)
1. Measure plasma osmolality, urine osmolality, and plasma **ADH (AVP=Arginine Vaso Pressin)**.
2. Deprive of water until either serum Na 146+, OR urine osmolality reaches a plateau (2 successive urines with less than 10% change) and patient has lost 2% or more of body weight (1.4 liters of fluid in a 70 KG man).
3. Re-measure plasma osmolality, urine osmolality, and plasma ADH (AVP=Arginine Vaso Pressin.
With increase in serum osmolality, if ADH does not increase, it is central DI; if urine osmolality does not increase with increase in ADH, it is nephrogenic.

RESPONSE TO DESMOPRESSIN (CONFIRMATORY. GIVE AS PART OF SAME SEQUENCE... MAY START HERE IF PATIENT IS ALREADY HYPEROSMOLAR.)
4. Give Desmopressin (AVP V2 receptor agonist), 1 micg subcu or IV.
5. Re-measure plasma osmolality, urine osmolality, and plasma ADH (AVP=Arginine Vaso Pressin.
Increase in urine Osm is 50%+ >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>> Central diabetes insipidus.
Increase in urine Osm is 10%- 50 % and low or blunted ADH >>>>> Central diabetes insipidus.
Increase in urine Osm is < 10% but elevated ADH >>>>>>>>>>>>>>>> Nephrogentic diabetes insipidus
Increase in urine Osm approaches 10% but ADH is appropriate to plasma osmolality >> Primary Polydipsia.

RX: Central DI: Give Desmopressin orally or intranasally. Nephrogenic DI: HCTZ, amiloride & low sodium diet.

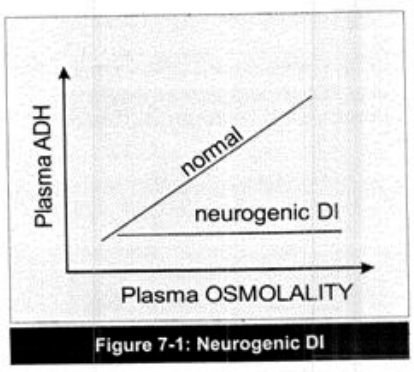


Figure 7-1: Neurogenic DI

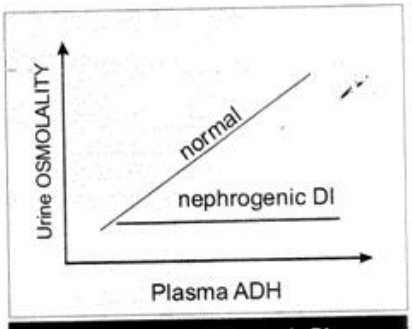


Figure 7-2: Nephrogenic DI

ACROMEGALY

CM≪s:
Gradual progression over years:
Increase soft tissue of face, hands, feet (90%)
Bony enlargement of face (90%)
DJD (70%)
Sweating, skin tags, colonic polyps.
Carpal tunnel syndrome or myopathy (50%)
Diabetes mellitus
HPT, cardiac disease (50%)
Hyperlipidemia
Sleep apnea

Signs of hyperprolactinemia or hypopituitarism in other endocrine systems, due to gland compression: e.g., hypogonadism, amenorrhea, or hypothyroidism. (Due to mass effect of the GH secreting pituitary tumor.)

DIAGNOSIS:
IGF-1 (random measurement) & IGF Binding Protein 3 are both elevated.
If elevated, do a 3 hr GTT and measure Growth Hormone to confirm.
If normal and acromegaly is strongly suspected, do a 3 hr GTT and measure Growth Hormone anyway (more sensitive than the random IGF-1, which depends on liver synthesis).

RX: (shortened life span if untreated. Agromegaly causes CV and musculoskeletal abnormalities)
1. Transphenoidal surgery at a center.

2. Retest. If still increased IGF-1, then give medical RX:
a) Octreotide (somatostatin analogue).
b) Pegvisomant
c) Radiotherapy

3. Do Colonoscopy for colon polyps and cancer!!

Growth hormone replacement therapy is complex and requires daily injections.

In hemochromatosis, phlebotomy reduces hepatosplenomegaly, improves liver function, reverses cardiac failure, and reverses hyperglycemia and skin pigmentation, lowers the risk of liver cancer, and lowers mortality. For unknown reasons, arthropathy and hypogonadism do not improve.

7 dehydrocholesterol >>(skin, sunlight)>>pre-Vit D3>>(skin)>>D3>>(liver)>>25HO D3 (measure this) >> (kidney, PTH) >> 1,25 HO2 D3.

Case
Eruptive xanthomas on back, buttocks, extensor surfaces.
Hepatosplenomegaly.
Recurrent pancreatitis.
Positive family history (AR)
Triglycerides > 1,000 mg/dL.
Dx: Lipoprotein lipase (LPL) deficiency.
Rx: Dietary fat restriction.

ADRENAL INSUFFICIENCY October 26, 2005

SX, SG, or Lab	Secondary or Central AI	Primary AI (Addison≪s Disease)

Fatigue, n,v,abd pain	YES	YES
Salt craving	NO	YES
Pigmentation	Pale	Hyperpigmented
Vitiligo	NO	YES
Sex ch≪cs	Amenorrhea, V libido, hair, testes	NO
DI	YES	NO
Hypothyroid	YES	NO
BP	V	VV
NA	V(often euvolemic, SIADH)	V(volume contraction) (88%)
BUN	NL or <10mg/d, like SIADH	^
Glucose	V	V
K	NL	^
Na in the urine		^
Cl		^
HCO3-		V (Type 4 RTA, non-anion gap)
pH		V
Eosinophilia	YES	YES
Anemia	YES	YES
ACTH (9-52 pg/ml)	Decreased or normal	High
Cortisol/Aldosterone/testosterone,DHEA	V / NL / NL	V / V / V

E.G.: A patient was on prednisone 30mg/day for SLE, was weaned off 6 months ago and is now admitted febrile with BP 70/40. Possible Dx: Functional AI with Subnormal steroid production during critical illness.
*In patients with severe stress, the random cortisol should be >18mcg/dL, unless there is hypoalbuminemia.
*Morning cortisol at 6 - 8AM <3 mcg/dL or >18mcg/dL indicate abnormal and normal adrenal function respectively.
*If doubt remains, give 4 mg I.V. of dexamethasone to treat his hypotension emergently.
*Give 250 mcg cosyntropin (=cortrosyn; see NEJM 1996;335:1206.) (Can be done with 1mcg with fewer false +vs.)
*Measure cortisol at 0, 30 & 60 minutes. Cortisol > 18 mcg/dL excludes primary AI: sensitivity 97%, specificity 95%. Cortisol < 9 mcg/dL >> ^risk of death.. (Cosyntropin stimulates the adrenal-pituitary axis.)
*For stress doses, continue coverage with equivalent of 100mg IV hydrocortisone (or 4 mg Dexamethasone) Q 6Hr until lab results return. (If there is a suggestion of primary AI, add fludrocortisone 50 mcg/day orally both for 7 days.) (See UpToDate, Treatment of Adrenal Insufficiency and MKSAP XIII, Pulmonary & Critical Care Syllabus, Q 95.)
If Secondary AI is suspected, do a low dose (1 mcg) cosyntropin test. A positive test is less than 18 mcg/dL even if the AI is of recent onset or mild AI.
If Primary AI, patients should have CT to determine whether adrenals are small (if so, then this represents autoimmune adrenalitis or adrenoleukodystrophy).
ACTH will be high in primary AI and low in secondary AI but the lab will not report it promptly enough to be useful.
If Secondary AI, patients should have MRI of pituitary and be screened for other hormone deficiencies.
Causes of Primary AI: 80% Auto-immune, 15% TB, the rest: other infections, sarcoid, amyloid, hemochromatosis, mets, infarct or hemorrhage. **Do CT & PPD.**
If suspct. chronic central AI, do 1mcg cosyntropin; get ACTH. If -, do metapyrone test:JAMA2005;294:2481
If albumin is <2.5 mg/dL, there may be low cortisol binding globulin so obtain a concurrent albumin.

Case
Non-Anion Gap acidosis with hyperkalemia.
Dx: Type 4 RTA. Causes: DM with renal insufficiency and hypo-reninemic hypoaldosteronism or Addison≪s disease (hyper-reninemic hypoaldosteronism). Rule out Addison≪s disease:
For suspected acute AI, Do the 250 mcg Cosyntropin ACTH stimulation test.

CUSHING≪S SYNDROME September 12, 2004

	Normal	Obesity, stress, alcohol	Cushing≪s Disease (Central) (60%)	Ectopic ACTH (1) (12%)	Cushing≪s syndrome (2) (10%)
Frequency			80%	10%	10%
24 hr urine free cortisol(3)	< 90 mcg	90-250 mcg	>250 mcg	> 250 mcg	> 250 mcg
11PM salivary cortisol	nl	nl	hi	hi	hi
ACTH level: Normal: 9 - 52 pg/ml			NL or sl ^ e.g., 55 ACTH dependent.	High: e.g. 280 ACTH dependent.	Low (ACTH independent)
CT					of Adrenals
CRH stimulation test (replacing the 8 mg dex suprressinon test) (5)			^ ACTH & cortisol within 4 minutes.	No response	no response
8 mg Dex at 11 PM Serum cortisol 8AM (4)	< 5 mcg / dL	< 5 mcg/ dL	< 5 mcg/dL OR Cortisol is relatively decreased	> 5 mcg/ dL	> 5 mcg/ dL
MRI of pituitary			if negative, do BIPSS		
Bilateral Inferior Petrosal Sinus Sampling, & simultaneous peripheral ACTH			BIPSS/PVS >3 and attempt to lateralize L or R pituitary	BIPSS/PVS <2.5	
CT				Of Lung for carcinoid	

Tests for cushings are said to have a higher rate of false positivity in the hospital: Q85, MKSAP 12.
1. Ectopic tumors secreting ACTH are from lung, either small cell, bronchial carcinoid. Also: thymic tumor, pancreatic islet cell tumor, pheochromocytoma, medullary thyroid carcinoma. Carcinoid tumor sometimes suppresses on hi dose Dexamethasone test, which makes the BIPSS necessary.
2. There is no category for ectopic cortisol... only ectopic ACTH!!
3. Some authors screen with 1 mg dexamethasone PO at 11 PM and serum cortisol at 8 AM: Normal is less than 5 mcg/dL; in all other conditions including obesity, the serum cortisol exceeds 5 mcg/dL.
4. Some interpretations require a level <5 mcg/dL for Central Cushings; however, the cortisol may be above 5 mcg/dL but still suppressed relative to the 1 mg Dex test (e.g., 26 mcg/dL after 1 mg versus 8 mcg/dL after 8 mg). These results point to Cushing≪s Disease (Central Cushings).
RX: Pituitary tumor: 1) Surgery. 2) If unsuccessful (10%), give ketoconazole or metyrapone and do RT (which may take years to become effective. 3) Bilateral adrenalectomy may lead to Nelson≪s syndrome (enlargement of an ACTH secreting tumor).
5. The patient fasts for 4 hours and then 1mcg/kg CRH and ACTH and cortisol are measured at baseline and at intervals after the test..

Ectopic Tumor: As required.

Adrenal Tumor: Surgery. May have central AI for up to 12 months and threfore must be given cortisol RX and taper until pituitary axis recovers.

MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

	MEN 1	MEN 2a	MEN 2b
Pituitary Adenoma	Y		
parathyroid hyperplasia	Y	Y	
Pancreatic insulinoma or gastrinoma	Y		
C-cell hyperplasia leading to Medullary Thyroid Carcinoma		Y	Y
Pheochromocytoma		Y	Y
marfinoid habitus and mucosal neuromas			Y
Comment	3 P≪s	Neck+pheo	Mct,Pheo+

(2a and 2b have been referred to as MEN II and MEN III respectively.

PORPHYRIAS November 28, 2005

	PCT: Porphyria Cutanea Tarda	AIP: Acute Intermittent Porphyria
Cutaneous	Blistering of sun exposed areas	
Liver	Increase AST, ALT; increased risk of hepatocellular ca Increase in porphyrins in liver.	Increase risk of hepatocellular ca.
Neurologic		Abd pain 90% vomit 65% constipation 70% muscle weakness 50% Limb, H & N pain 50% HPT 45% convulsions 15% respiratory paralysis 12%
precipitants	Sun, ETOH, hep C inf≪n, estrogen use, pregnancy, smoking, hemodialysis, iron excess	Pre-menstrual, decreased calories, many drugs, surgery, infection, etoh excess, cigarettes.
urine	increase uroporphyrin	Increase ALA and PBG, aminolevulinic acid, and porphobilinogen (only during an attack; may be normal otherwise)
serum	increase porphyrin (best diagnostic test) > 10 ug/dL	
Other		HypoNatremia, SIADH
Treatment	Cease precipitants, particularly alcohol. Phlebotomy Low dose chloroquine	Avoid certain drugs: AceI, CCBs, sulfa, many many others. IV heme preparations. IV carbohydrates.

CASE:

Confusion, seizures, Chvostek≪s and Trousseau≪s signs, prolonged QT. (Hypomagnesemia will also cause tetany.)

HYPOCALCEMIA. WORK UP?

1) Check ionized calcium. The total plasma Ca=Ca bound to sulfate, lactate & citrate (15%) + Ca bound to albumin (40%... 0.8 mg/dL of Ca for 1gm/dL of Albumin) + Free calcium (45%). The last is the active portion.

PTH and Vitamin D regulate the ionized calcium.

Albumin: For every 1gm/dL deficiency in albumin add 0.8 mg/dL to the measured calcium.

Myeloma. Rarely, a monoclonal protein has a high affinity for Ca, leading to a marked increase in measured calcium but a totally normal ionized calcium and thus no symptoms.

Acute respiratory alkalosis can cause seizures and tetany by increasing the free calcium bound to albumin.

Hyperparathyroidism cancause a normal total calcium with an increase in ionized calcium.

Hyperphosphatemia can reduce ionized and total calcium.

Normal >> Low serum albumin.

Increased. **2) Check PTH**

Low >> Hypomagnesemia, renal wasting (gentamycin), irradiation, surgery, or Hypoparathyroidism: autoimmune, infiltration, idiopathic.

High >> Pancreatitis, ^ PO4, v Vitamin D, Drugs (e.g., phenytoin), or pseudo-hypoparathyroidsm.

HYPOCALCEMIA: Causes and mechanisms.

1. Artifactual:

Every decrease in albumin gm/dL causes a decrease in Ca of 0.8mg/dL.

Calorimetric measurement is effected by gadolinium particularly in renal insufficiency.

2. Loss of Calcium from circulation

a) ^PO4:

1) Chronic: e.g., renal failure decreases 1-25 HO vit D synthesis which decreases Ca absorption and Ca absorption from bone. **^ PO4, ^ PTH, ^ Alk phos** (PO4 and PTH are excreted by the kidney and PTH is metabolized by the kidney). Renal failure >> ^PO4 >> ^PTH

2) Acute: Rhabdomyolysis and tumor lysis cause sudden increase in PO4 which pushes Ca into bone.

b) Acute pancreatitis

c) Osteoblastic metastases

d) I.V. complexing **^ or nl PO4, v PTH, nl Alk phos.**

>Increases in citrate from massive blood transfusion, plasma exchange, or leukopheresis. Here the total Ca is **normal** and clinician must examine the ionized calcium.

>Lactate in sepsis

>foscarnet and EDTA

3. Hypoparathyroidism **^ PO4, v PTH, nl Alk phos**. v PTH secretion >> v renal PO4 excretion.

>Post neck surgery or parathyroidectomy. Hungry bone syndrome

>Idiopathic:

*Familial with childhood onset: Chronic mucocutaneous candidiasis and primary adrenal insufficiency.

*Poly glandular autoimmune dysfunction with primary adrenal and parathyroid insufficiency.

>Infiltration of the gland ≐ rare

>HIV infection ≐ rare

4. Pseudohypoparathyroidism:**^ PO4, ^PTH, nl Alk phos**: Renal resistance to PTH >> ^PO4 & v Ca >>^PTH. Diagnosis: infuse PTH and show no increase in urinary PO4. Albright≪s syndrome: Child, round face, short neck. (Q72, MKSAP 12.)

5. Magnesium defiency: nl PO4, nl or v PTH.

>V Mg defiency of Alcoholism or anorexia causes PTH resistance. VVV Mg def >> v PTH secretion.

>Cyslplatinin causes hypomagnesemia.

6. Vitamin D deficiency: **v PO4, ^ PTH, ^ Alk phos, v 25HOVitD3**. v 25HOVitD3 >> vCa >> ^PTH >> v PO4.

>Bone pain & bone tenderness; proximal muscle weakn ess; pseudofractures in femur, pubic bone, scapula

>Malabsorption or decreased vitamin D intake ≐ hypovitaminosis.

>Liver disease: Decreased metabolism in liver.

>Kidney disease: Decreased calcitriol production by kidney.

>DPH, phenobarb, steroids >> increased microsomal enzyme activity >> breakdown of vit D.

7. Drugs and toxins:

>Drugs: 5FU + leucovorin causes decreases calcitriol production.

Cysplatinin causes hypomagnesemia.

>Fluoride intoxication

Case 50 y.o. Northern dwelling female shut in.
CM: Bone Pain in lower weight bearing extremities & proximal muscle weakness, waddling gait.
Lab: v 25 HO vit D3, v or low nl Ca, v PO4, ^ Parathyroid hormone
Radiologic: Pseudo fractures at Looser Zones ≐ e.g,. Femoral neck, pelvis
Dx: Differential diagnosis of bone pain: osteomalacia, Paget≪s disease, multiple myeloma, osteoporosis.
Here the diagnosis is: Osteomalacia (In children, there is bowing of tibia: rickets.)
Causes: Vast majority of cases are vit D deficiency (due to sprue, GI surgery, pancreatitis, or Prim Biliary Cirrhosis.)
Other causes: chronic Renal Failure, Proximal RTA, and mineralization inhibitors (endemic fluorosis, aluminum, bisphonates other than alendronate).

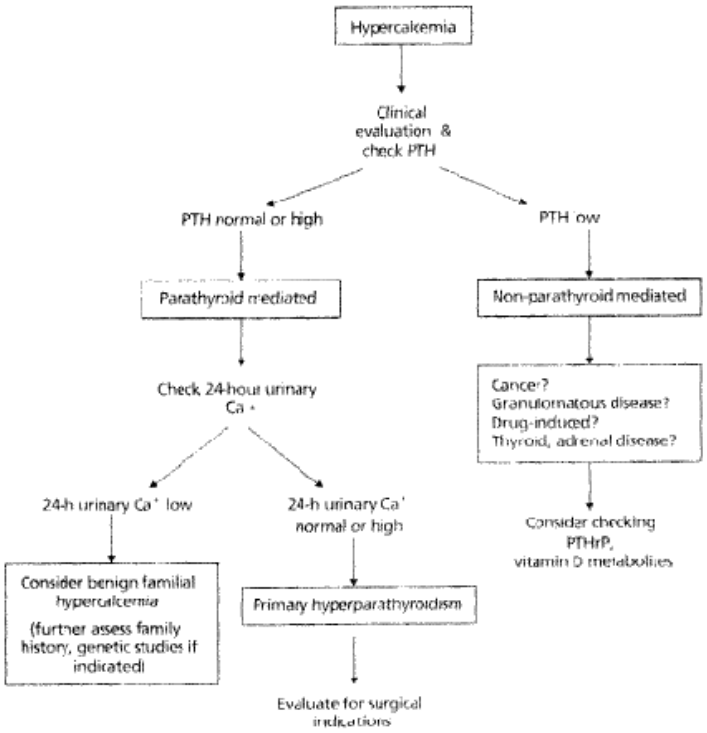
Laboratory Findings in the Different Causes of Osteomalacia and Osteoporosis

Disorder	Serum phosphate	Serum calcium	Serum alkaline phosphatase
Vitamin D deficiency with secondary hyperparathyroidism	Low	Low to low normal	Elevated
Conditions associated with urinary wasting	Low	Normal	Normal
Metabolic acidosis	Normal	Normal	Normal
Proximal renal tubular acidosis	Low	Normal	Normal
Hypophosphatasia	Normal	Normal	Low
Osteogenesis imperfecta and axial osteomalacia	Normal	Normal	Normal
Osteoporosis	Normal	Normal	Normal

SECONDARY CAUSES OF OSTEOPOROSIS:
Alcoholism
ENDOCRINE
Hypogonadism

Hyperthyroidism
Hyperparathyroidism
Cushings syndrome

Parathyroid carcinoma



PTHrP is cause of ↑ Ca in Malignancy except for some breast Ca, lymphoma, & myeloma

FIGURE 7.
Proposed evaluation of the routine patient with hypercalcemia (renal function normal).

PTH = parathyroid hormone, PTHrP = parathyroid hormone-related protein

Idiopathic hypercalciuria (Q44, MKSAP 13)
Thalasemia
Multiple myeloma
Malabsorption
Meds; Heparin, Prednisone
Case:
Weakness
Constipation
Hypertension
Stones
Pancreatitis

CM≪s: Stones, Bones, Abdominal groans, & psychiatric overtones. Constipation, n,v, abd pain, confusion, depression, coma, nephrolithiasis, Type 1 RTA, polyuria, v QT interval, & arrythmias.
Check Albumin and total protein for artifactual increase.
Check PTH

1) If PTH is High, do 24 hr urinary calcium or Fractional excretion of Calcium(CAur/CRur)/(CAser/CRser).
If high (urinary Ca > 24 mg/kg/24hr OR Fractional excretion of Calcium>1%), this indicates Prim. Hyperparathyroidism (Although PTH increases Ca reabsorption in the distal tubule, the increased Ca delivery overwhelms this and Ca in urine is normal or increased.) There will be nl or v PO4, nl 25HO Vit D3.

*Single adenoma (most common cause of ^ Ca in OPD)
*Multiple adenomas
*Parathyroid hyperplasia (MEN I:Pituitary & Pancreas, or MEN II: pheo & MCT w/ ^ calcitonin)

*Parathyroid carcinoma

If Low (24 urine Ca < 1mg/kg or FEC < 1%), consider benign familial hypercalcemia: ≙familial hypocalciuric hypercalcemia≙: mild hypercalcemia & ^PTH leads to net Ca reabsorption. Chromosome 3.

2) If PTH is Low, this means it is non parathyroid mediated:

Work up primary hyper parathyrodiusm with technetium 99M sestamibi parathyroid scan and then Ultrasound.

Blastic cancers (most common cause in hospital): nl or v PO4, nl 25HO Vit D3
Lytic cancers: MM, breast ca, lymphoma: nl or ^ PO4, nl 25HO Vit D3
Granulomatous: sarcoid (^ production of 1-25HO Vit D in macrophages) or TB nl or ^PO4, nl 25HO Vit D3
Hypercalcuria.
Vit D intoxication: nl or ^ PO4, ^^ 25 HO Vit D3.
Other causes: **Thiazides, hyperthyroidism**, immobilization, milk alkali syndrome (calcium carbonate), lithium, Addison≪s disease.

Milk Alkali syndrome: ^ C, ^ PO4 (2ndary to v PTH), nl Vit D, ^ HCO3. ^ Creatinine due to ^ Ca.

Treatment for hypercalcemia of malignancy: (1) Hydration with normal saline. (2) Bisphosphonates or calcitonin.

Three common causes of constipation include hypothyroidism, hypercalcemia (need the ablumin), and GI cancer.

Heparin and cyclosporine cause osteoporosis.

Hypophosphatemia

Presentation: Muscle weakness, encephalopathy, hemolysis, platelet dysfunciton.

Causes:

Increased Excretion:^PTH: primary hyperparathyroidism, vit D deficiency
Extra-cellular to intracellular shift: Refeading, insulin, sepsis, burns, hungry bone syndrome.
Decreased absorption (least common): Diarrhea, steatorrhea, aluminum or Magnesium.

Paget's has increased osteoblastic activity, osteoclastic activity, vascularity, and bone fibrosis and may exhibit bowing of a femur.

Steroid mechanisms of bone loss:
>Inhibition of Ca absorption from GI tract
>Increased Ca loss via kidneys
>Inhibition of ACTH >> decreased adrenal sex steroid synthesis.
>Proximal muscle weakness >> inactivity.

Parathyroid adenomas can occur in tracheo-esophogeal groove, retropharyngeal space, at the angle of the jaw or the anterior mediastinum. 5% of people have more than four glands.

Case
20 y.o. woman, multiple fractures since childhood, kyphoscoliosis, blue sclerae, blue-gray teeth, conductive hearing loss, AD family history.
Dx: osteogenesis imperfecta: Defect of Type I procollagen

Case
Young man, long thin extremities,pectus excavatum, murmurs of mitral valve prolapse and aortic insufficiency, ectopia lentis (abnormal vision), arachnodactylty, autosomal recessive family history.
Dx: Marfan Syndrome. Fibrillin & glycoprotein 350 kDa.

Hypoglycemia:
1. Insulinoma: glucose < 45 mg/dL and insulin > 5 microunites/ml
2. ILGF-2 from mesenchymal tumors.
3. Tumor consumption.
4. Starvation, alcoholism, and liver dysfunciton.

5. Addisons, disease, Pituitary failure of ACTH and growth hormone.
Hypercalcemia develops in **chronic renal failure** due tertiary hyperparathyroidism due to gradually autonomously functioning parathyroid gland. The calcium is increased, patient develops osteitis fibrosa with fractures. Patient is treated with aluminum salts ≐ ≙binders≙.

ADRENAL INCIDENTALOMA WORK UP October 25, 2005 (WF Young, Jr. NEJM 2007;356:601).

Two concerns exist: 1) a hormone secreting tumor ≐ about 30% , cortisol, pheo, aldo ≐ causing diabetes, osteoporosis or hypertension, and 2) cancer ≐ primary or metastatic

1) Work up for hormone secreting tumor (a functioning tumor indicates need for adrenalectomy):
   a) Cortisol tumor (25%): 24 urine free cortisol. NL is less than 90 mcg.
   b) Pheo (5%): Measure a plasma free metanephrine
   c) Primary Aldosteronism:

(1) An AM aldosterone (ng/dL)/Plasma renin (ng/ml) > 30 plus a morning aldosterone >20 ng/dL indicates hyperaldosteronism. This has to be verified with a short stay infusion of 2L of NS over 4 hours in recumbant patient. PAC < 6 ng/dL=Normal; > 10 ng/dL = hyperaldo.

2) Malignancy work up: Bottom line: Size > 4cm goes to surgery, while size < 3 cm are followed.
Size > 6 cm have a 25% probability of malignancy.
Size < 4 cm have a 2% malignancy probability; see below.
Size < 3 cm should be followed for 4 years with repeat CT every 6 to 12 months.

CT FEATURES OF BENIGN VERSUS MALIGNANT TUMORS

	Border	homog eneous	Intensity like liver	Vascularity/ Enchancing	Necrosis, bleed, calcification
Benign	Smooth Round or oval	Yes	Yes (≤10 Hounsfield units)	Low vascularity Rapid washout Non-enhancing	rare
Malignant	Irregular	No	No (>10HU)	High vascularity Slow washout Enhancing.	Common

EVALUATION OF PITUITARY INCIDENTALOMA:
If 10+ mm, do 1) visual fields, and 2) Prolactin, T4, IGF 1, 24 hour urinary CTSDs, FSH, LH.
If <10 mm and there are clinical abnormalities, do the appropriate tests.
If <10 mm and no clinical abnormalities, do prolactin only.
If 5-9 mm, do MRI in 2 years; if stable, then no further work up is necessary.
If < 5 mm, do no further testing after prolactin.

Beta hydroxy butyrate is converted into aceto-acetate and acetone. Nitroprusside reacts with aceto-acetate and acetone but not beta hydroxybutyrate. Beta hydroxy butyrate makes up 75% of ketones in DKA, but this can reach 90% in alcoholic keto-acidosis or concurrent lactic acidosis. Hence keto-acids may not be measured. One way to follow the improvement is to look at the correction of the anion gap. Another way is to add hydrogen peroxide to the urine to convert the Beta hydroxybutyrate to acetoacetate and then measure the aceto-acetate.

GLUCOSE METABOLISM

Impaired fasting glucose (fasting gluc 110-125)>> ^ CV risk; 40% get frank diabetes in 10 years.

People with diabetes and microalbuminuria have 2x the CVD risk of those with normal urine albumin (NKF-KDOQ1 2007; NIDDK 2004).

Insulin has an anti-natriuretic effect and may contribute to poor BP control in those on insulin.

Patients with diabetic kidney disease benefit more from protein restriction (10% of total calories) than those with nondiabetic kidney disease; however, a diet than provides protein from sources other than red meat may be a reasonable alternative to the 10% protein restriction (NKF-KDOQ1 2007).

Chlorthalidone is more effective than HCTZ in achieving BP control (Khosla 2005).

In diabetes, ^ TG and v HDL but nl VLDL. However, VLDL particles are more atherogenic, smaller, denser and more easily glycated and are more susceptible to oxidation. Goals for diabetics, regardless of CV status:LDL<75, TG<150, HDL >45 in men and >55 mg/dL in women and triglycerides <150 mg/dL.

Highest incidence of DM 1: Scandinavia. Highest incidence of DM 2: Pacific Islands.

In Type 1 DM the monozygotic concordance is 25%, while dizygotic is 5%.

Case

14 y.o. presents with non-ketotic hyperglycemia:

□ of 1st degree relatives have diabetes. AD with complete penetrance.

Mutation of glucokinase gene on Chromosome 7

Dx: maturity-onset diabetes of the young (MODY).

Monitoring those on oral hypoglycemic agents or those who are not adjusting insulin (e.g., single daily ultralente) require hemoglobin A1c Q3 months, occasional random sugars, but no daily glucose checks.

HA1c will be lower than expected in shortened RBC life span (G6PD, SSA) and longer than expected in long RBC life span (B12 or folate deficiency).

Also note that HgbA1c can be falsely low with hemolysis, liver disease, or splenomegaly, with transfusions, HIV infection, dialysis, and pregnancy, and can be falsely high in patients with splenectomy, iron defiency, and in the elderly (Pallais NEJM 2011;364:957)..

Case

40 y.o. woman with Fasting glucose is 113 and 119 mg/dL.

Dx: impaired fasting glucose (IFG).

Increased risk for CV disease and progression.

Management: Diet and exercise reduces progression to frank diabetes.

Polyglandular syndromes

	Skin	Other	Hypogonadism & AI.
Type I	Chronic mucocutaneous candidiasis	v PTH: 89%	Hypogonadism 45% Adrenal insufficiency: 60%
Type II*		Autoimmune thyroiditis: 70% DM 1: 50%	Hypogonadism 35% Adrenal insufficiency 100%

*AKA ≙Schmidt≪s syndrome≙.

DIABETIC AUTONOMIC NEUROPATHY: Decreased CV reflexes, postural hypotension, tachycardia, gastroparesis, diarrhea, neurogenic bladder, and impotence. Gabapentin is used in peripheral neuropathy of DM: JAMA 1998; 280: 1831.

Decreased renal function causes decreased insulin clearnance and hypoglycemia (Q18, MKSAP 13).

Albuminuria occurs with exercise (Q 66, p 98).

Antibodies to Glutamic Acid Decarboxylase (Anti GAD) can be used to identify Type I DM

Symptoms of nocturnal hypoglycemia can be nightmares and waking in cold sweat. Check glucose at 3 AM.

The Somogyi phenomenon ≐ high FBS in AM due to overnight hypoglycemia owing to excess evening insulin ≐ is debated. In any event, the ≙dawn phenomenon≙ ≐ the rise in glucose from 3AM to 8AM ≐ is far more common than the Somogyi phenomenon and is treated by changing the timing of NPH from Supper NPH to HS NPH.(UpToDate).

Case
78 y.o. woman with BP 146/94 on two occasions, FBS 238 on two occasions, chol 287 and TG 681. ? Management procedure.
Answer: Diet, exercise, and ACEI (?) Per med study.
? I would argue that the cholesterol and TG are not going to be controlled by diet alone. Further, w/u for 2ndary hpt and baseline Creatinine important before beginning ACEI, and should be started on HCTZ first.

APPROACH TO PATIENT WITH DKA
Initial Assessment:
Clinical: Determine magnitude of dehydration, hyperosmolality, and acidosis.
Lab: Glucose, ketones, pH, potassium, renal function, CBC.
Consider sepsis, CVA, or other precipitants

Hour 1:
Fluids: NS at rate to assure normal circulation and fluid output. Usually 500-1,000 ml/Hr
Insulin: Load with 5 - 10 Units of regular IV. Then IV infusion at 0.1 U/kg/hr.
Potassium: 10-30 meq/hr when K is < 5.0 meq/L and urine output is good.
Bicarb: Only if pH < 7.0 and circulatory collapse: 50-100 meq Nabicarb in 0.45% NS over 1hr.

Hour 2:
Fluids: Saline at 500 ml/hr. Maintain calculated osmolality > 285 mosm/L.
Insulin: Adjust infusion so glucose falls about 90 mg/dL but not below 200 mg/dL.
Start 5% glucose, when glucose approaches 200 mg/dL.
Potassium: Keep level between 4 and 5 meq/L
Observe for cognitive and neurologic symptoms (cerebral edema)

Hours 5-8:
Fluids: NS at 250 mL/hr.
Insulin: infuse until keto-acidosis has cleared and pH > 7.35.
Potassium: continue at 10-30 meq/hr
Phophate: Replace if serum phosphate is < 2.0 mg/dL.

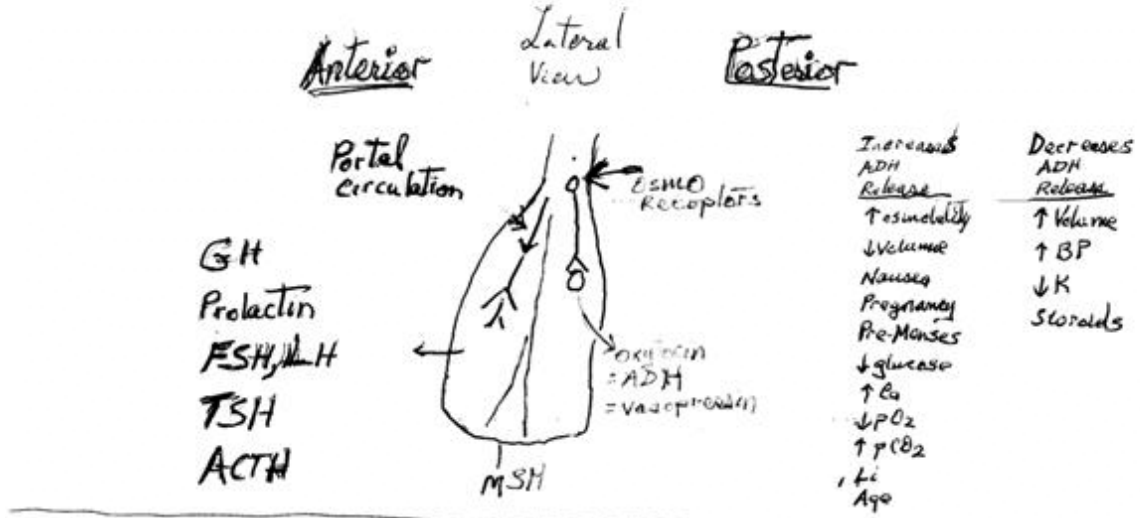
Hours 8-24:
Start oral fluids.

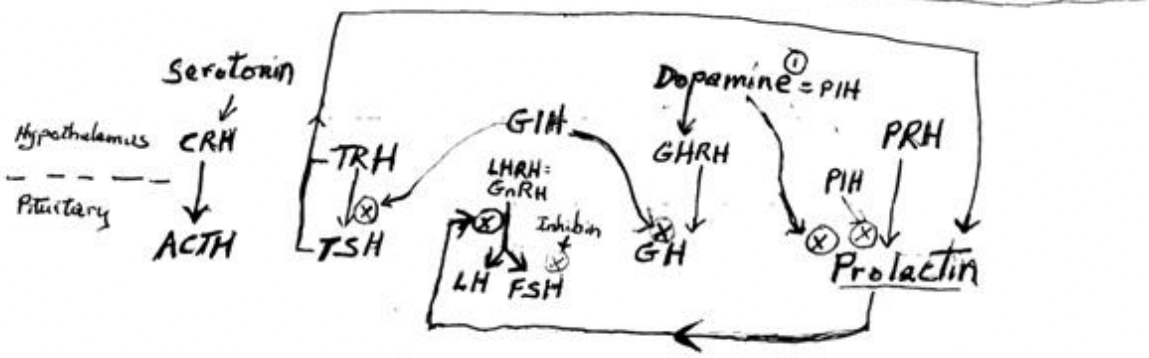
COMPLICATIONS OF DKA:
DIC, acidosis, hypokalemia, hypophosphatemia, hypoglycemia, and cerebral edema.
Persistent acidosis can be due to alcohol withdrawal, volume expansion acidosis (due to lack of bicarbonate consumption), premature discontinuation of insulin.

Whipple≪s Triad for Hypoglycemia:
1) Sx≪s of hypoglycemia: e.g., tachycardia, sweating, altered mental status.
2) Low glucose at time of sx≪s.
3) Relief of Sx≪ when glucose is raised (e.g., with glucagon or with glucose administration).

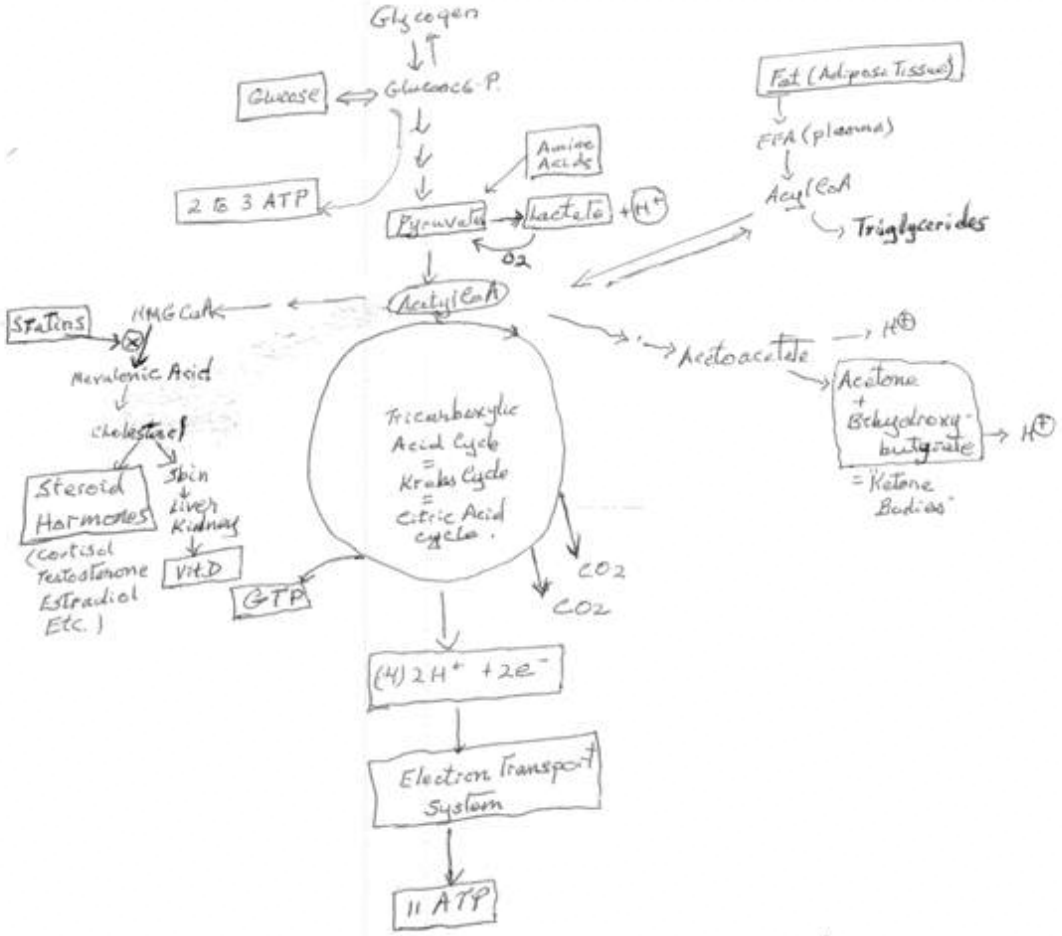
Post prandial hypoglycemia: eat complex carbohydrates, eat small but more frequent meals, use propantheline to delay gastric emptying if post gastrectomy.

Sulfonureas stimulate insulin secretion (including C-peptide), and therefore, when the c-peptide is high in parallel with insulin, it does NOT point to insulinoma instead of factitious hypoglycemia due to sulfonureas. (See Q 84, p 102, MKSAP 13).





① Estrogen, chlorpromazine (Thorazine) and phenothiazines, metoclopramide, + amitryptiline will deplete dopamine stores, causing an increase in prolactin and decrease in LH, FSH.



When oxygen is lacking in the tissues as in hypoperfusion, Lactate can not be converted back to pyruvate and therefore lactate and H^+ accumulate causing lactic acidosis.

When insulin is lacking, glycogen and fat and amino acids are consumed. Glycogen and amino acid consumption cause hyperglycemia. Fat catabolism causes Aceto-acetate, acetone, and β-hydroxybutyrate and H^+ formation OR "Keto Acidosis". In alcoholism, decreased carbohydrate intake reduces insulin and causes keto-acidosis > but primarily β-Hydroxybutyrate

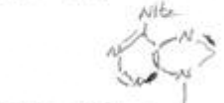
Glucose $C_6H_{12}O_6$ = a Saccharide

Glycogen = Poly-saccharide = chains of saccharides
More than 100 saccharide elements.
AKA Animal starch.

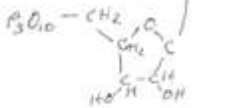
Pyruvate : $C_3O_3H_4$ $CH_2=\overset{OH}{\underset{|}{C}}-CO_2H$

$CH_3-\overset{OH}{\underset{|}{C}}H-CO_2H$

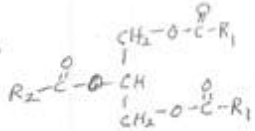
Lactate $C_3O_3H_6$



Adenosine Tri Phosphate (ATP)



Triglycerides :



R_1 is $C_{17}H_{35}$ or thereabouts.

Acetyl CoA $CH_3-\overset{O}{\underset{\|}{C}}-S-C_2H_3N-C_3O_3H_{14}N-P_2O_2-C_5O_2P-C_5N_5H_2$

Acetyl — Mercapto-ethyl-amine — Pantothenic Acid — Ribose — Adenine

Citric Acid $C_6O_7H_8$ $CO_2H-CH_2-\overset{OH}{\underset{|}{C}}(CO_2H)-CH_2-CO_2H$

"Ketone Bodies"

- Aceto acetate $C_4O_3H_4$ $CH_3-\overset{O}{\underset{\|}{C}}-CH_2-CO_2H$ → CO_2 → $CH_3-\overset{O}{\underset{\|}{C}}-CH_3$ Acetone C_3OH_6
- β Hydroxy butyrate $C_4O_3H_8$ $CH_3-\overset{OH}{\underset{|}{C}}H-CH_2-CO_2H$ (NADH + H⁺ → NAD⁺)

(Urine Tests for ketone bodies do not detect β Hydroxybutyrate which may be present in diabetics on low calorie diets, high fat diets, stress, exercise, fasting, or alcoholics. In alcoholic keto-acidosis, more than 40% of ketones can be β hydroxybutyrate (rather than 75% as in DKA). The β hydroxybutyrate can be converted in the lab to aceto-acetate (detectable) by adding H_2O_2 to the urine.)

ADRENAL HORMONES

Adrenal Cortex
Zona Glomerulosa >> Aldosterone
Zona Fasciculata >> Cortisol
Zona Reticularis >> Dehydroepiandrosterone, Androstenedione

Adrenal Meddula >> Epinephrine, Norepinephrine, Dopamine

Epinephrine is the major hormone from the adrenal medulla and does not interact with post-synaptic sympathetic ganlgia. Norepinephrine is the usual hormone in the post-synaptic sympathetic ganglia.

HYPERPROLACTINEMIA: Secondary causes:
>Pituitary mass blocking dopamine release.
>Psychotropic meds blocking dopamine: antipsychotics, tricyclics, SSRIs, methyldopa, metaclopramide, cocaine, opioids.
>Hypothyroidism
>Neurogenic: chest wall and spinal cord lesions.

>Mild increases in prolactin and large pituitary tumors do not have prolactinomas and should not be treated with prolactin lowering drugs.
>For all non-prolactin pituitary tumors, the treatment is transphenoidal surgery.

Diabetic mononeuropathyies:
*Median and ulnar nerves: wrist drop.
*3,4, & 6th cranial nerves.
*Sciatic or femoral nerves: foot drop.

Diabetic amyotrophy: Proximal muscle pain, atrophy and fasciculations.

Familial hypercholesterolemia: xanthelasma (eyes); tendinous xanthomata.

TG > 1,000 mg/dL >>> pancreatitis, eruptive xanthomata, lipemia retinalis.

HYPOPITUITARISM:
*Mass lesions in the sellar or suprasellar region:
*Pituitary adenoma
*Non-pituitary mass: craniopharyngioma, meningioma, metastases, aneurysm.
*Vascular
*Infiltrative: sarcoid; hemachromatosis.
*Infection
*Genetic PROP 1 mutations; pituitary 1 mutaitions.