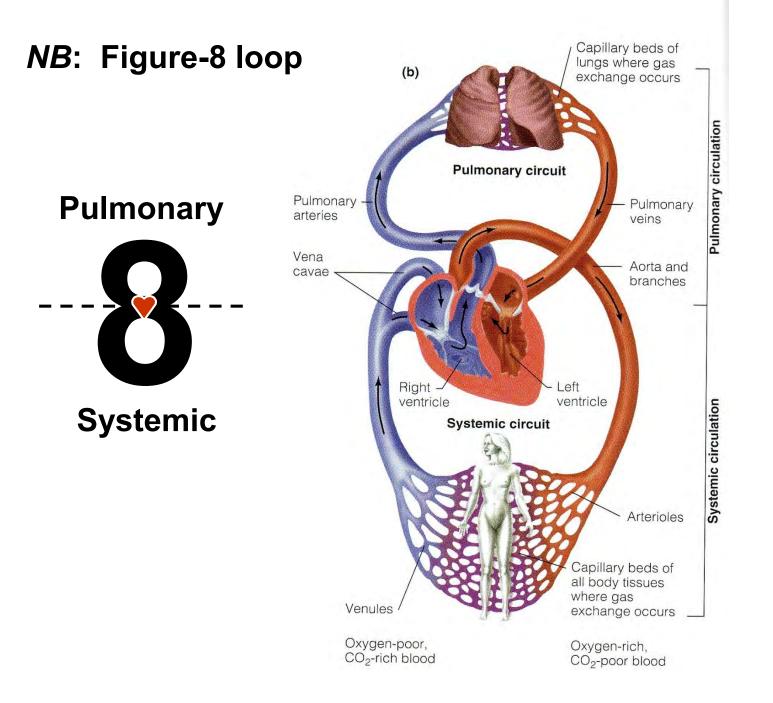
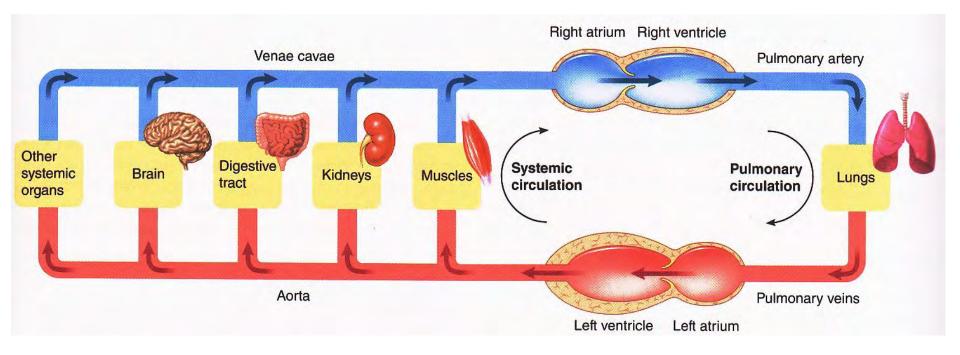
BI 121 Lecture 8



- I. <u>Announcements</u> Tomorrow HR & BP Lab 4 + <u>Required</u> <u>Notebook Check</u>. Turn in today? Thurs Blood Chemistry Lab 5. Please read Lab 5 twice prior to Thursday. Thanks!
- II. <u>Cardiovascular System</u> LS 2012 ch 9, Torstar Books 1984, DC 2013 Module 4, Guyton & Hall (G&H) 2011 +...
 - A. Circulatory vs Cardiovascular (CV)? cf + parts LS pp 229, CV vs Lymphatic, DC pp 23, 31
 - B. CV Pulmonary & Systemic circuits DC fig 4-1 p 24, LS fig 9-2b p 231
 - C. Arteries, capillaries, veins G&H + Torstar
 - D. Varicose veins? Phlebitis? DC
 - E. Values, inlets, box, chambers, values, inlets, outlets
 LS fig 9-4 p 233, fig 9-2a p 231; DC pp 23-6
 - F. Normal vs abnormal blood flow thru ***** & CV system Billy has a hole in his ***** SI Fox 2009 fig 13.16, 13.17
- III. Comments on Midterm & Tests Returned



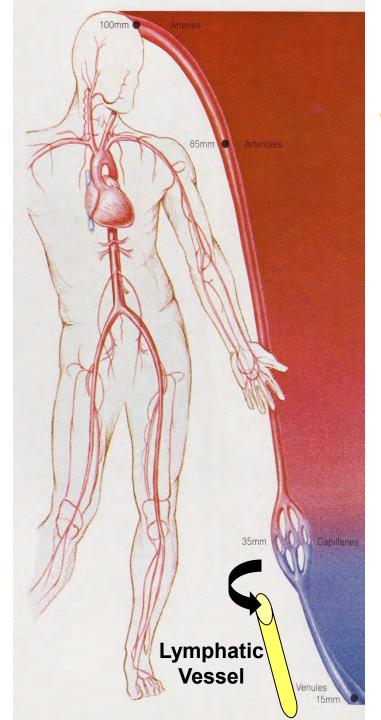
Dual Pump Action & Parallel Circulation



LS 2012 fig 9-2b p 231

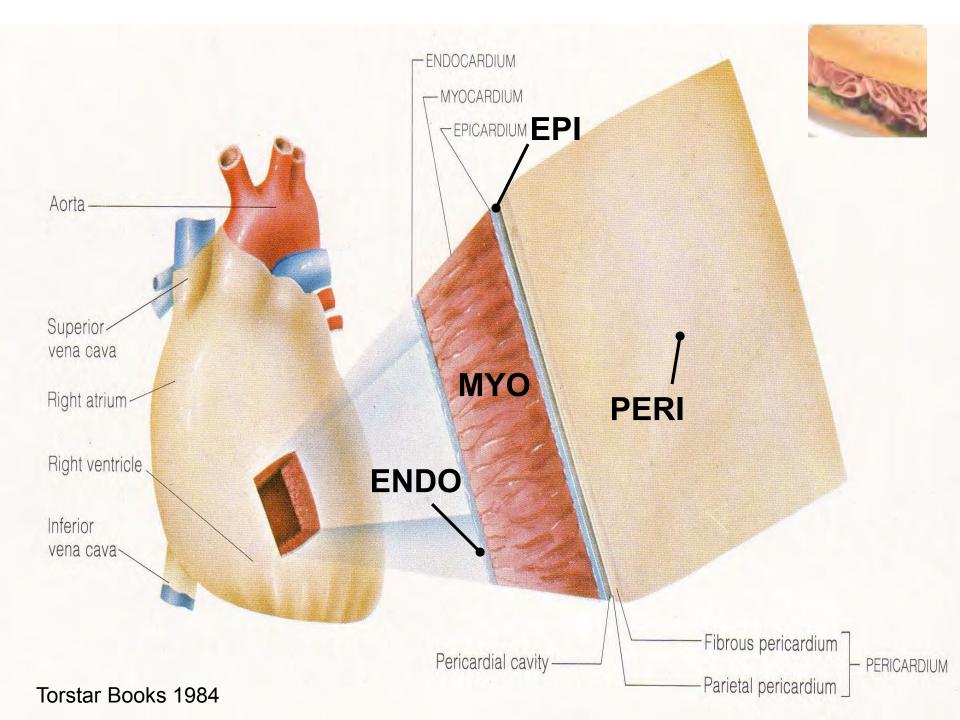
Lymphatic System Blockage in Elephantiasis from Mosquito-borne Parasitic Filaria Worm

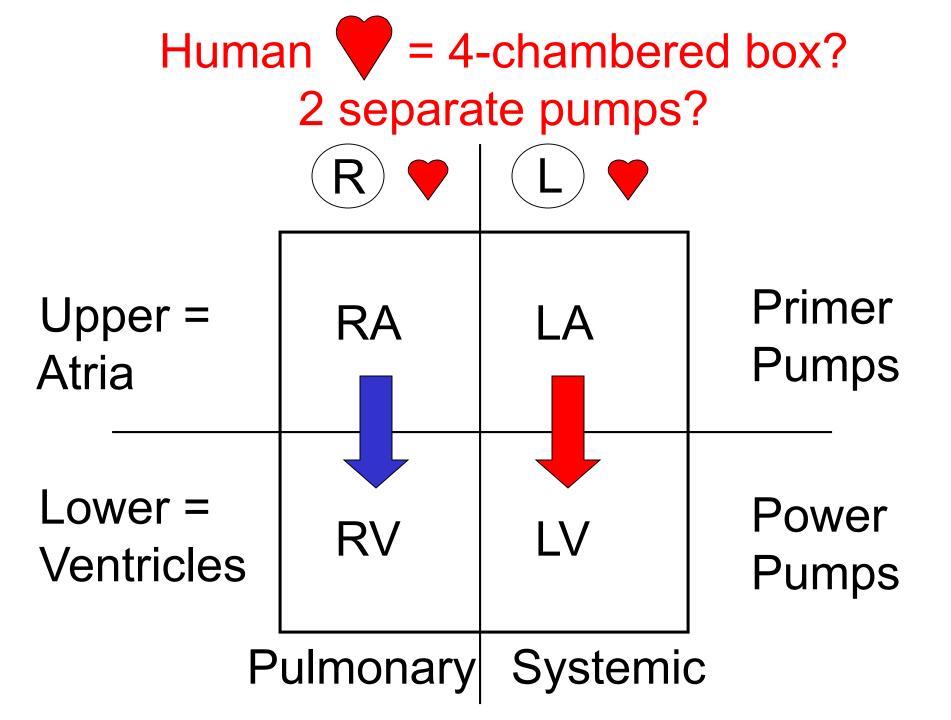




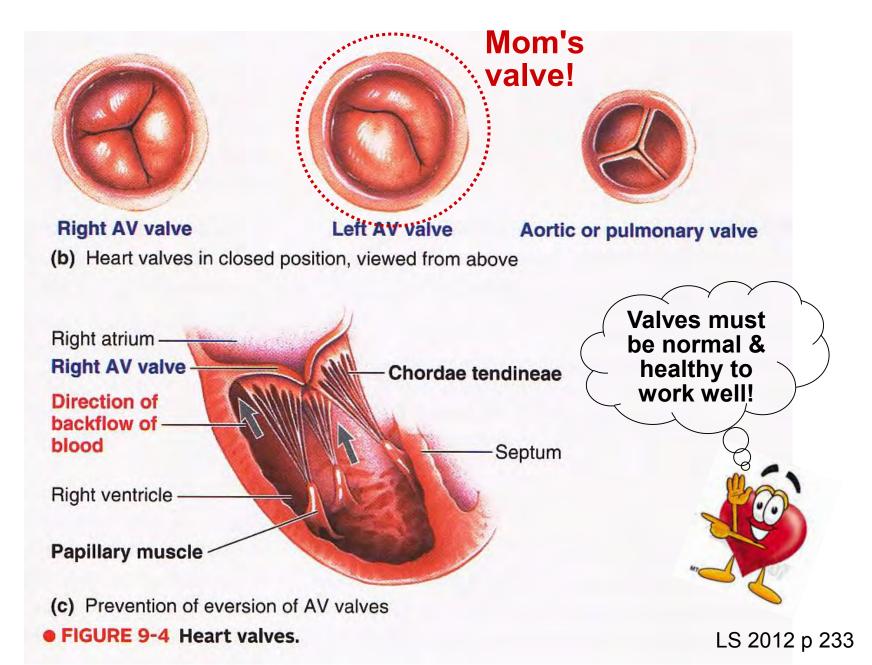
Lymphatics collect runoff & are parallel to venules/small veins!

Torstar Books 1984

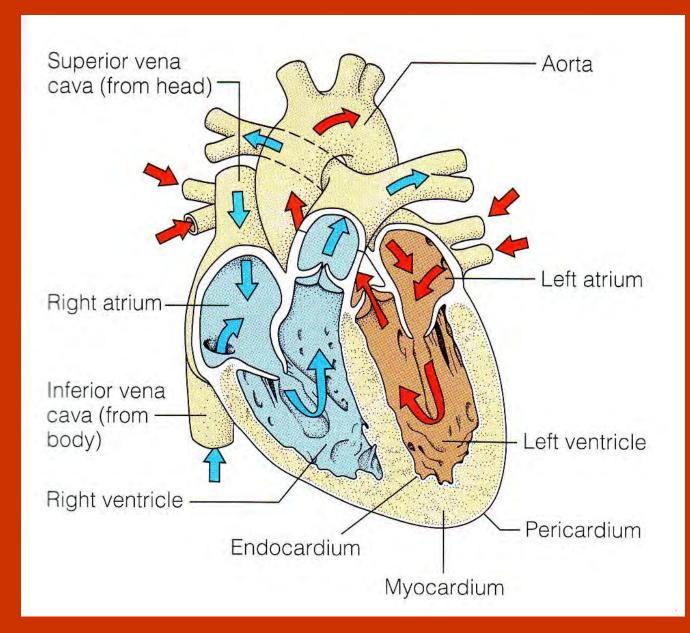




Heart Valves Ensure Unidirectional Blood Flow!



Veins → Atria → Ventricles → Arteries



BI 121 Lecture 9

I. <u>Announcements</u> Lab notebook due today! Lab 4 HR & BP. Thursday, Lab 5 Blood Chemistry. Read pp 5-1 thru 5-6 x2. Q?

II. <u>Overview of Labs</u> HR & BP. Blood chem lab review

III. <u>Cardiovascular Connections</u> LS 2012 ch 9

A. Cardiac cyle? Contract-relax!

B. **\vec{b}**'s electrical highway + Pacemaker activity

LS fig 9-7 p 235, tab 9-1 p 236, fig 9-8 p 237

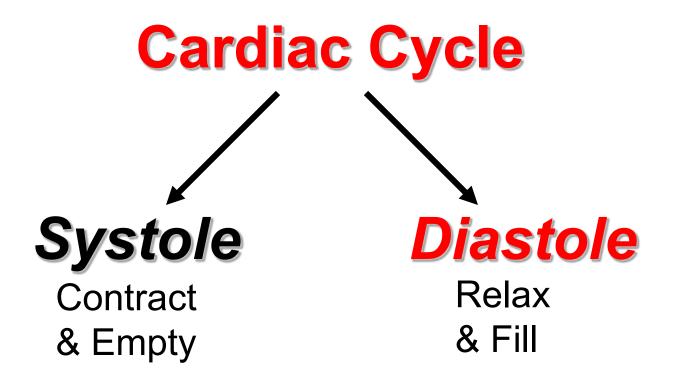
- C. NHLBI & AHA websites
- *IV.<u>CV Physiology in the News</u>* NHLBI & AHA websites

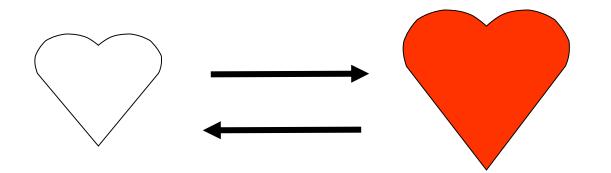
Exercise & Nic? Exercise guidelines: ACSM, AHA, CDC

- V. <u>CV Pathophysiology & Risk Reduction</u> LS ch 9, 10 +...
 - A. AMI, CVA, CVD, PVD, TIA, HTN? + surgical treatments
 - B. Atherosclerosis? LS fig 9-27, 9-25, 9-26 pp 266-8
 - C. How to minimize risk of CVDs? Treatment triad: Exercise, Diet, Drugs + Surgery
 - D. Food choices make a difference? What's HAPOC?

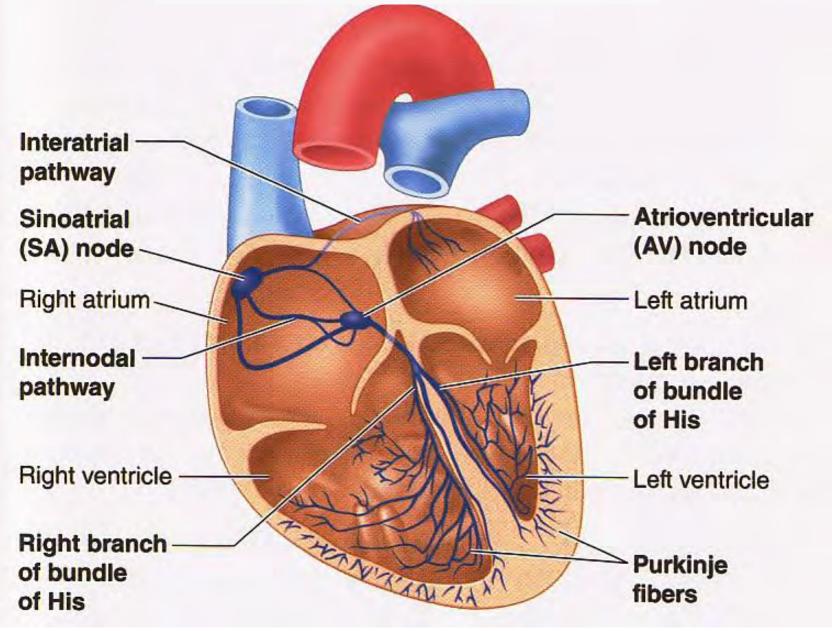


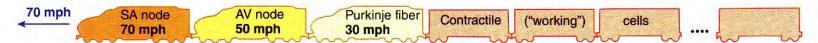




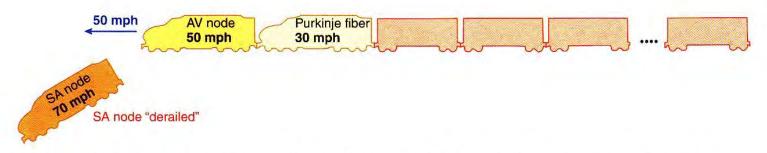


Heart's Electrical Highway!

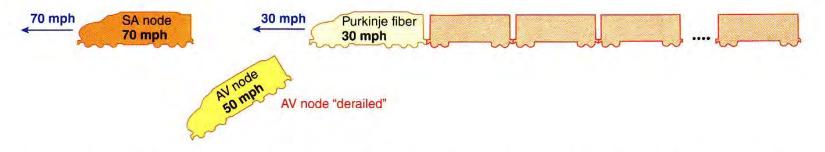




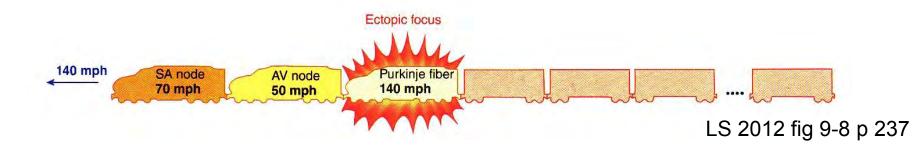
(a) Normal pacemaker activity: Whole train will go 70 mph (heart rate set by SA node, the fastest autorhythmic tissue).



(b) Takeover of pacemaker activity by AV node when the SA node is nonfunctional: Train will go **50 mph** (the next fastest autorhythmic tissue, the AV node, will set the heart rate).

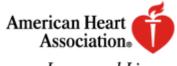


(c) Takeover of ventricular rate by the slower ventricular autorhythmic tissue in complete heart block: First part of train will go **70 mph**; last part will go **30 mph** (atria will be driven by SA node; ventricles will assume own, much slower rhythm).



American Heart Association (AHA) & National Heart, Lung & Blood Institute

http://www.my.americanheart.org



Learn and Live ...

http://www.nhlbi.nih.gov/

Department of Health and Human Services · National Institutes of Health

National Heart Lung and Blood Institute

People Science Health





Do moderately intense aerobic exercise 30 min/d, 5 d/wk

OR

Do vigorously intense aerobic exercise 20 min/d, 3 d/wk

AND

Do 8-10 strength-training exercises 8-12 repetitions/each exercise, 2 d/wk

CVDs

AMI

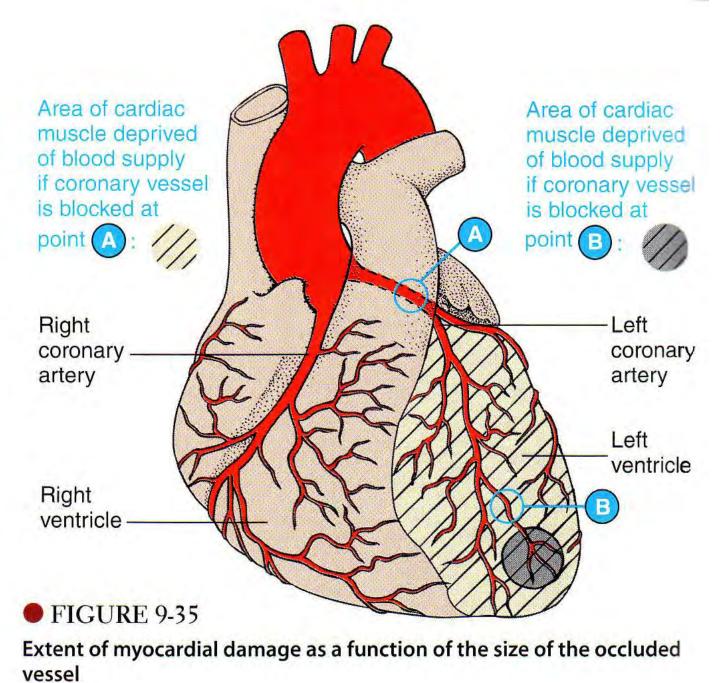
TIA



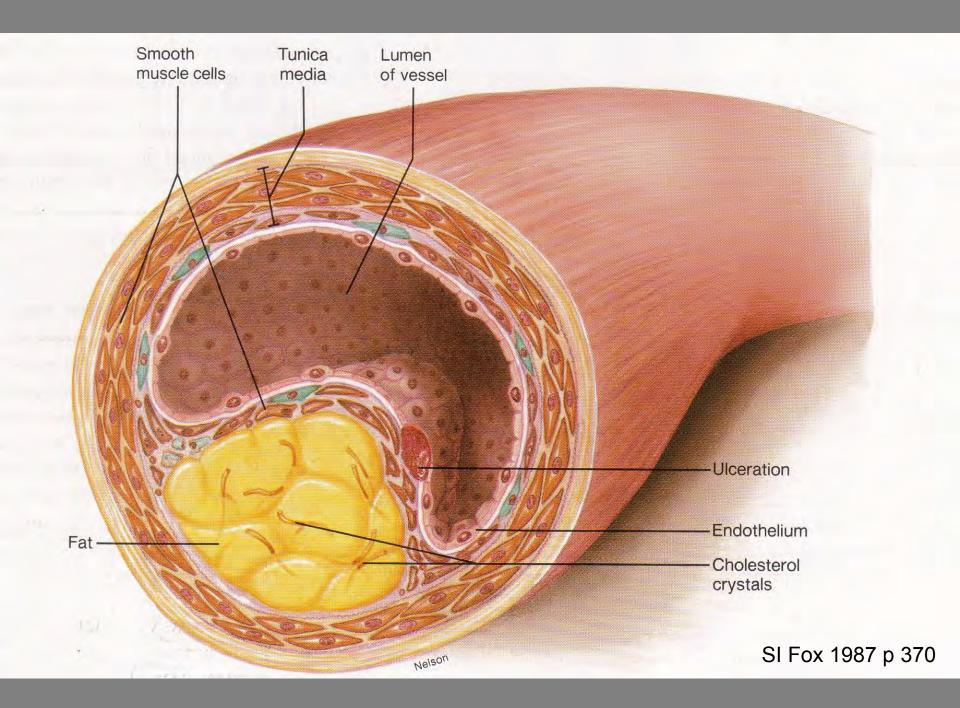


HTN

PVD



L Sherwood 2004 p 336



Treatment Triad

<u>NB</u>: Last blasted resort!!

Drugs/Surgery



Dietary Modification

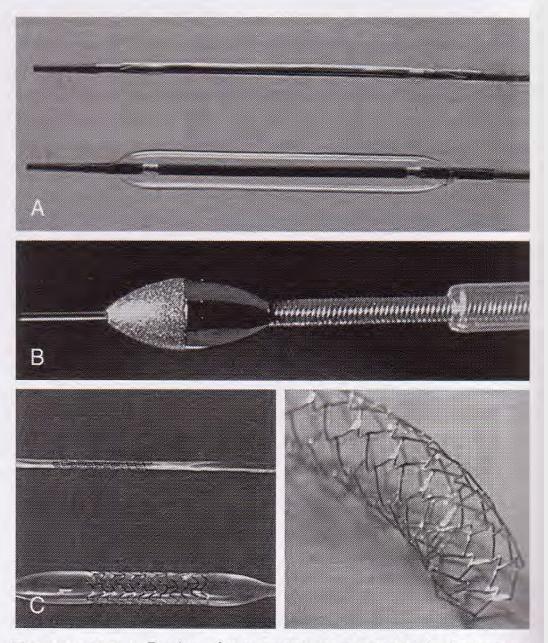
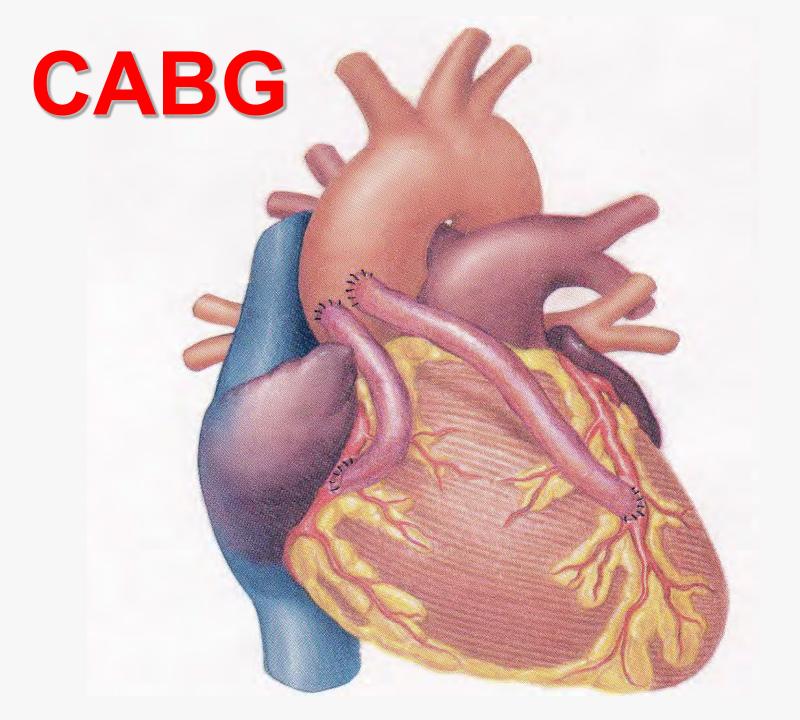
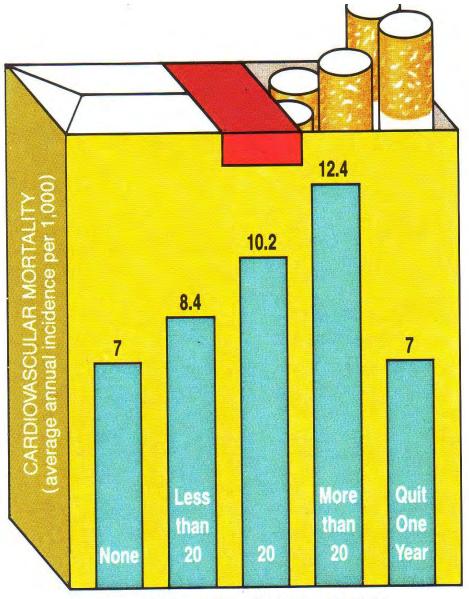
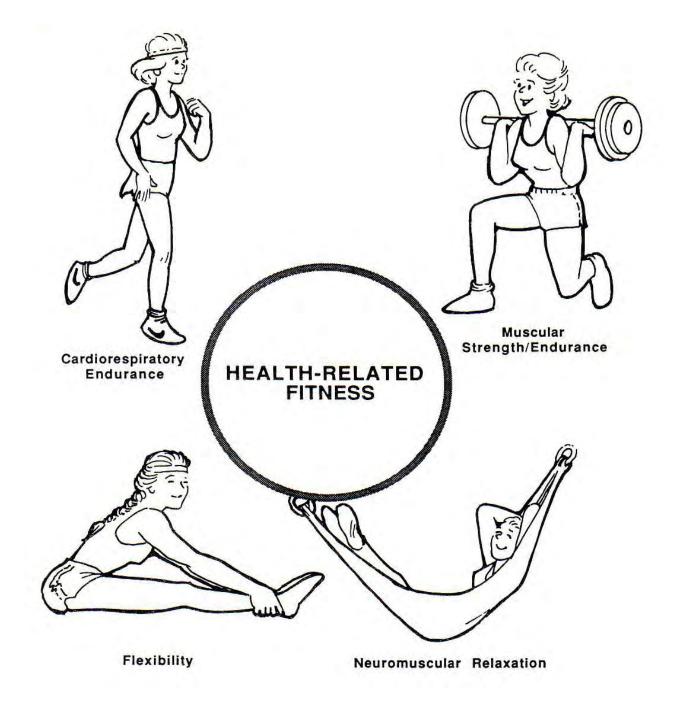


FIGURE 37–1 Devices for percutaneous transluminal coronary interventions. **A**, Coronary balloon. **B**, Rotational atherectomy burr (Rotablator). **C**, Coronary stent.



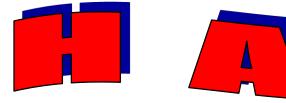


CIGARETTES SMOKED PER DAY



Pick an abundance of whole grains, legumes, nuts, vegetables & fruits!

Healthy Oils to Minimize Atherosclerosis HAPOC?

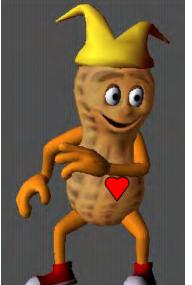
























....Fun lab week with much personal data!

BI 121 Lecture 10

- *Announcements* Remember to read Lab 5 before Thursday. Thanks for helping us be well-prepared. Q from last time? Calculating grade from estimated final. Keys to success? Q?
 CVD & Oil Connections Anti-inflammatory vs. inflammatory? S&W ch 5
- III.<u>Blood Form & Function</u> LS ch 11 pp 296-304, 309-12
 - DC Module 5 + SI Fox + National Geographic Lennart Nilsson
 - A. Formed vs. nonformed/cells vs. plasma fig+tab 11-1
 - B. <u>Red blood cells</u>/erythrocytes: <u>O₂-carrying</u> sickle cells, ABO blood typing, Rh factor pp 299-304.
 - C. <u>White blood cells</u>/leukocytes: <u>Defense/immunity</u> differential + general functions pp 309-12
 - D. <u>Platelets</u>/thrombocytes: <u>Initial clotting</u> p 304

IV.<u>Blood Glucose & Diabetes Mellitus</u> LS ch 17, DC Module 13

Essential Fatty Acids: Ω-6 Linoleic & Ω-3 Linolenic Acids



Linoleic \rightarrow Arachadonic Acid \rightarrow Inflammatory Cascade Linolenic \rightarrow EPA, DHA \rightarrow Anti-inflammatory









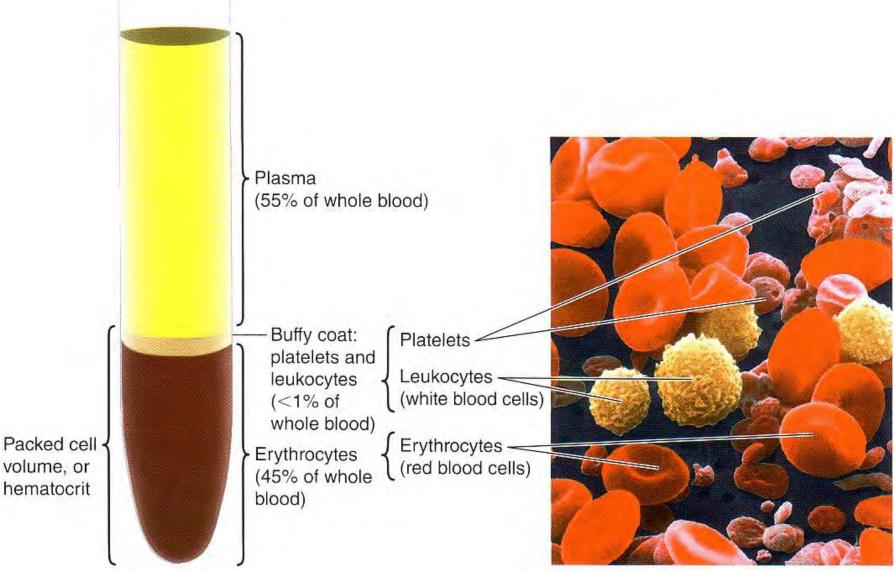


Deep cold water fish are fabulous sources of Ω-3 fatty acids!



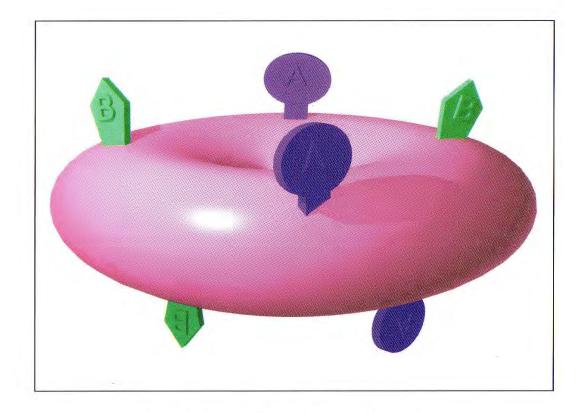
S&W p 167

What's in Blood? Plasma & Blood Cells



LS 2012 fig 11-1



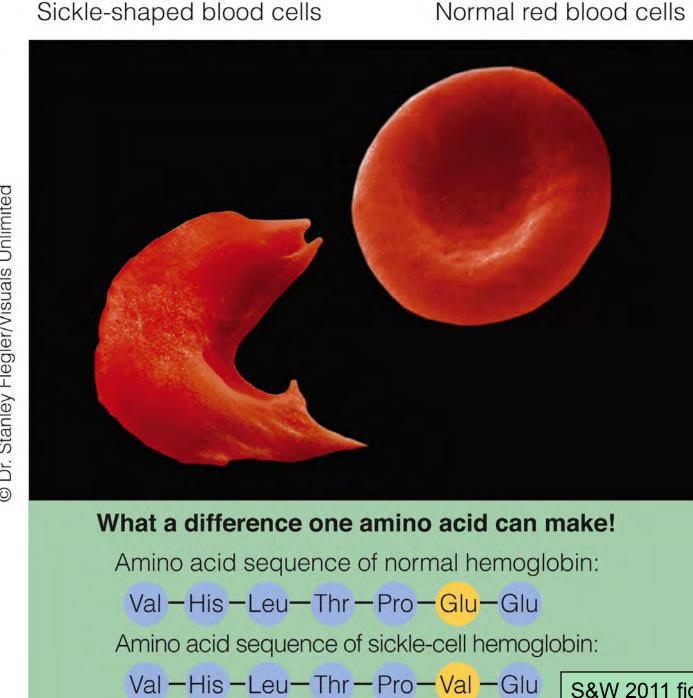


A & B Antigens (Agglutinogens)

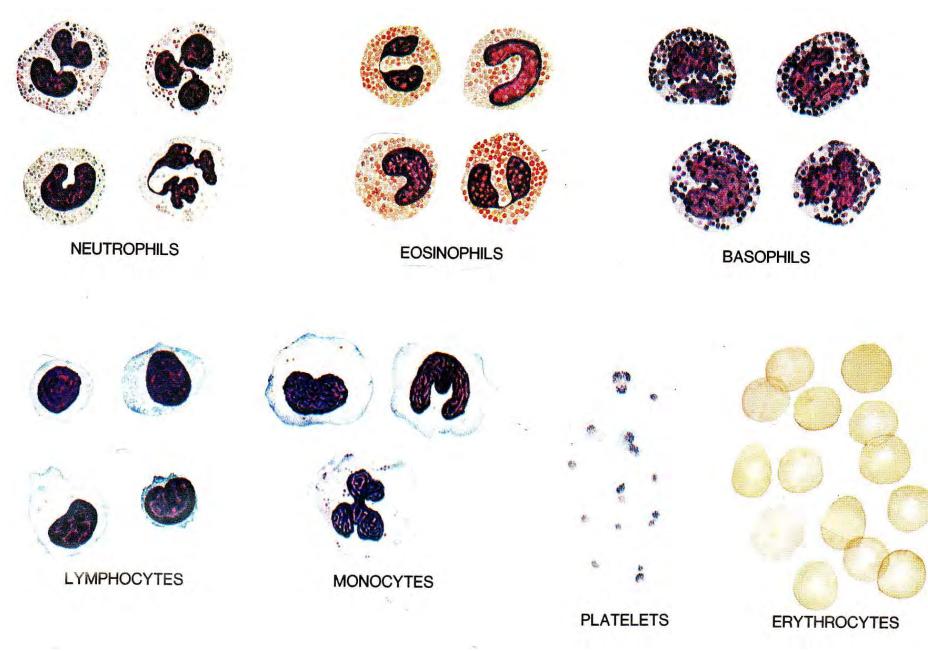
Erythroblastosis Fetalis?

eg, Rh-mom Rh+baby

http://www.nlm.nih.gov/MEDLINEPLUS/ency/ article/001298.htm#Alternative%20Names

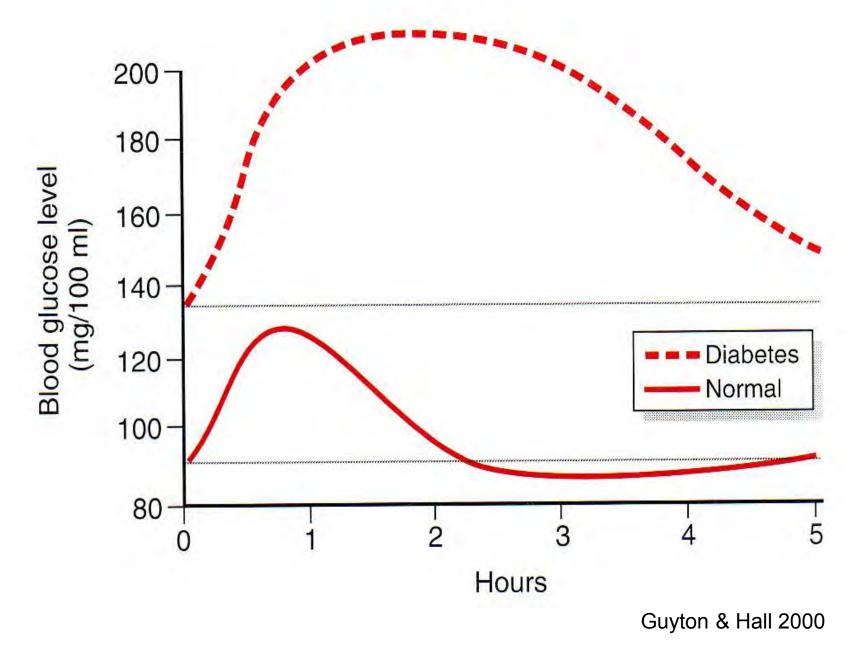


S&W 2011 fig 6-5 p 194

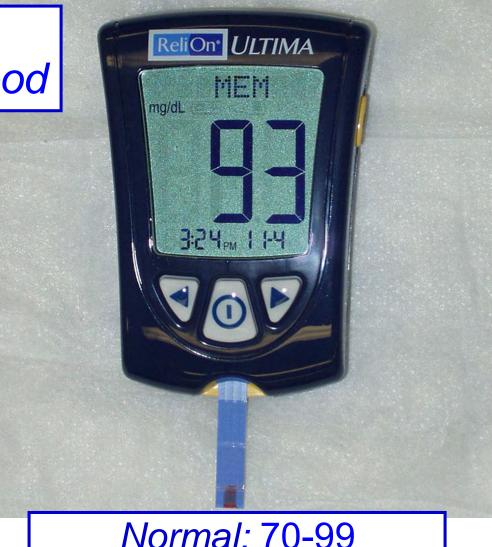


SI Fox 2009 fig 10-2

Diabetic & Normal Response to Glucose Load



<u>Glucose</u>: Sugar in Blood



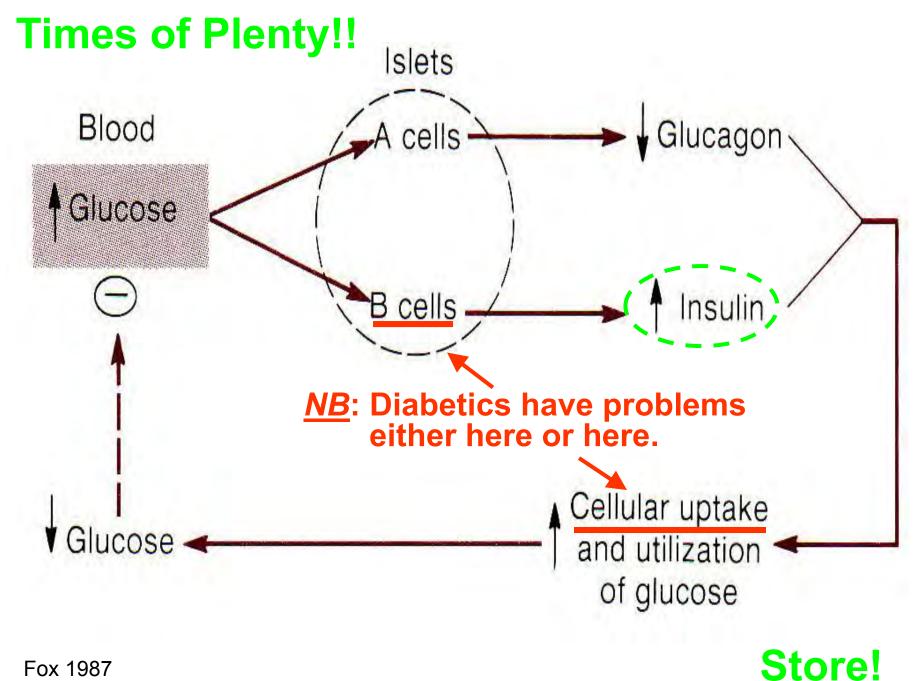
Normal: 70-99 <u>Pre-Diabetes</u>: 100-125 <u>Diabetes</u>: ≥ 126 mg/dL

4-7 Warning Signs of Diabetes

These signs appear reliably in type 1 diabetes and, often, in the later stages of type 2 diabetes.

- Excessive urination and thirst
- Glucose in the urine
- Weight loss with nausea, easy tiring, weakness, or irritability
- Cravings for food, especially for sweets
- Frequent infections of the skin, gums, vagina, or urinary tract
- Vision disturbances; blurred vision
- Pain in the legs, feet, or fingers
- Slow healing of cuts and bruises
- Itching
- Drowsiness
- Abnormally high glucose in the blood

S&W 2011 tab 4-7 p 131



Fox 1987

Diabetics must constantly juggle diet, exercise & medication to control blood glucose!



Like others, diabetics benefit from whole grains, vegetables, fruits, legumes & non-/low-fat milk products!



BI 121 Lecture 11

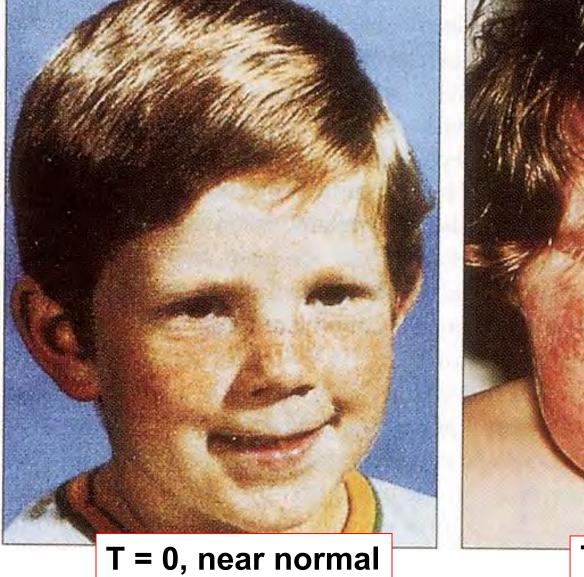
Fun lab today! Data for a lifetime! Thanks for being prepared!

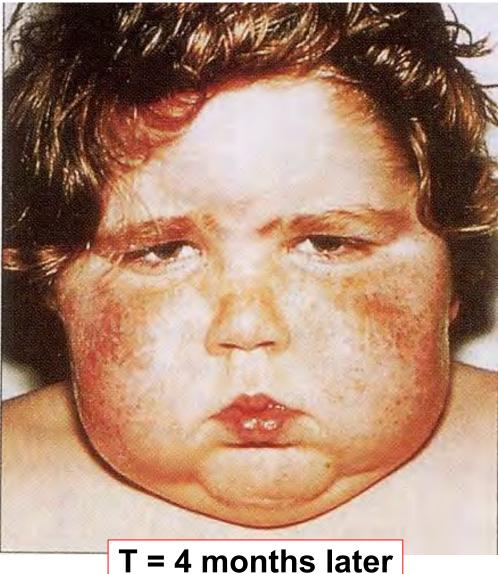
- I. Lab 5 Review: Safety & Techniques Q?
- II. Introduction to Endocrinology LS ch 17, DC Module 13, SI Fox+
 - A. Endocrine vignette: Cushing's syndrome LS fig17-20 p 521-2
 - B. Endocrine system DC p 103 fig 13-1, LS fig 17-1, tab 17-1
 - C. What's an endocrine? + classes ~ LS pp 495 6
 - D. Hypothalamus (Master) Pituitary (subcontroller)
 DC pp 104-6 + LS pp 499-506
 - E. Posterior pituitary + hormones DC p 108, LS fig 17-4 p 502
 - F. Anterior pituitary + hormones DC pp 105-7, LS pp 502-6
 - G. GH: Body builder's dream? Fountain of youth? LS pp 506-11
 - H. Peripheral endocrine organs DC pp 109-13, LS pp 513-36
 - 1. Pancreas (insulin, glucagon, diabetes) 2. Thyroid 3. Adrenals

III. Nervous System & Excitable Cell Connections LS ch 5, 4, 7

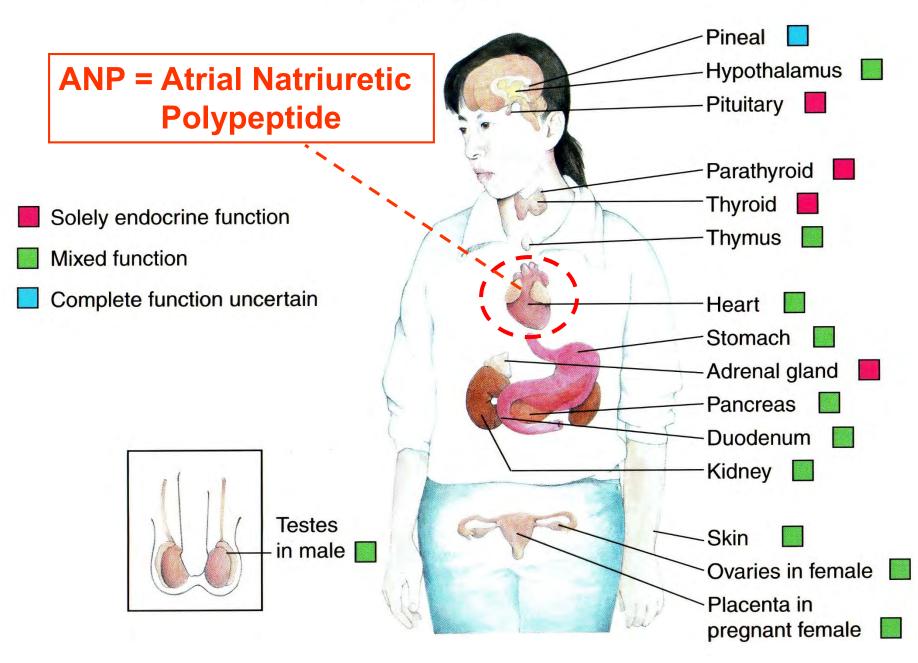
- A. How is the nervous system organized? fig 5-1 p 108
- B. Neurons? What kind? fig 5-2 p 109
- C. Brain structure & function fig 5-7, 5-8 pp 116 7
- D. Protect your head with a helmet! Bicycle head injury statistics, NHTSA & BHSI

Cushing's Syndrome = Hypersecretion of Cortisol: Hypothalamic (CRH), Pituitary (ACTH), or Adrenal (Cortisol)





Endocrine System



Hormone/Endocrine Classifications

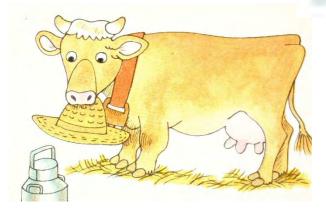
T4

T3

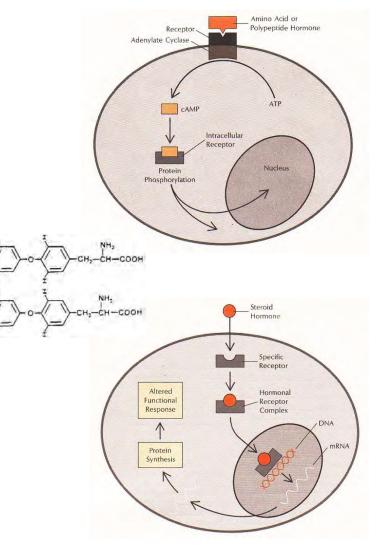
Exogenous

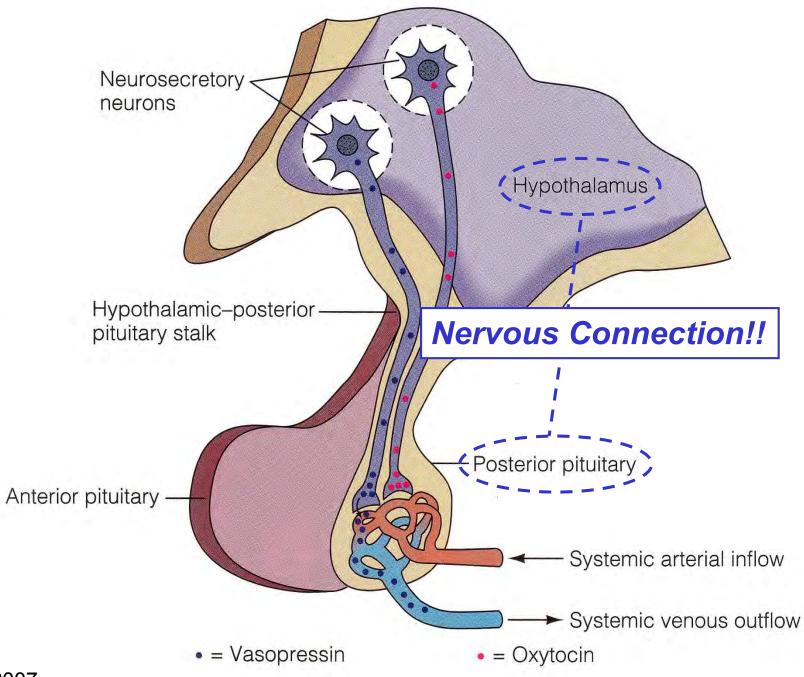




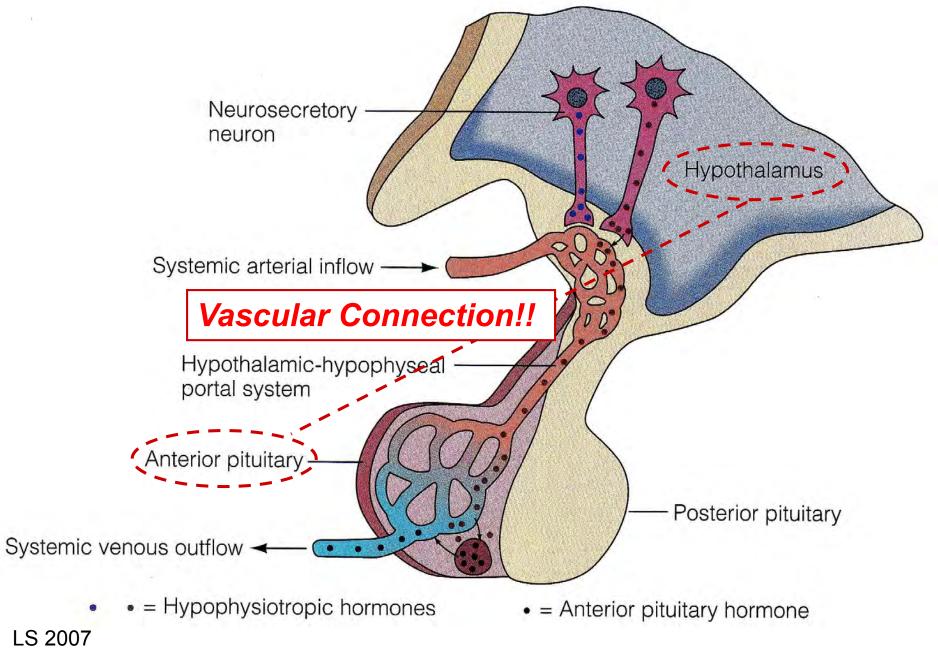


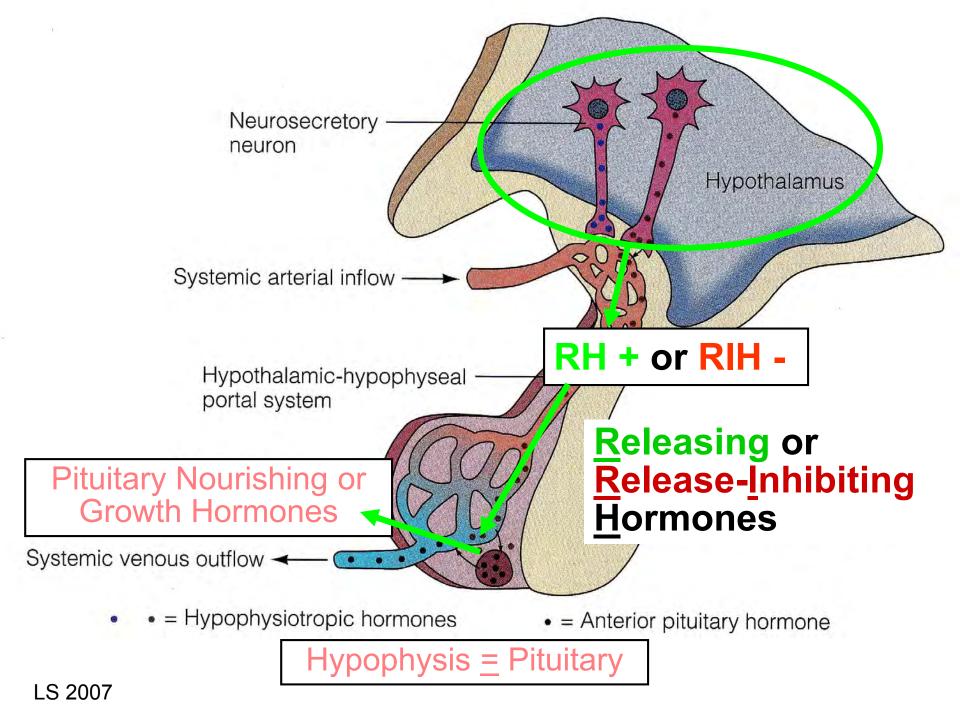
Endogenous

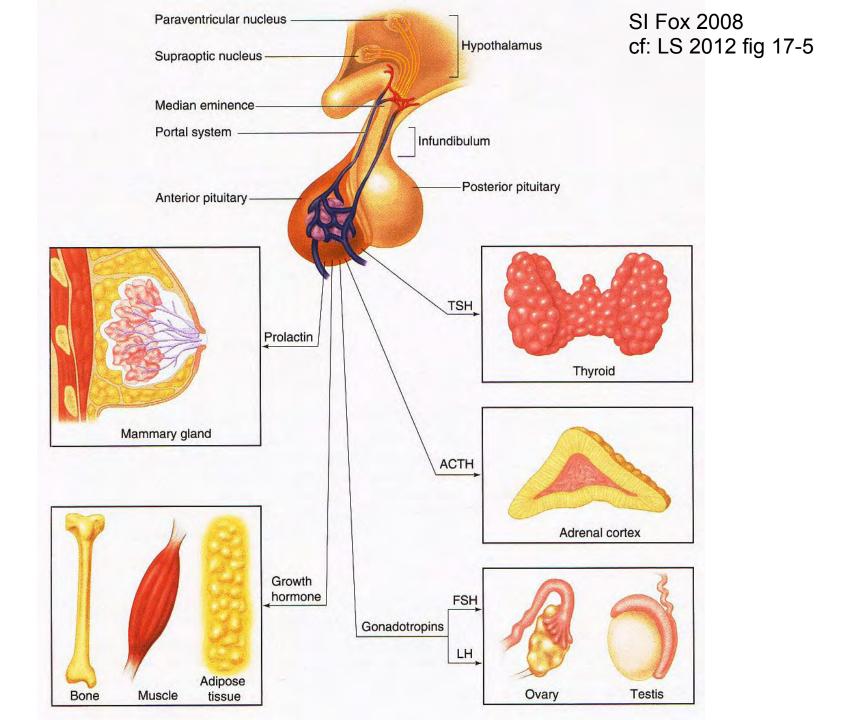




Hypothalamus-Anterior Pituitary Vascular Connection!





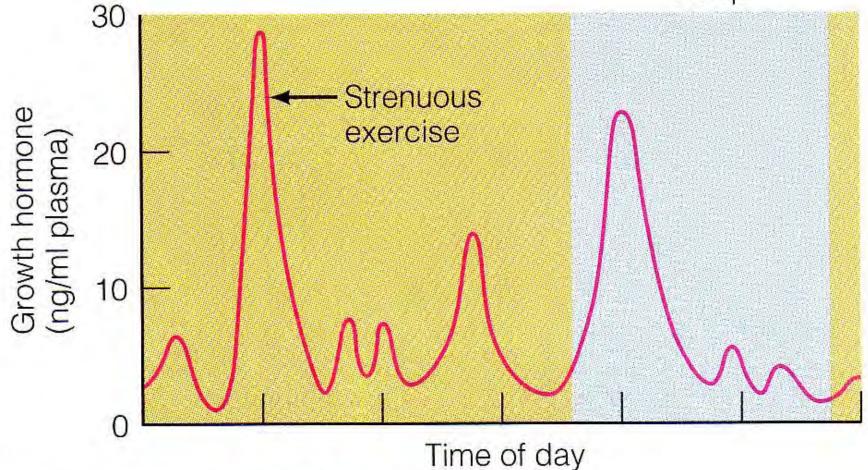


GH/STH Effects: Insulin Resistance/Type II Diabetes?

- † Amino Acid uptake & Protein synthesis
- † Lipolysis & Fatty Acid mobilization
- ↓ Glucose uptake
 (skeletal muscle & adipocytes)
- † Glucose production
 (liver glycogenolysis)
- 1 Insulin secretion

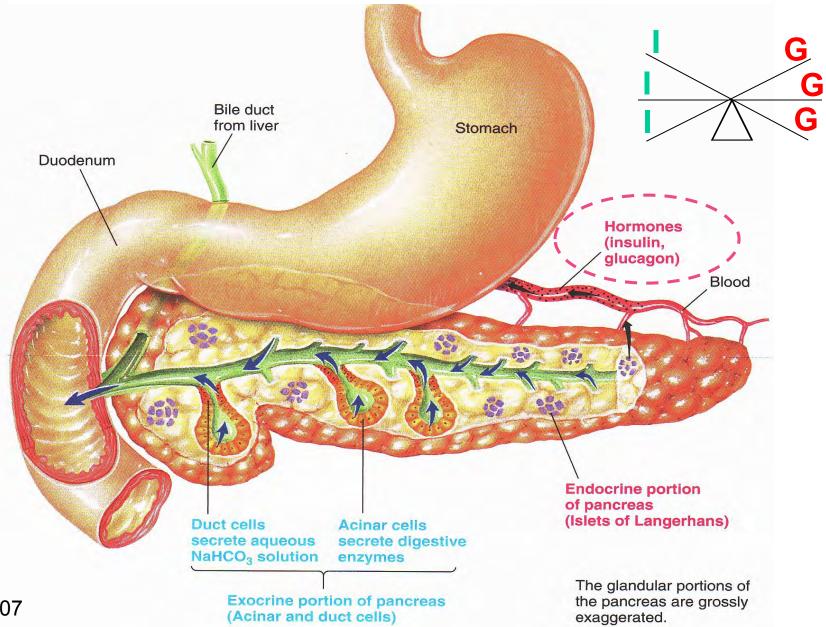
Increase GH naturally with exercise & sleep!!

Sleep

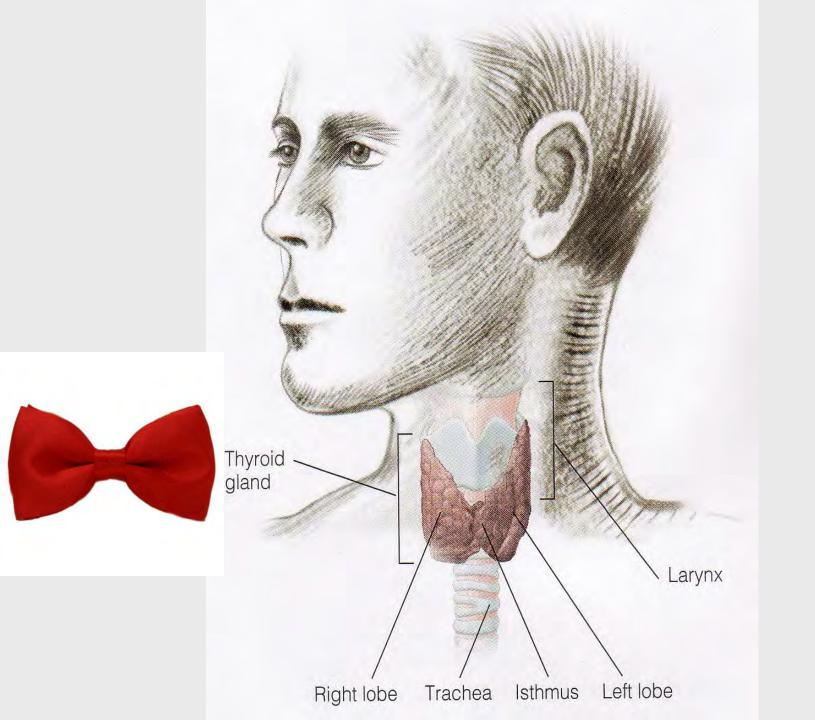


ng/ml = nanograms per mililiter

Endocrine Pancreas: Insulin (I) & Glucagon (G) See-Saw Hormones in Regulating Blood Glucose

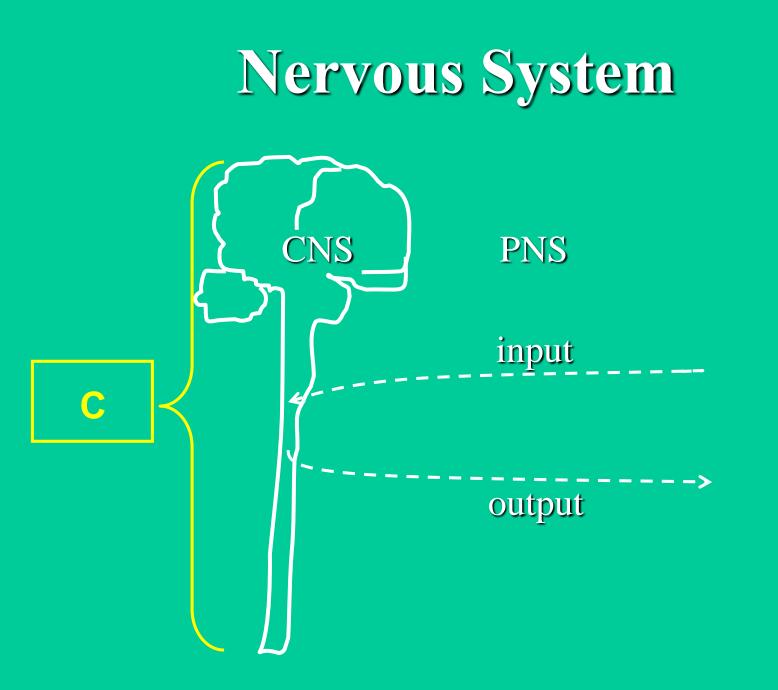


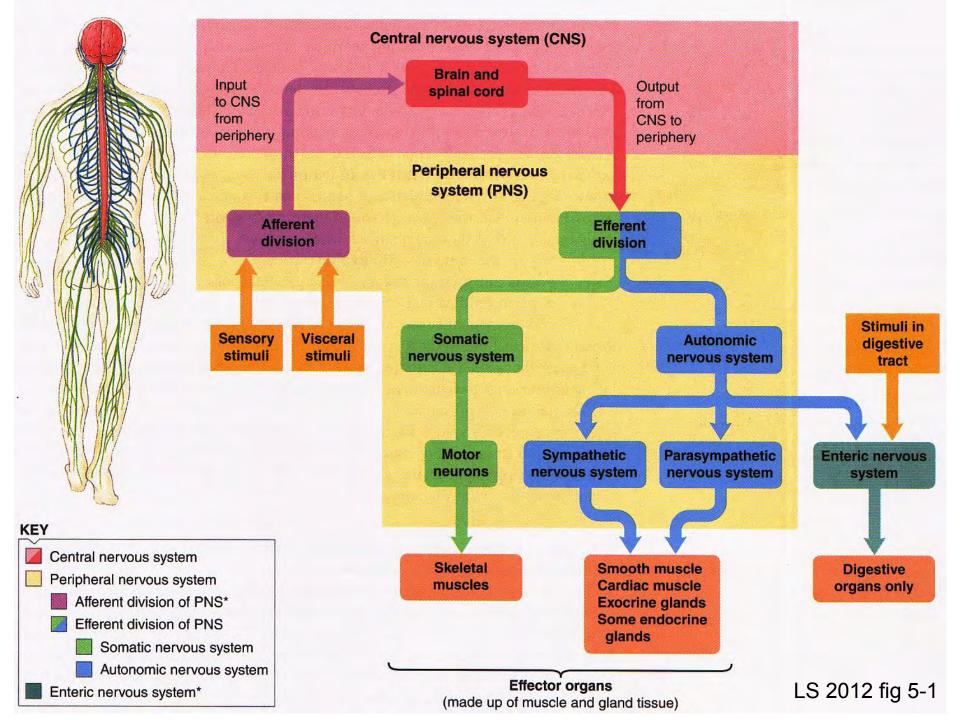
LS 2007

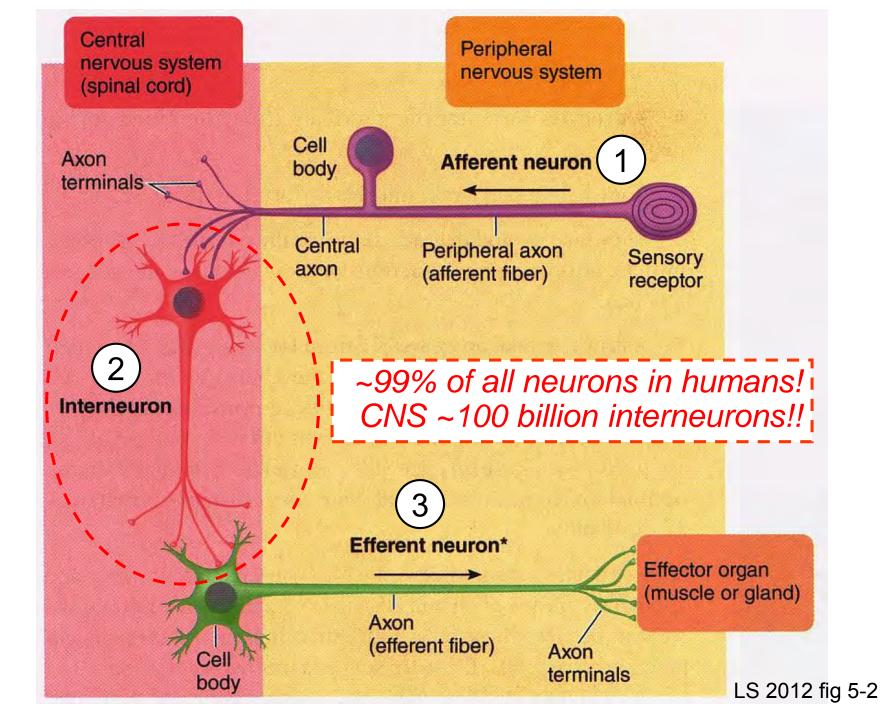


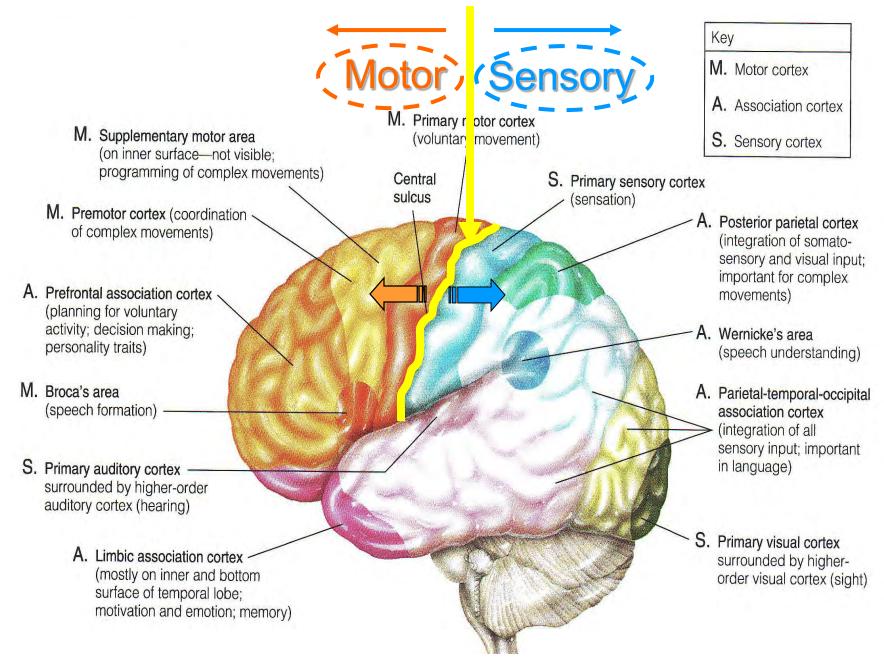
DC 2003











LS 2006, cf: LS 2012 fig 5-8a



Helmets Cheap, Brains Expensive!! Use Your Head, Get a Helmet!! <u>http://www-nrd.nhtsa.dot.gov/pubs/811156.pdf</u> <u>http://www.bhsi.org/stats.htm</u>

~540,000 bicyclists/yr visit emergency rooms 67,000 head injuries, 1 in 8 brain injuries 716 cyclists died in 2008 \equiv 2% of all traffic fatalities $\frac{1}{2}$ of deaths children < 15 yr 53,000 cyclists have died since 1932

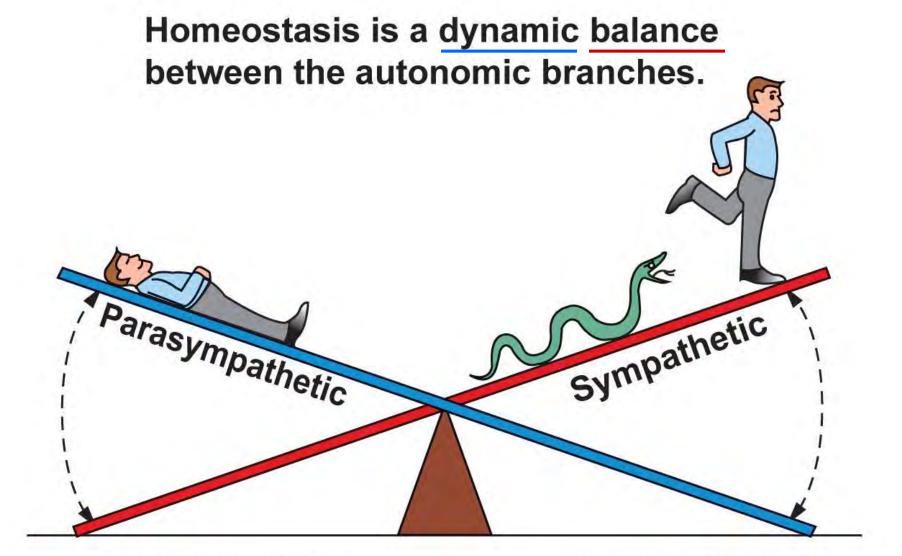


that's more than the population of Springfield, OR 52,864 Bend, OR 52,029 Corvallis, OR 49,322



Bicycle crashes & injuries are under reported, since majority not serious enough for ER visits. Helmets may prevent 45-88% of brain injuries! ~\$81 million/yr = direct injury costs from not using helmets! BI 121 Lecture 12 Thanks for your help with the blood chemistry lab!...

- *I. <u>Announcements</u> Optional notebook check + Lab 6 tomorrow.* Pulmonary Function Testing. Final exam > your Q on Wed. Q?
- II. Autonomic Nervous System Overview LS pp 178 85
 - LS Table 7-1 p 183 + stories to remember *fight-or-flight!*
- III. <u>Neuromuscular Connections</u> LS ch 7 pp 186-92, DC pp 69-71 How does the signal cross the nerve-muscle gap? LS fig 7-5
 - A. Normal function? Ca2+ for bones!...but what else? LS p 190
 - A. Normal function? Ca2+ for bones!...but what else? L5 p 190
 - B. What do black widow spider venom, botulism, curare & nerve gas have in common? Botox? LS p 189-91
- *IV.<u>Muscle Structure, Function & Adaptation</u> LS ch 8, DC Module 12*
 - A. Muscle types: cardiac, smooth, skeletal LS fig 8-1 p 194-6
 - B. How is skeletal muscle organized? LS fig 8-2, DC fig 12-2
 - C. What do thick filaments look like? LS fig 8-4, DC fig 12-4
 - D. How about thin filaments? LS fig 8-5
 - E. Banding pattern? LS fig 8-3, fig 8-7
 - F. How do muscles contract? LS fig 8-6, 8-10
 - G. What's a cross-bridge cycle? LS fig 8-11 +...
 - H. Summary of skeletal muscle contraction
 - I. Exercise adaptation variables: *mode*, *intensity*, *duration*, *frequency*, *distribution*, *individual* & environmental char...?
 - J. Endurance vs. strength training continuum? fiber types...



Rest-and-digest: Parasympathetic activity dominates. Fight-or-flight: Sympathetic activity dominates.

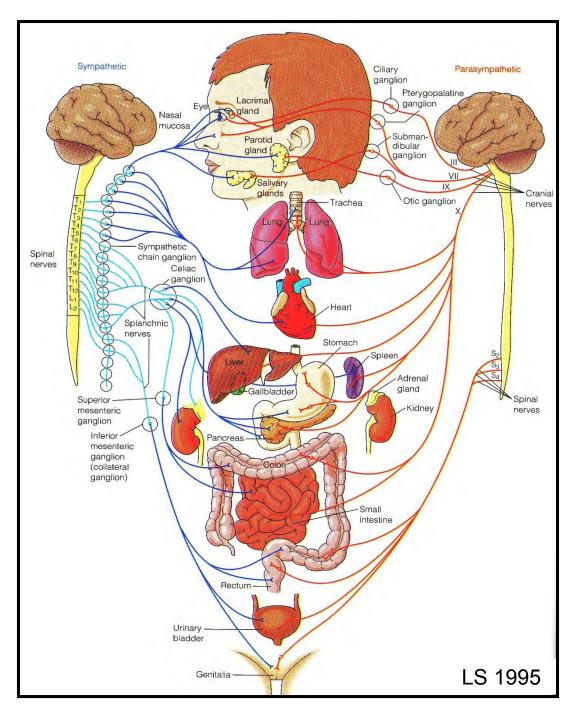
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D Silverthorn 2010

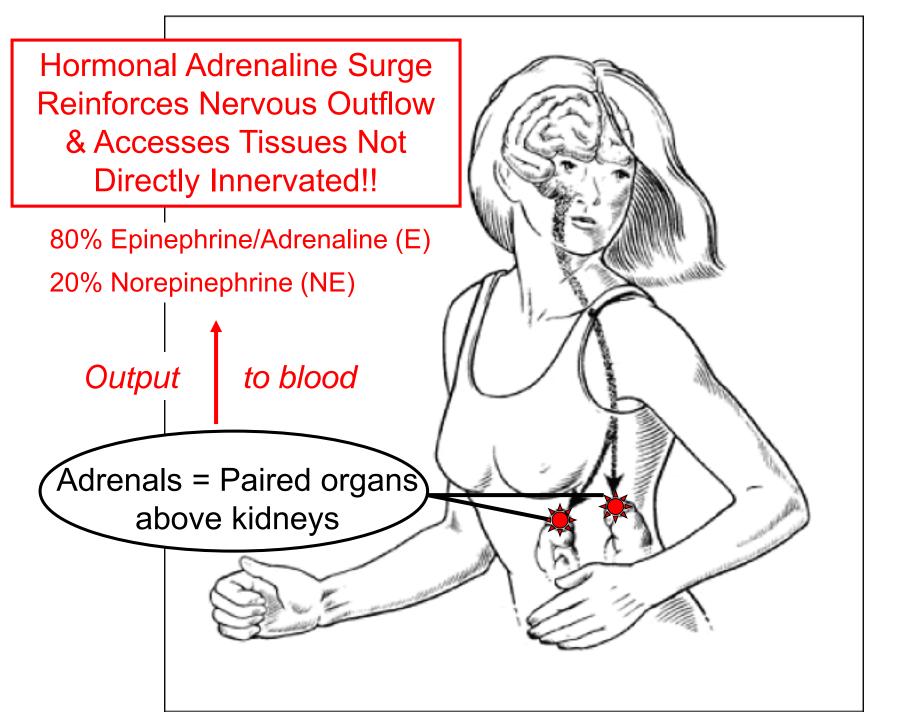
Autonomic Nervous System

Why overlap or dual innervation?

Fine-tune control & safety!

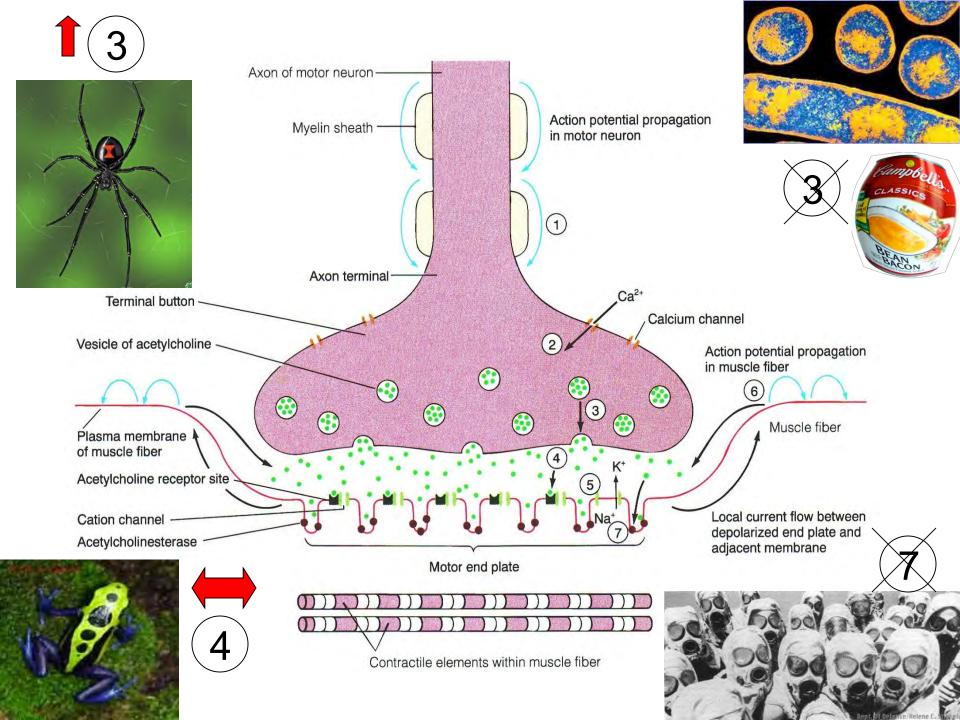


cf: LS 2012 fig 7-3



▲ Table 7-1 Effects of Autonomic Nervous System on Various Organs

	Organ	Effect of Sympathetic Stimulation	Effect of Parasympathetic Stimulation
	Heart	Increases heart rate and increases force of contraction of the whole heart	Decreases heart rate and decreases force of contrac- tion of the atria only
	Blood Vessels	Constricts	Dilates vessels supplying the penis and the clitoris only
	Lungs	Dilates the bronchioles (airways)	Constricts the bronchioles
	Digestive Tract	Decreases motility (movement)	Increases motility
		Contracts sphincters (to prevent forward movement of tract contents)	Relaxes sphincters (to permit forward movement of tract contents)
		Inhibits digestive secretions	Stimulates digestive secretions
	Urinary Bladder	Relaxes	Contracts (emptying)
	Eye	Dilates the pupil	Constricts the pupil
		Adjusts the eye for far vision	Adjusts the eye for near vision
	Liver (glycogen stores)	Glycogenolysis (glucose is released)	None
	Adipose Cells (fat stores)	Lipolysis (fatty acids are released)	None
	Exocrine Glands		
	Exocrine pancreas	Inhibits pancreatic exocrine secretion	Stimulates pancreatic exocrine secretion (important for digestion)
	Sweat glands	Stimulates secretion by sweat glands im- portant in cooling the body	Stimulates secretion by specialized sweat glands in the armpits and genital area
	Salivary glands	Stimulates a small volume of thick saliva rich in mucus	Stimulates a large volume of watery saliva rich in enzymes
	Endocrine Glands		
	Adrenal medulla	Stimulates epinephrine and norepinephrine secretion	None
	Endocrine pancreas	Inhibits insulin secretion	Stimulates insulin secretion
	Genitals	Controls ejaculation (males) and orgasm contractions (both sexes)	Controls erection (penis in males and clitoris in females)
	Brain Activity	Increases alertness	None LS 2012



Skeletal Muscle Histology: Microscopic Anatomy

Muscle fiber or cylindrical cell

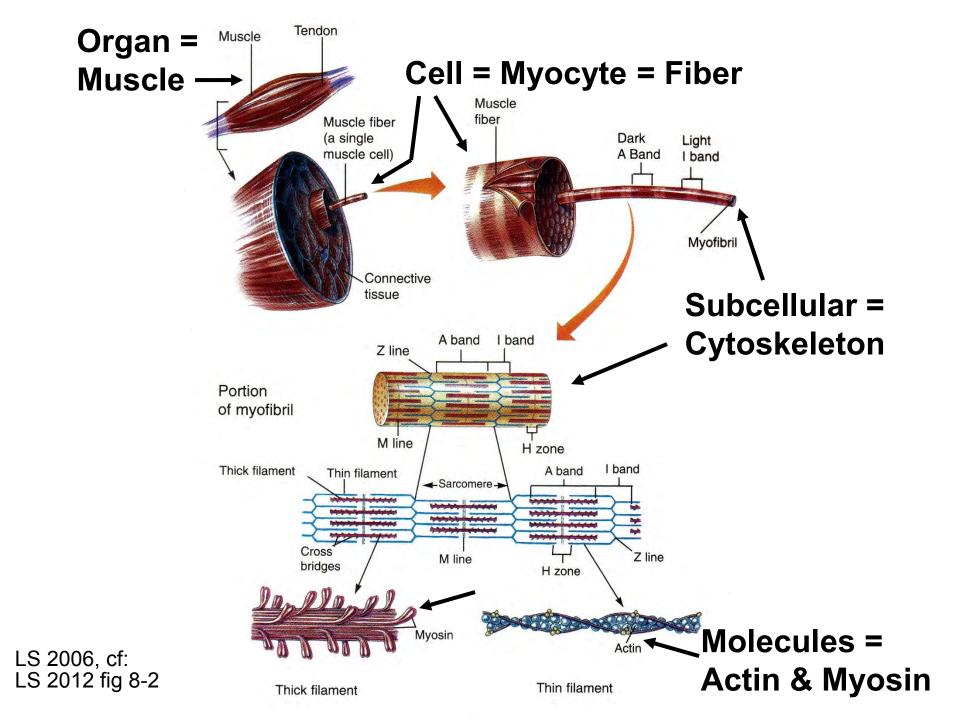
Nucleii

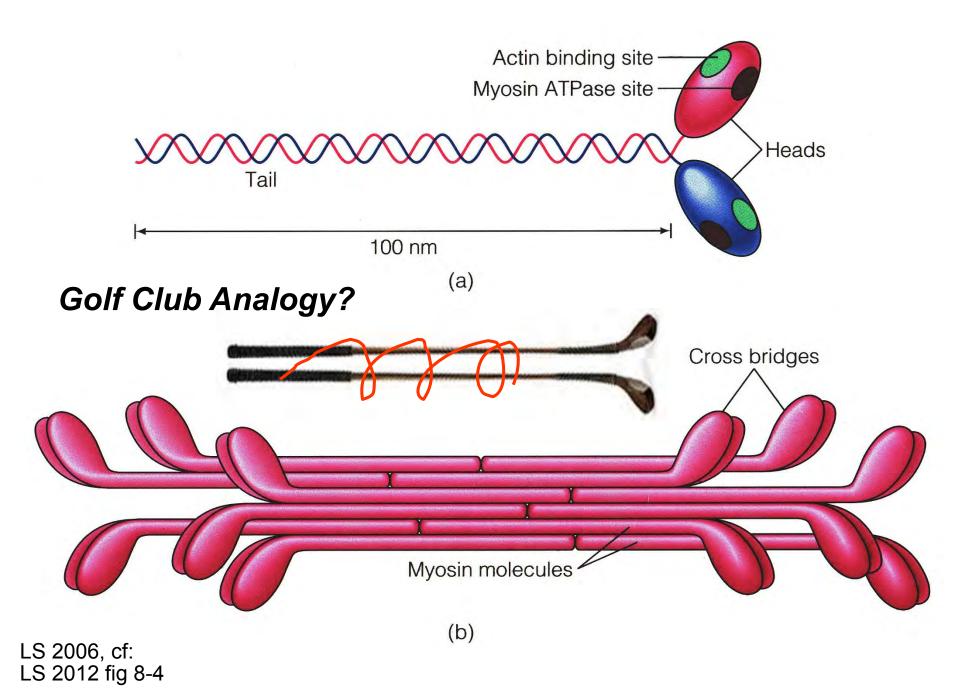
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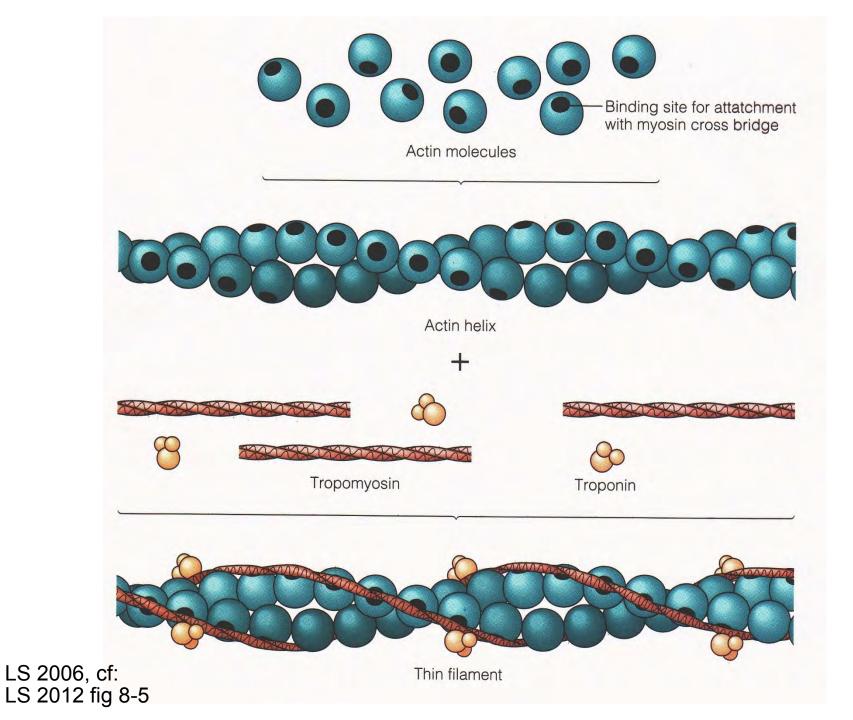
 $ffff \\ Dark-Light...bands \equiv Overlapping thick & thin filaments \\ file of the second second$

→ "Threads" ≡ Myofibrils

H Howard 1980.







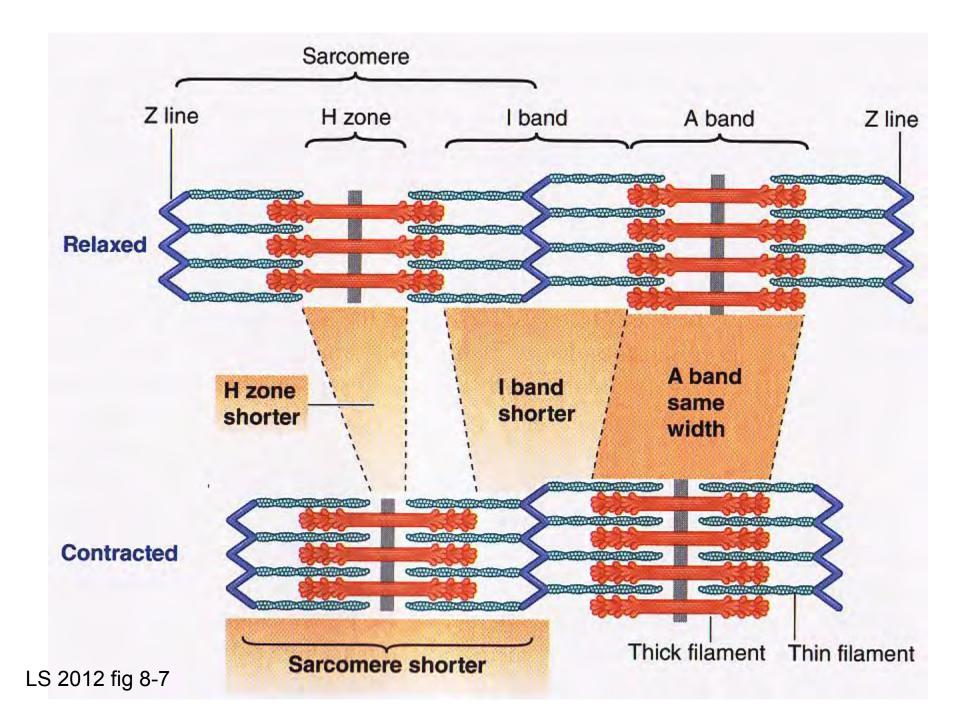
Triad ≡ T tubule abutting cisternae

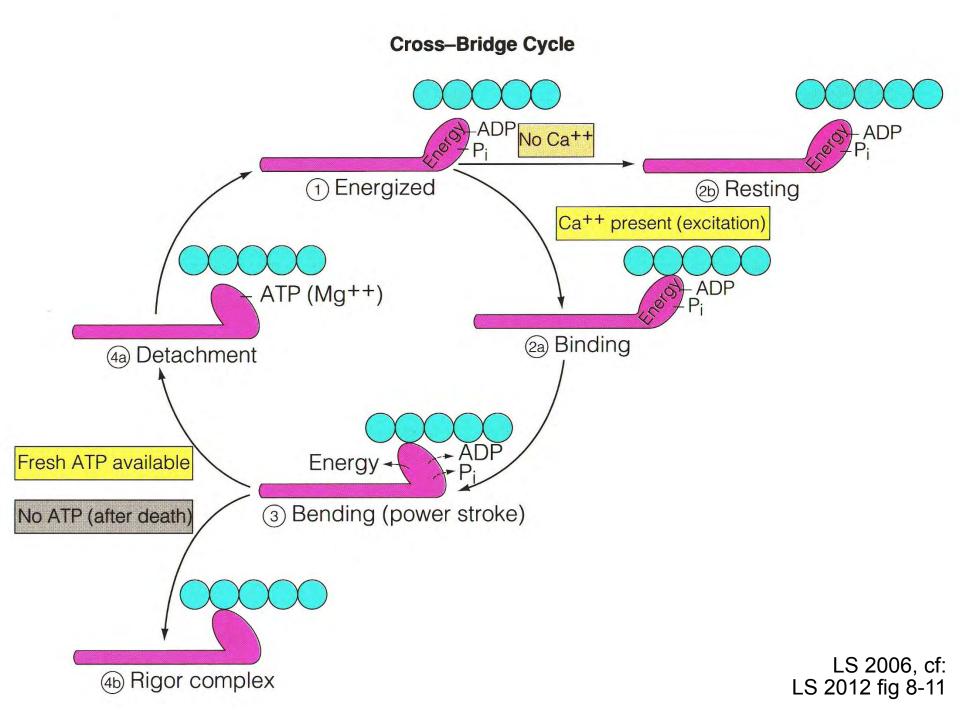
Sarcomere

Mitochondria

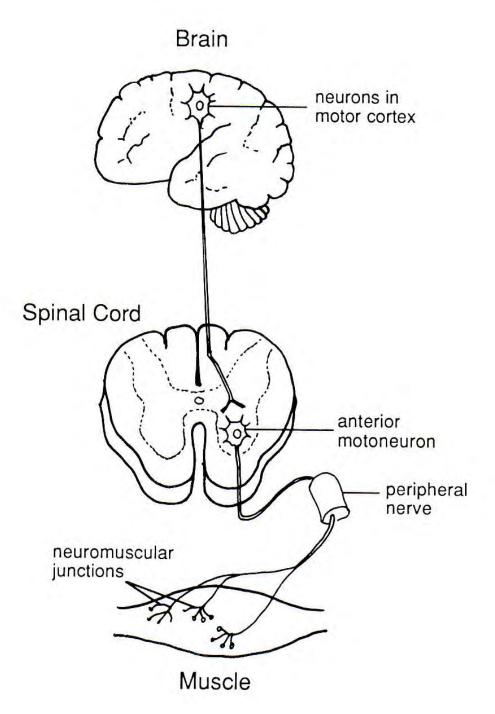
C

Sarcomere





LLM p C - 4

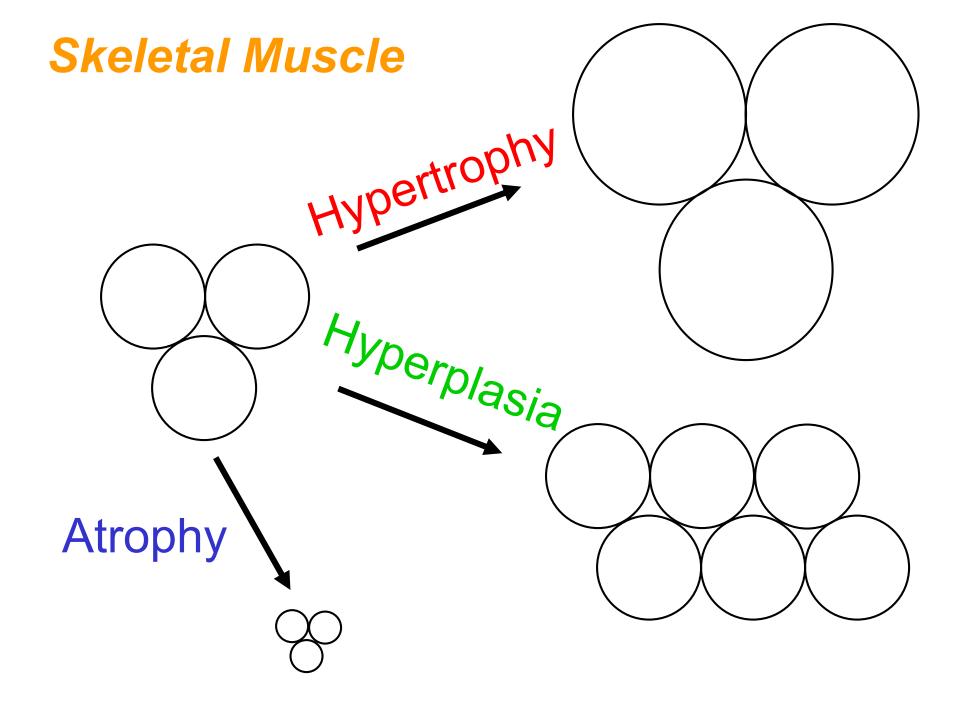


Acetylcholine released by LS 2006 cf: axon of motor neuron Action potential generated LS 2012 fig 8-10 crosses cleft and binds to in response to binding of receptors/channels on acetylcholine and subsequent motor end plate. end plate potential is Action potential in T tubule propagated across surface triggers Ca2+ release from **Terminal button** membrane and down T tubules sarcoplasmic reticulum. of muscle cell. H)(H) T tubule Surface membrane of muscle cell Acetylcholinegated cation Acetylcholine channel Ca2+ Lateral sacs of sarcoplasmic reticulum Ca2+ Ca2+ Calcium ions released from Tropomyosin Ca2+ Troponin lateral sacs bind to troponin on actin filaments; leads to With Ca2+ no longer bound tropomyosin Cross-bridge binding Actin G Ca²⁺ actively to troponin, tropomyosin slips being physically site taken up by back to its blocking position over Myosin cross bridge moved aside to sarcoplasmic binding sites on actin; contraction uncover crossreticulum when ends; actin passively slides back bridge binding Myosin cross bridges attach to actin and bend, there is no longer to original resting position. sites on actin. pulling actin filaments toward center of local action sarcomere; powered by energy provided by ATP. potential.

Adaptations to Exercise?

Mode, Intensity, Duration, Frequency, Distribution of Training Sessions? Conditions of Environment? Individual?

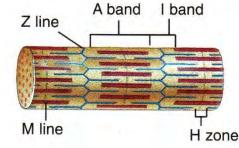






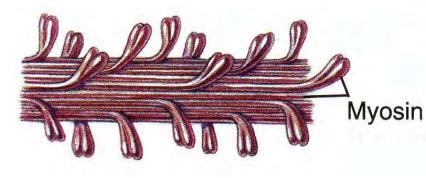
Hypertrophy: Increased

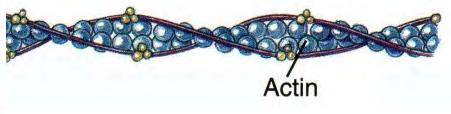
Number of Myofibrils



Thick & Thin Filaments

Myosin & Actin Molecules

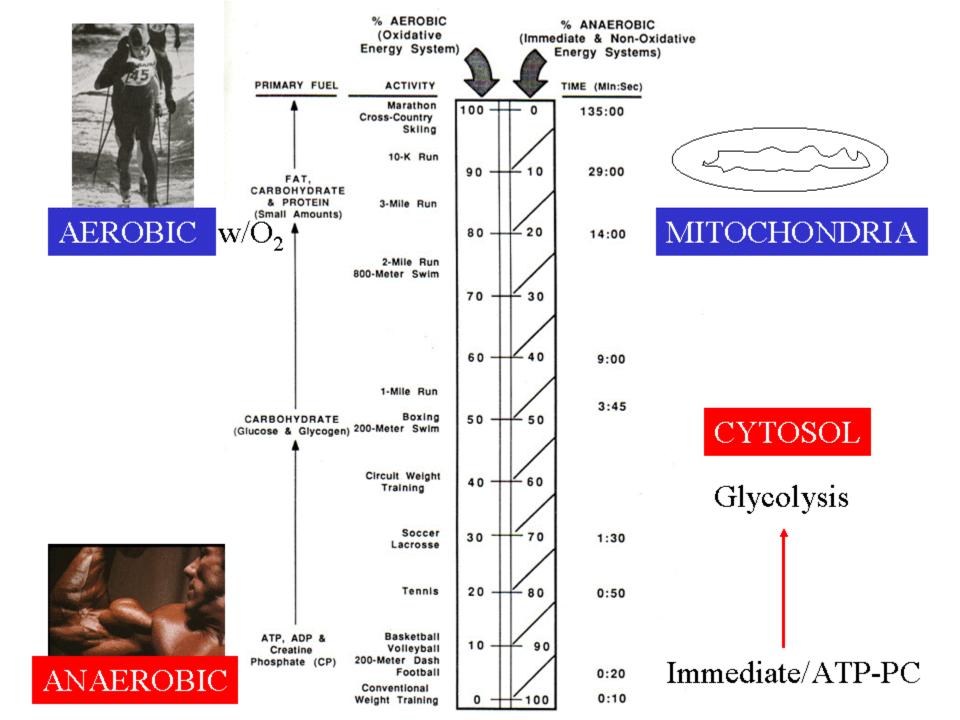


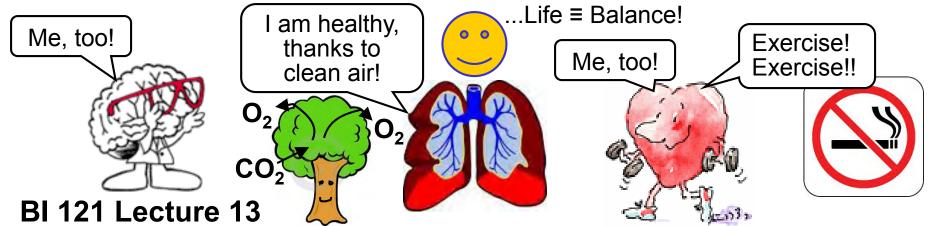


Characteristics of Skeletal Muscle Fibers

	TYPE OF FIBER		
 Characteristic	Slow Oxidative (Type I)	Fast Oxidative (Type IIa)	Fast Glycolytic (Type IIb)
Myosin-ATPase Activity	Low	High	High
Speed of Contraction	Slow	Fast	Fast
Resistance to Fatigue	High	Intermediate	Low
Aerobic Capacity	High	High	Low
Anaerobic Capacity	Low	Intermediate	High
Mitochondria	Many	Many	Few
Capillaries	Many	Many	Few
Myoglobin Content	High	High	Low
Color of Fibers	Red	Red	White
Glycogen Content	Low	Intermediate	High
			$2012 \text{ tab } 8_1 \text{ modified}$

LS 2012 tab 8-1 modified > VP Lombardi 1989





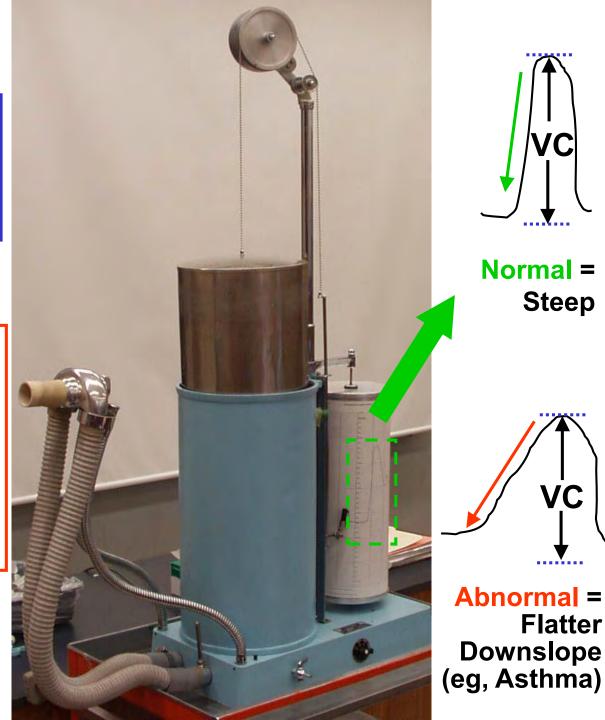
- *I. <u>Announcements</u> Optional notebook check today. Discussion-Review followed by final exam tomorrow. Q?*
- *II. <u>Introduction to PFT Lab 6</u> Pulmonary <u>Function Testing</u> <i>III.<u>Respiratory System</u>* LS ch 12, DC Module 7, SI Fox +...
 - A. Steps of respiration? External vs. cellular/internal? LS fig 12-1 pp 345-7
 - B. Respiratory system anatomy LS fig 12-2 p347, DC, SI Fox +...
 - C. Histology LS fig 12-4 pp 347-9, DC
 - D. How do we breathe? LS fig12-12, fig12-25 pp 349-56, 373-8
 - E. Gas exchange LS fig 12-19 pp 362-5
 - F. Gas transport LS tab 12-3 pp 365-70

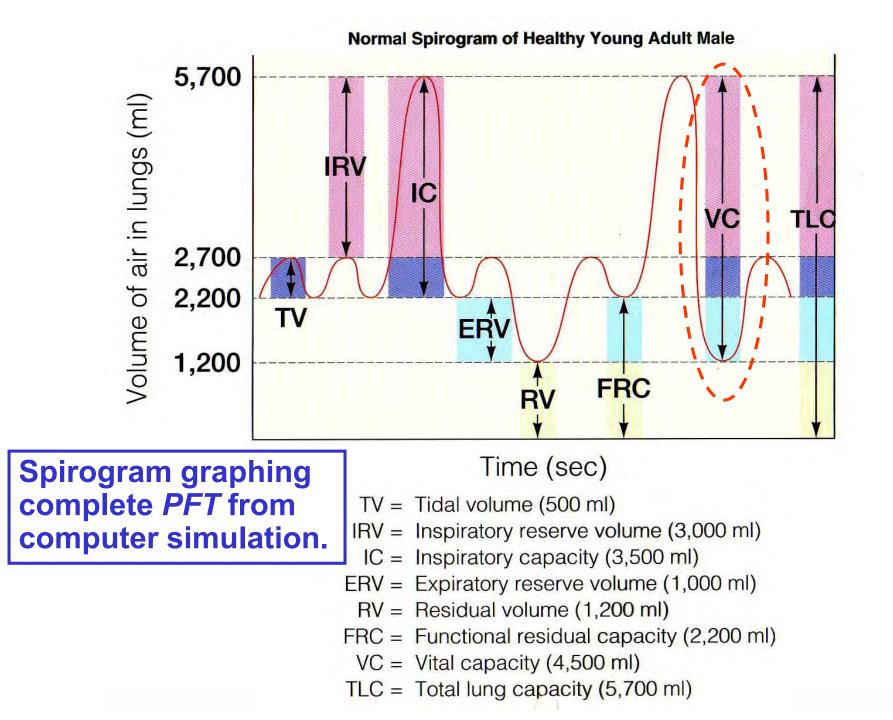
IV.Physiology of Cigarette Smoking

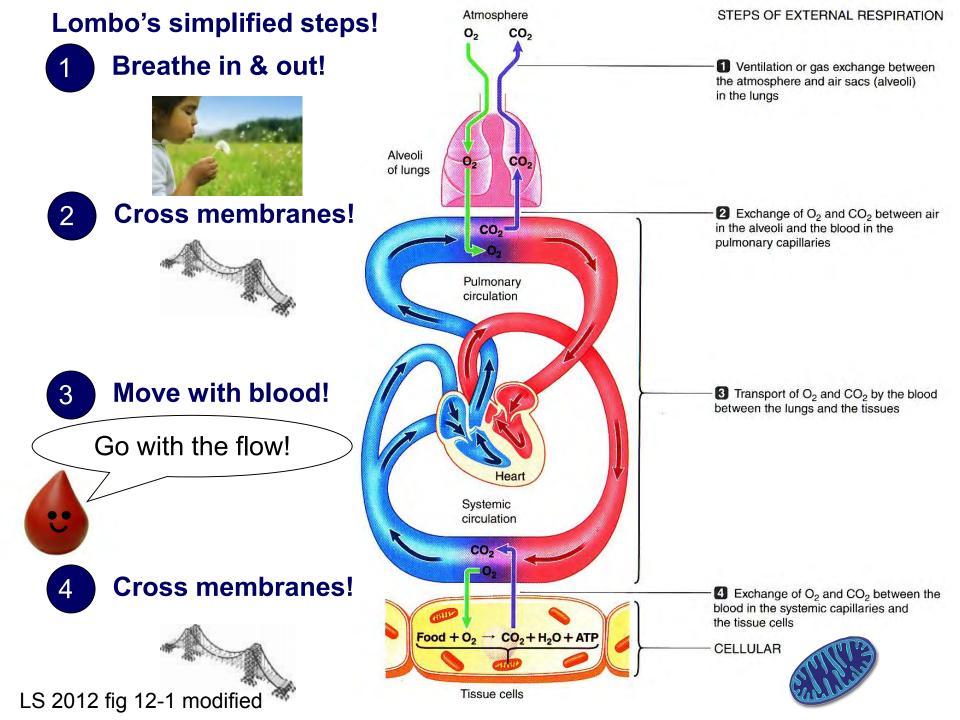
- A. ANS, autonomic nerves & nicotine? Route of chemicals,...
- B. Emphysema? 2nd-hand smoke?... p 356, 365
- C. UO Smoke-Free since Fall 2012! Help is available!

Respirometer → measures complete <u>Pulmonary Function</u> <u>Test</u> or PFT!

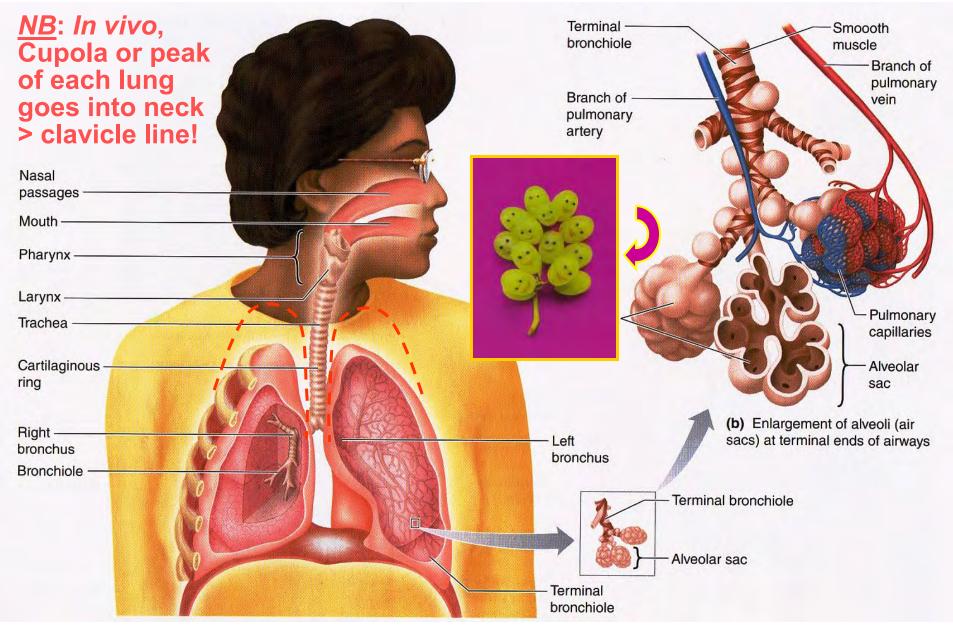
<u>NB</u>: Should be able to blow out \geq 75 - 85% of VC/FVC in 1 second! That's FEV_{1.0}/FVC \geq 0.75 - 0.85. If less, may indicate asthma or other lung disease.



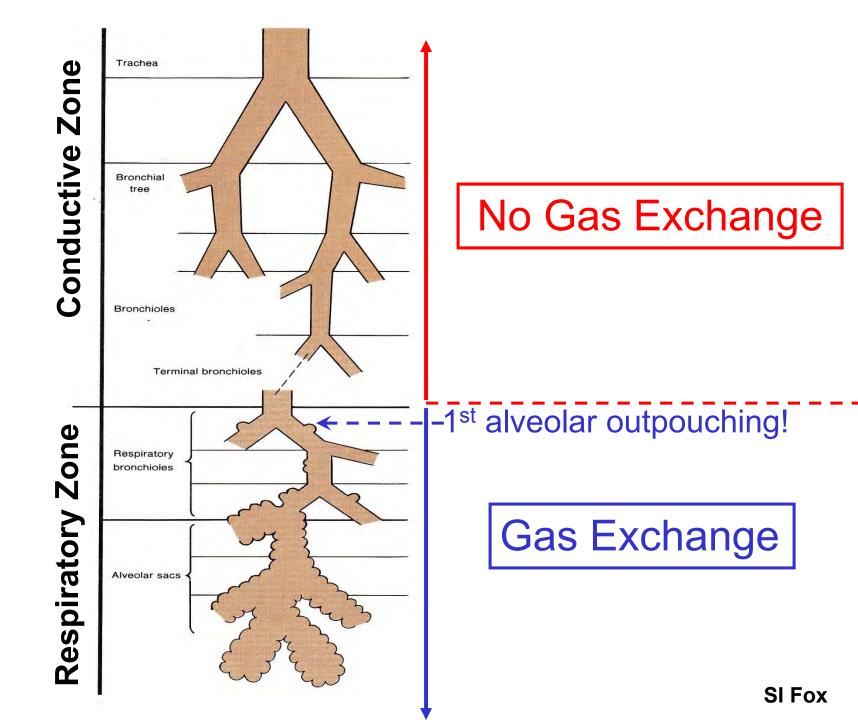


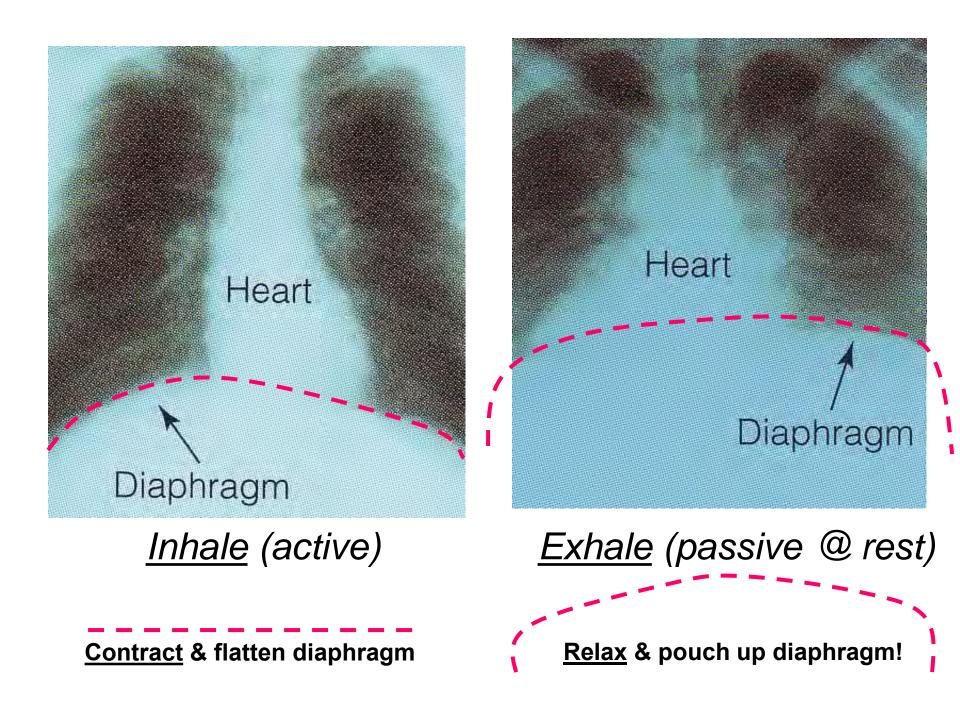


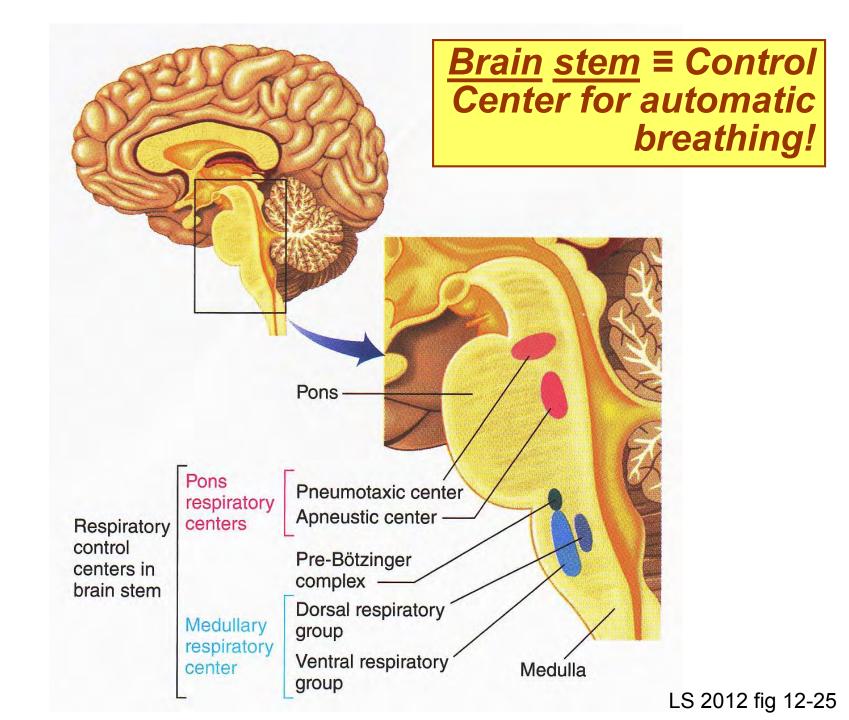
Respiratory System Anatomy

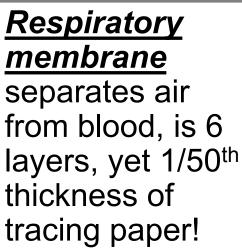


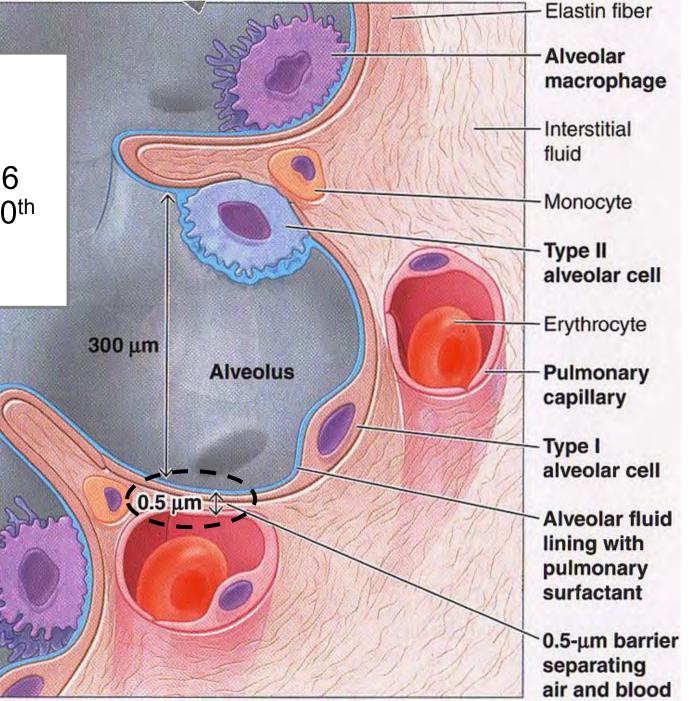
LS 2012 fig 12-2











LS 2012 fig 12-4a

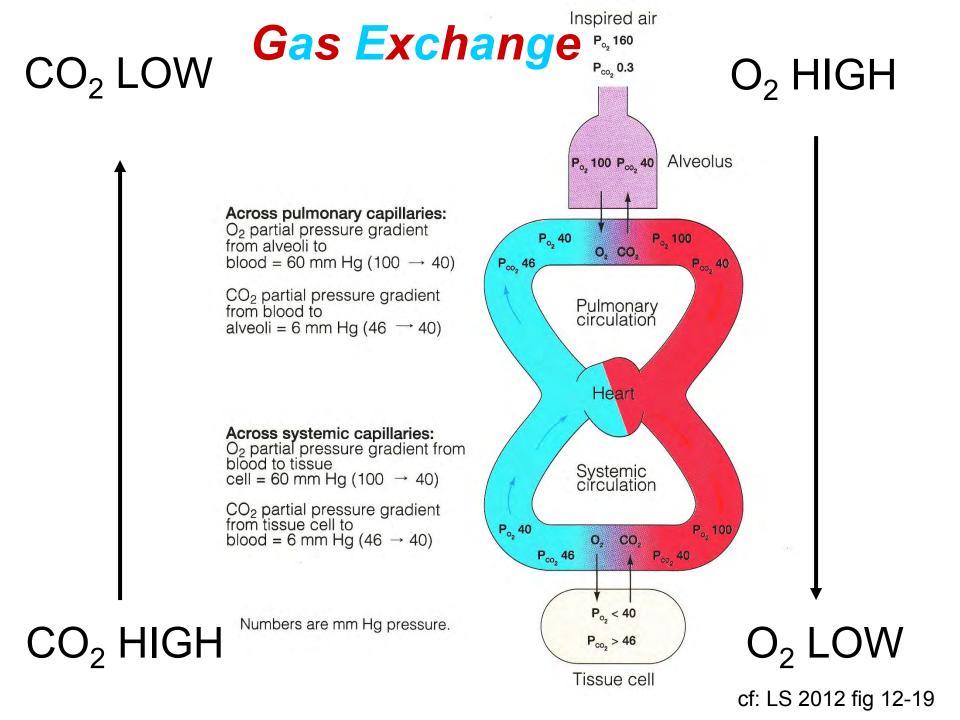


TABLE 12-3

Methods of Gas Transport in the Blood

GAS	METHOD OF TRANSPORT IN BLOOD	PERCENTAGE CARRIED IN THIS FORM
0,	Physically dissolved	1.5
	Bound to hemoglobin	98.5
co,	Physically dissolved	10
-	Bound to hemoglobin	30
	As bicarbonate (HCO_3^{-})	60

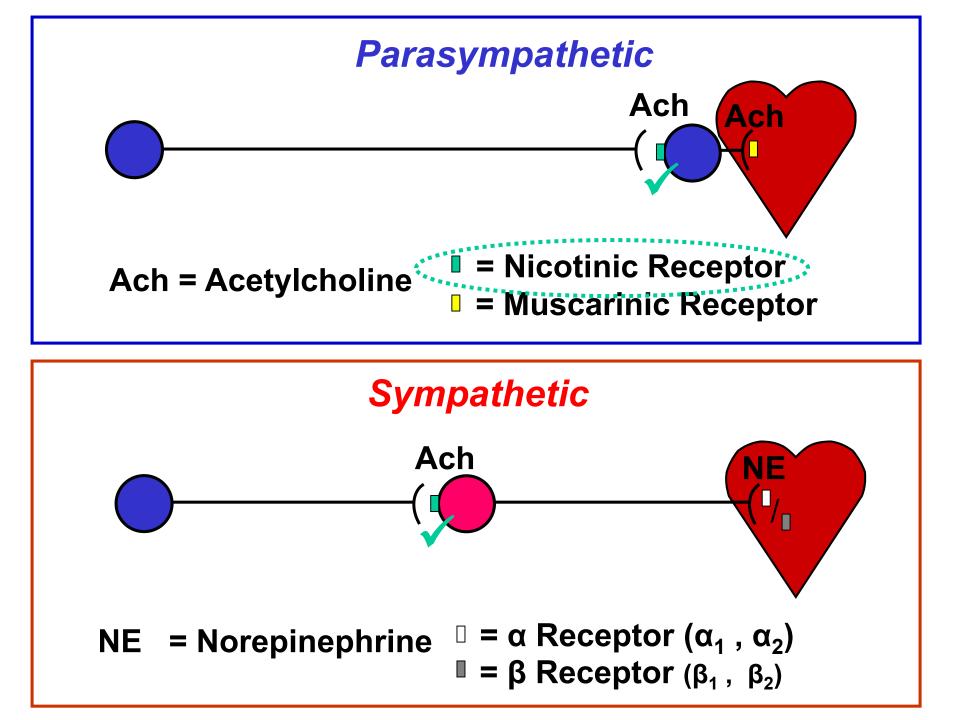
Not only the Lungs, but the Heart, Brain & 100s of Other Tissues & Organs Adversely Affected!



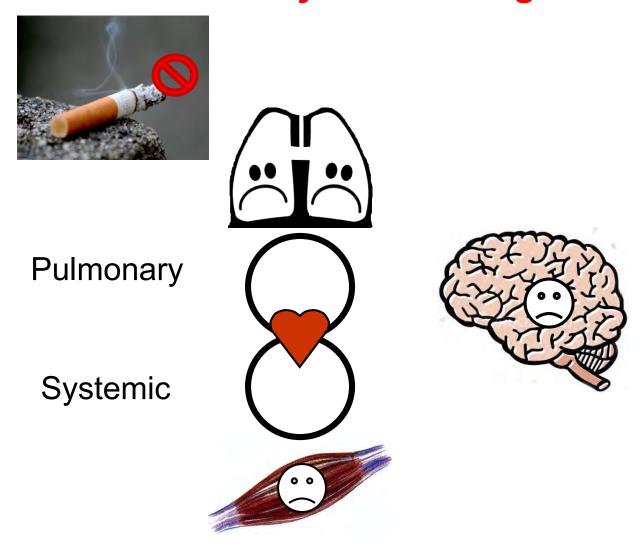
Tobacco smoke = Deadly mix of > 7000 chemicals!

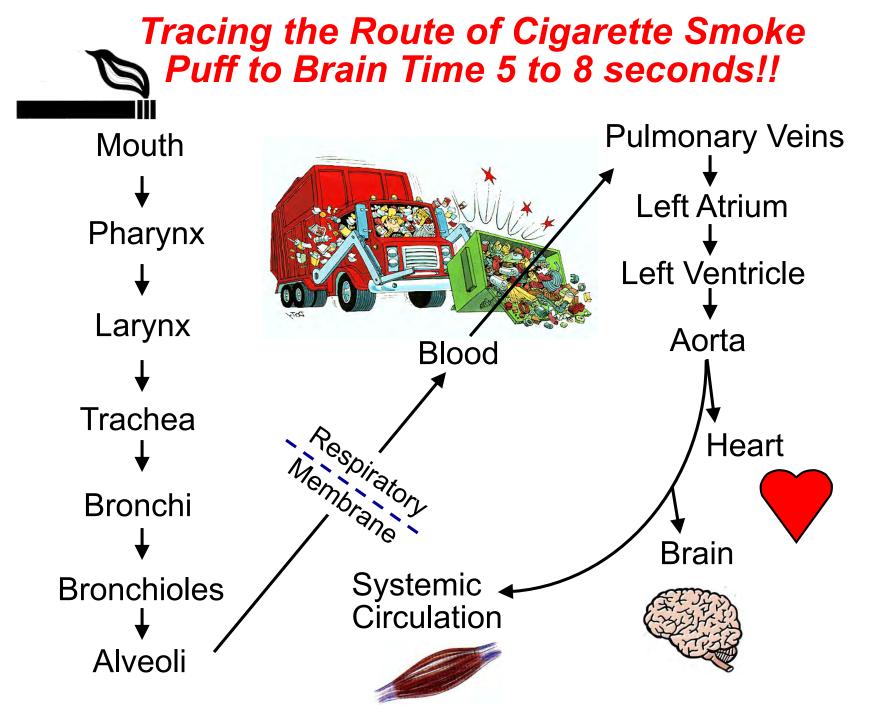
<u>http://www.cdc.gov/tobacco/data_statistics/sgr/</u> 50th-anniversary/index.htm#fact-sheets

<u>http://www.cdc.gov/tobacco/data_statistics/sgr/</u> 2010/consumer_booklet/chemicals_smoke/



Cigarettes ≡ <u>Patient-Assisted Drug-Delivery System</u> Inhaling Bypasses the Systemic Circulation & Is Powerfully Reinforcing!





Keep it Basic? Cigarette smoking is the most important preventable cause of premature death in the **U.S.** accounting for 443,000 annual deaths.

<u>http://www.cdc.gov/tobacco/data_statistics/fact_sheets/</u> <u>health_effects/tobacco_related_mortality/#cigs</u>

Cigarette smoking causes 87% of lung cancer deaths and is responsible for most cancers of the larynx, oral cavity & pharynx, esophagus, & bladder

Emphysema ≡ Corrosion of Alveolar Walls with ↓ SA & Labored Breathing



Internet Journal of Pathology Mayo Clinic Health

Why you have to tell your gynecologist you smoke. Even if it's only at parties.

You figure an occasional cigarette can't hurt, and you really don't want to listen to the "stop smoking" lecture from your doctor. But if you want any type of hormonal birth control, smoking is a vitally important issue.

Hormonal birth control is a prescription drug, and while the risks are rare, they can be serious, and smoking, even a little, increases the risks, especially if you're over 35.

Risks include blood clots, stroke, and heart attack. If you have a history of these conditions or certain cancers, you shouldn't use hormonal birth control.

Of course, you should tell your healthcare professional if you could be pregnant, and because hormonal birth control doesn't protect against HIV or sexually transmitted diseases, learn how to stay safe and healthy.

Hormonal birth control has been used safely by millions of women for 45 years, and is 99% effective when used correctly.

It could be a good choice for you. To find out, talk to your healthcare professional. And to help you get started, there's a list of questions to ask at: www.orthowomenshealth.com

ORTHO WOMEN'S HEALTH

Be smart about your body. Be smart about your birth control.

On the Pill & Smoke?

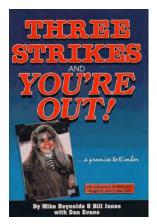
Increased Risk of:

1. Blood Clots

2. Heart Attack

3. Strokes!





2nd-hand smoke is the 3rd leading preventable cause of death in the US!

"Mind if I smoke?"

"Care if I die?"

Each year ~45,000 Americans die due to 2nd-hand smoke exposure!



News: Health, Toxicology, Pollution

Health risks of e-cigarettes emerge

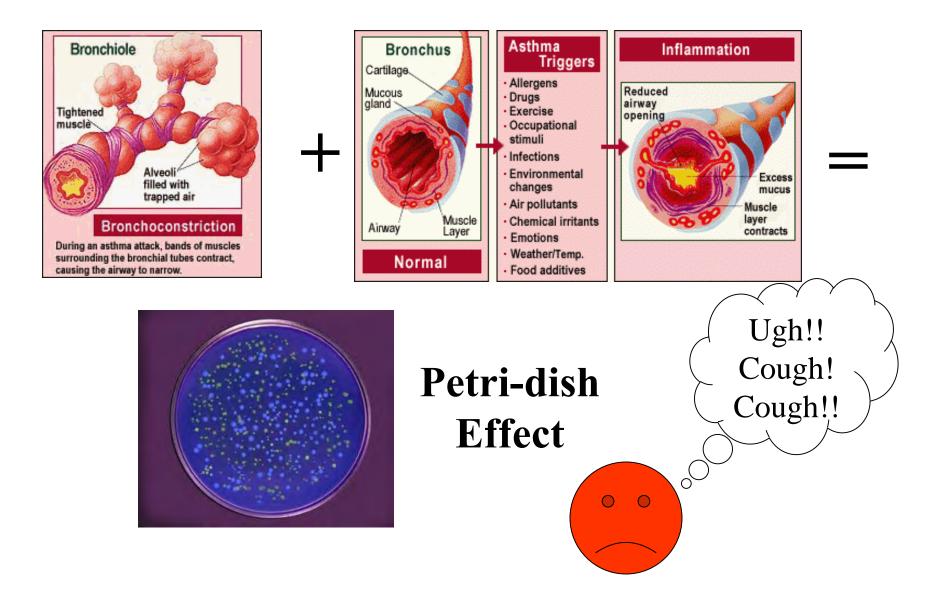
Vaping pollutes lungs with toxic chemicals and may even make antibiotic-resistant bacteria harder to kill

By JANET RALOFF 4:31PM, JUNE 3, 2014



https://www.sciencenews.org/article/health-risks-e-cigarettes-emerge

SMOKING \equiv **ASTHMA**?





freebase nicotine!!

Ammonia converts nicotine, the addictive agent in tobacco, into a more volatile form, Pankow said. "Ammonia is the thing that helps tobacco companies hook the smoker by providing a means of delivering the nicotine."

Last October a former tobacco industry employee revealed that secret industry documents indicated that ammonia was added to tobacco to double the impact of nicotine. The Oregon Graduate Institute study confirms the contention that

Nicotine Addiction & Help Quitting Smoking

http://www.cancer.org/healthy/stayawayfromtobacco/guide toquittingsmoking/guide-to-quitting-smoking-help-phys-nrt

2nd-Hand Smoke or ETS & 3rd-Hand Smoke?

<u>http://www.cancer.org/cancer/cancercauses/tobaccocancer/</u> <u>secondhand-smoke</u>

2nd-Hand Smoke Addictive?

http://www.ncbi.nlm.nih.gov/pubmed?term=2nd%20hand %20smoke%20addictive

http://www.ncbi.nlm.nih.gov/pubmed/20211642 http://www.ncbi.nlm.nih.gov/pubmed/19936715 http://www.ncbi.nlm.nih.gov/pubmed/21840504