Lipids

An introduction

Rendering Lipids Esthetic

- Freshly pressed olive oils
- Freshly pressed seed oils
- Freshly processed milk fat products

Do NOT need further refinement

Lipids Containing

- Carotenoids
- Lipoproteins
- Sterols
- Gums
- Lipopolysaccharides
- Phosphoglycerides
- Lipid auto-oxidation products

- Polymerization products
- Anabolic steroid residues
- Lipid-soluble hydrocarbon
 pesticides
- Mycotoxins due to fungal invasions
- Foul smelling ketones and aldehydes

<u>DO</u> require further refinement

Most Common Refining Techniques

- Neutralization
- Degumming
- Bleaching
- Deodorizing
- Winterization

NEUTRALIZATION

- 1. Addition of alkali produces oil-Insoluble soaps from FFA called "foots" when present in great quantities, are called "soap stock".
- 2. High Temperature steam distillation with greatly reduced prtessures drives the removal of the volatile FA's from the acylglycerols.
- 3. Liquid-liquid extraction of FFA with C_3H_8 has been reported NOT financially feasible for human consumption

DEGUMMING

• Removes mucilaginous substances, proteins, phosphatides from crude fat

- Performed by:
 - Adding dilute H₃PO₄
 - Adding brine
 - Adding alkaline phosphate solutions
 - Steam

- Many times, degumming is done to isolate crude lecithins to form edible emulsifiers for margarines, pastas and other fat-containing foods.
- After de-gumming, oils are centrifuged at high speeds to separate the PL's from the degummed oil.
- De-gummed oils last longer because CHObased gums are removed as a source of energy for micro-organisms



- Removes undesirable colors from oils
- Conventional bleaching uses different "earths":
 - Bentonite
 - Activated clay
 - Natural clay
 - Activated charcoal
- These compounds also adsorb:
 - Soap residues
 - Gum residues
 - Heavy metals (from hydrogenation 3 examples???)
 - Phosphatides
 - Water

DEODORIZING

- Removes naturally occurring and/or secondarily occurring (oxidative or hydrolytic) flavor/odoriferous compounds.
- Done by vacuum/steam distillation: 210-280°C and 1-6 mm Hg
- Removes volatile FA's to point where 0.02-0.05% FA's are remaining.

Coconut and Palm Kernel Oils

- Need MAJOR deodorizing
- Compounds in them include
 - Aromatic methyl ketones
 - Unsaturated aldehydes
 - Ketoacids
 - Alcohols
 - Peroxide decomposition products
 - Hydroxy acids

Olive Oil and Some Prime Animal Fats

- Do not require deodorization
- They have desirable odors and flavors

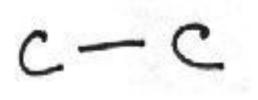
WINTERIZATION

- History: cottonseed oil legacy
- When cottonseed oil was stored in tanks in winter, about 25% of it solidified.
- The oil left over ("winter oil") was used for bottling or for mayonnaise.
- fats cooled to ppt lipids that would cause clouding of the liquid lipid when stored at refrigerator temperature.
- Solids are centrifuged or filtered.

- Liquid oil remaining evaluated by the "cold test"
- = rated by the amount of time required for the liquid fraction to become cloudy at 0° C.
- Olive oil, corn oil, sunflower seed oil usually are NOT winterized.
- Soybean oil is hydrogenated and winterized to remain clear at regular fridge temps since it's used as salad oil.

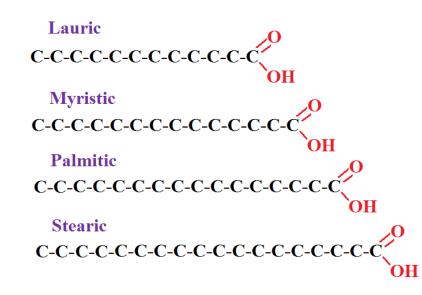
Fatty Acids

- The simplest lipids are the fatty acids.
- These are long chain hydrocarbons with carboxyl groups (COOH groups).
- We are interested in two groups of fatty acids: saturated and unsaturated fatty acids.
- Saturated fatty acids are so called because each carbon atom in the chain holds all the possible hydrogen atoms it can.
- These lipids tend to be solids at room temperature.
- These are also the sorts of lipids found around organs in the human body, acting a cushions.
- The only bonds present between the carbon atoms are single bonds.



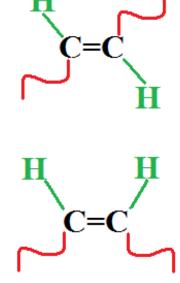
Fatty Acids – Special Carboxylic Acids -- Saturated

Lauric Acid	Myristic Acid	Palmitic Acid	Stearic Acid
C ₁₂ H ₂₄ O ₂	C ₁₄ H ₂₈ O ₂	C ₁₆ H ₃₂ O ₂	C ₁₈ H ₃₆ O ₂
Dodecanoic acid 12:0	Tetradecanoic acid 14:0	Hexadecanoic acid 16:0	Octadecanoic acid 18:0
found in coconut oil	found in coconut oil	found in lard	found in lard



Fatty Acids – Special Carboxylic Acids – Un-Saturated

- Unsaturated fatty acids do not have all the hydrogens they can hold, for there are occasional carbon-carbon double bonds in addition to the single bonds between carbon atoms.
- These fatty acids tend to be liquids at room temperature and are the primary type of lipid found in skin deposits.
- Naturally occurring unsaturated fatty acids contain double bonds that are in the "cis" form and artificial unsaturated fatty acids contain double bonds that are in the "trans" form.
- The trans-fatty acids are found in oleo and margarine and have a high link with heart disease.
- Below is a graphic of the two types of double bonds.
- The squiggly lines represent the rest of the molecule.
- The top graphic shows the hydrogens across from each other in the double bond. This is the "trans" form.
- The bottom graphic shows the hydrogens on the same side of the double bond. This is the "cis" form.



- There are 4 unsaturated fatty acids that are important to remember, as well.
- NOTE: EFA = essential fatty acid.
- There are three items that need discussion, here, before examining the fatty acids:
 - 1) the "n-" nomenclature,
 - 2) the "w" (omega) system of nomenclature and
 - 3) the "delta" system of nomenclature.
- The "n-" system of nomenclature comes from going to the CH₃ end of the molecule and counting in from the end (end - [e + d] = n) to the carbon with the first double bond.
- The omega system is the same system, just another name.
- The delta (Δ) system of nomenclature of fatty acids, specifically unsaturated fatty acids, is equally as simple: the first number is the number of carbon atoms in the hydrocarbon chain.
- The number after the colon is the number of double bonds in the whole molecule between carbon atoms.
- The numbers superscripted above the delta (Δ) sign tell you the location of the double bonds, e.g., Δ9, 12, 15: the double bonds are between carbons 9 and 10, 12 and 13 and 15 and 16, where we only identify the carbons by the lowest number in the double bonds.

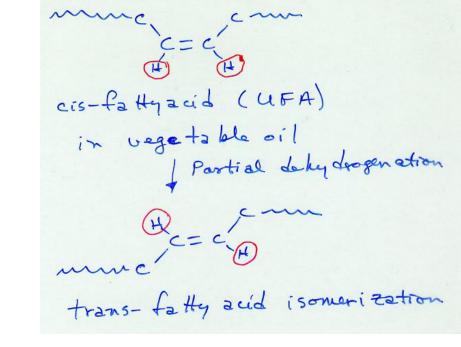
Mono-Un-Saturated Fatty Acids (MUFA)

- 18:1, n-9 or 18:1 ω 9 or 18:1 Δ ⁹
- Oleic Acid
- Cis-9-octadecenoic acid (trans isomer is elaidic acid and causes a great deal of cardiovascular troubles)
- Olive oil (best)
- Canola oil, grapeseed oil, avocado oil, avocado, almond oil, pecan oil, peanut oil, HOSO's (high oleic sun/safflower oil) pretty good, too
- Slows development of heart disease; seems to lower blood pressure in hypertensives
- Lowers total cholesterol levels
- Raises HDLs
- Lowers LDLs
- See also: <u>http://www.spectracell.com/media/supplement-oleic-acid.pdf</u>

Poly-Un-Saturated Fatty Acid (PUFA) Nomenclature

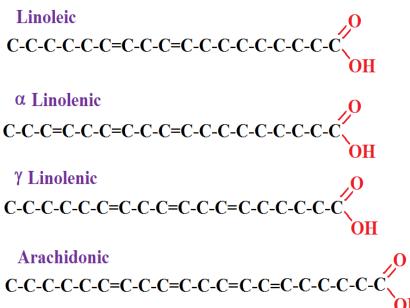
Linoleic Acid	α-Linolenic Acid	γ-Linolenic Acid	Arachidonic Acid	
9,12- octadecadienoic acid	9,12,15- octadecatrienoic acid	6,9,12- octadecatrienoic acid	5,8,11,14- eicosatetraenoic acid	
ESSENTIAL for life				
18:2 Δ ^{9, 12}	18:3 ∆ ^{9, 12, 15}	18:3 Δ ^{6, 9, 12}	20:4 Δ ^{5, 8, 11, 14}	
n-6 or ω 6 18:2, n-6	n-3 or ω 3 18:3, ω 3	n-6 or ω 6 18:3, n-6	n-6 or ω 6 20:4, ω 6	
found in corn oil, soybean oil, cottonseed oil	found in leafy vegetables and vegetable oils, flaxseed/meal (ALA), walnuts	found in leafy vegetables and vegetable oils	found in peanut oil, brain/nervous tissue	

Fatty Acid Anomalies



- "hydrogenated" margarines contain 15-40% trans fatty acids
- ↑ trans-fatty acids → hypercholesterolemia → ↑ CAD, ASHD, CHD

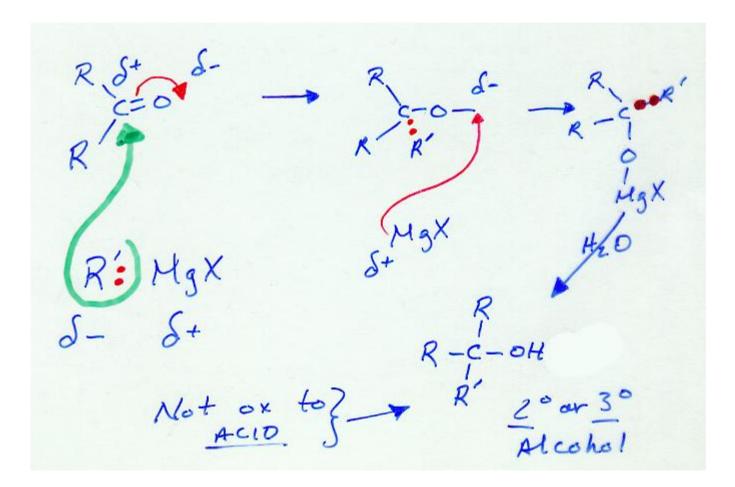
• PUFA Structures, below



Grignard Reaction and Reagent

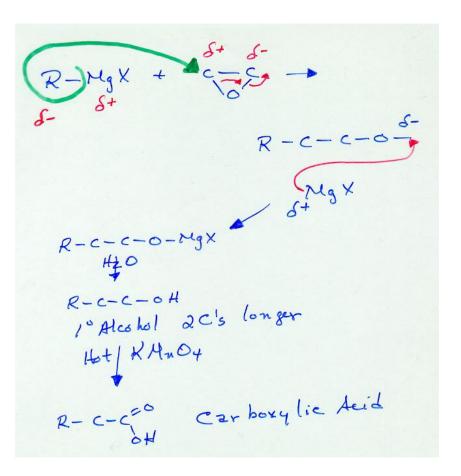
R-X + Mg ELOEL R-MgX X= Cl, Bror I Classically, Grignard Rx rxts E R- (=0 + (=0)

Grignard Mechanism -- 1

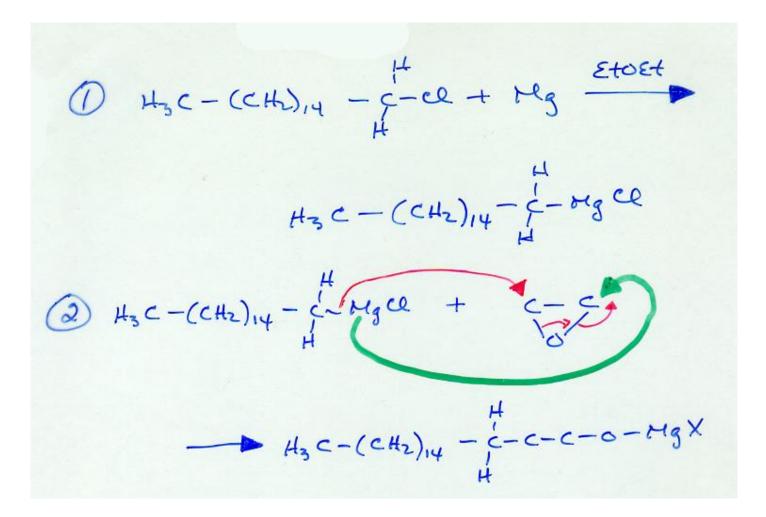


Mechanism -- 2

- Remember:
 - 1° alcohols are oxidized to aldehydes which may be oxidized to acids
 - 2° alcohols are oxidized to ketones



Sample Grignard Reaction -- 1



Sample Grignard Reaction -- 2

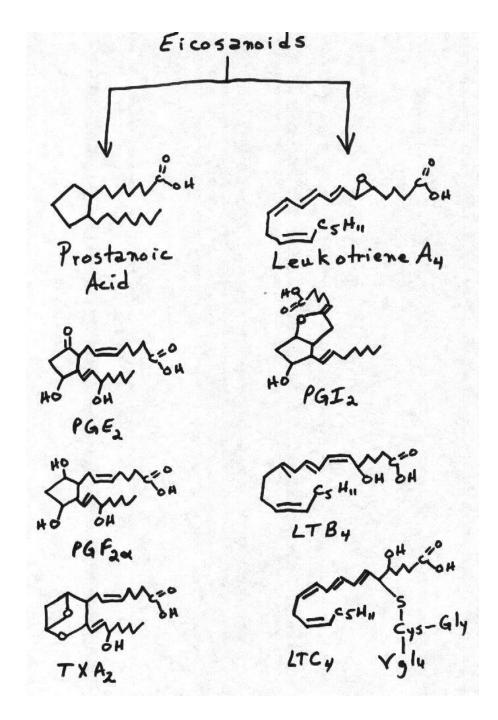
(3)
$$H_3(-(CH_2)_{14} - \frac{H}{\mu} - \frac{C-C-C-O-H}{\mu} \times H_2 O$$

 $H_3(-(CH_2)_{14} - \frac{H}{\mu} - \frac{C-C-O-H}{\mu}$
(4) $H_3(-(CH_2)_{14} - \frac{H}{\mu} - C-C-OH - \frac{Hot}{H} + \frac{Ho}{H} + \frac{Ho}{H$

Stearic acid synthesis in the organic chem lab.

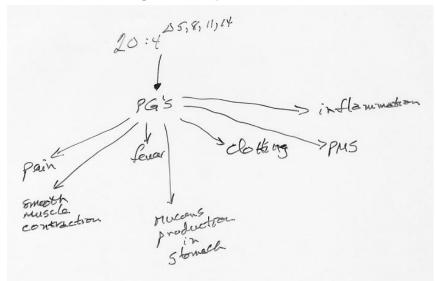
Arachidonic Acid

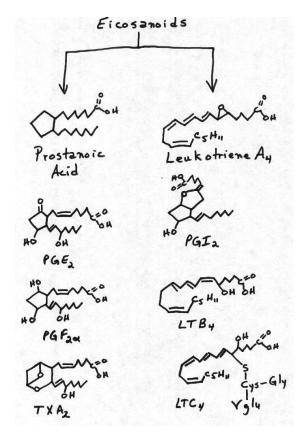
- Why is Arachidonic acid important?
- It is important because it is the precursor fatty acid for prostaglandin and leukotriene biosynthesis.
- These compounds are known as <u>eicosanoids</u>, i.e., compounds based off 20 carbons.

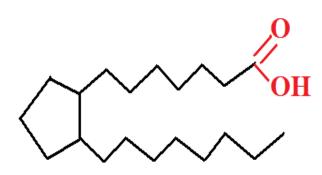


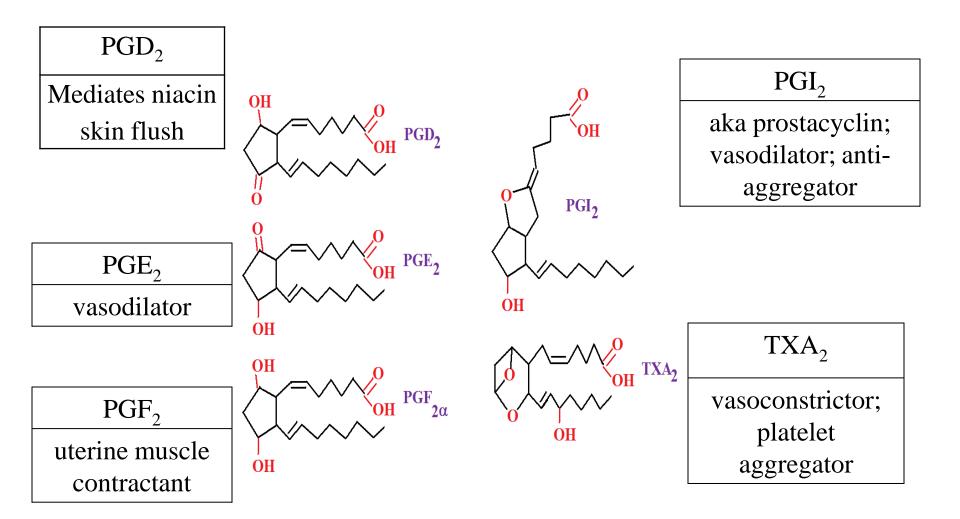
PG's and LT's

- Prostaglandins are based off prostanoic acid; representative PG's and leukotrienes (LT's) are shown, as well.
- There are nomenclature rules that follow prostaglandins, too. PG is short for prostaglandin.
- The **letter** tells us about the ring constituents and the **subscripted number** tells us how many double bonds there are on the side chains.
- PG's may be inhibited at the level of synthesis with aspirin; anti-leukotriene agents are now available for treating airway diseases.









ω 3 PUFA's

- Note that arachidonic acid gives rise to the PG_{"2"} series of prostaglandins most of these are pro-inflammatory and can lead to serious consequences, e.g. myocardial infarction.
- Recently, two significant PUFA's (EPA and DHA) in fish oils have found more and more use for the treatment of various hyperlipidemias because they are n-3 fatty acids which produce the PG_{"3"} family which are primarily anti-inflammatory and, hence, heart healthy (EPA and DHA are illustrated above).
- There is some preliminary research (2010) that suggests that mammalian cells can elongate ALA (18:1, n-3) to 20:5, n-3 (EPA) the conversion is not very efficient: 11 g of ALA (10 Tbsp of flaxseed meal a day!) are needed to biosynthesize 1 g EPA.
- It also seems that 20:5, n-3 is elongated to 22:6, n-3

PUFA Update: PI-PUFA

Sources (09/14/2011): <u>http://www.cyberlipid.org/fa/acid0001.htm</u> http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=102&abstractID=79929

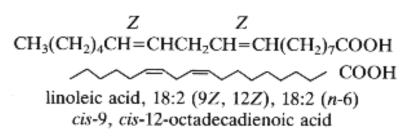
To describe the unsaturated fatty acids, two methods are available:

The chemist's terminology:

The carbon atoms are counted from the carboxyl group which put the emphasis on the double bond closest to this group (Δ -notations).

As an example:

- 18:2 Δ9,12 or 18:2 ^{Δ9,12}
- cis-9, cis-12-octadecadienoic acid,
- the trivial name: linoleic acid.



The double bonds have usually a Z (cis) configuration (but can have also an E (trans) configuration): Z9,Z12octadecadienoic acid

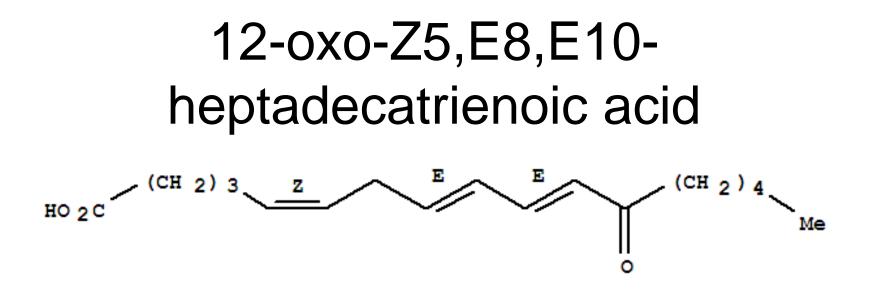
The biochemist's and physiologist's terminology:

Holman RT proposed in 1964 a new numbering system for the unsaturation of fatty acids, the "omega nomenclature". The double bonds are counted from the methyl group determining the metabolic family, noted by ωx (ω for the terminal carbon) or the equivalent n-x (n for the total number of carbon, x being the position of the distal double bond) method. The other double bonds are deduced from the first one by adding 3 (this is the most frequent structure, non-conjugated fatty acids, but sometimes by adding 2, these double bonds are called conjugated).

Thus, linoleic acid or cis-9, cis-12-octadecadienoic acid is also named using the shorthand nomenclature 18:2 (n-6). This compound has 18 carbon atoms, 2 double bonds and 6 carbon atoms from the last double bond to the terminal methyl group. In the old literature it was designated 18:2 ω 6: 18-6=12, 12-3=9, hence Δ 9,12.

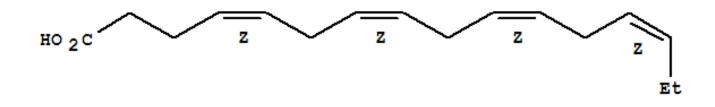
cisplatin Clower NH₃ Clower NH₃

- Cisplatin is a cancer chemotherapeutic agent which is used in treating cancers including: sarcoma, small cell lung cancer, germ cell tumors, lymphoma, and ovarian cancer.
- It is often considered an alkylating agent, however, it contains no alkyl groups and does not instigate alkylating reactions, so is most appropriately designated as an alkylating-like drug.
- It causes DNA cross-linking and drives apoptosis to kill the malignant cells.
- NCI link: <u>http://www.cancer.gov/cancertopics/druginfo/cisplatin</u>



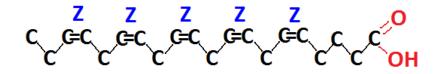
- KHT (acronym)
- Platinum Induced PolyUnsaturated Fatty Acid: PI-PUFA
- Inhibits action of some cancer chemotherapeutic agents, e.g., cis-platin
- Also found in Fish Oils NOT to be taken with many chemotherapy agents!

16:4 (n-3) hexadeca-Z4,Z7,Z10,Z13-tetraenoic acid (HDTA)



- Also CA Tx inhibitory PI-PUFA
- Also found in fish oils
- Also need to stop if receiving CA Tx

20:5 (n-3) all-Z-5,8,11,14,17-Eicosapentaenoic acid (EPA)



- One of three important n-3 fatty acids
- Other two are:
 - 22:6, n-3 (DHA)
 - 18:3, n-3 (ALA)
- EPA used as control in PI-PUFA determination: no impact on the PI-PUFA biosynthesis

Alzheimer's Disease -- 1 Form

- Alzheimer's is inherited in a confusing manner: there seems to be at least 3 genes involved in this disease (21pter-q21; 14 (early onset) and 19 (late onset of this disease). Additionally, there is an incredible amount of reduced penetrance. It could be inherited autosomal dominant OR recessive. The involved protein is β-amyloid protein. This disease causes 50-70% of the cases of senile dementia. β-amyloid protein forms the core of plaque formation outside nerve cells and plays a role in the formation of neurofibrillary tangles in 2 regions of cells in the brain. Alzheimer's alters language skills, personality and causes seizures.
- NOTE: there seems to be some sort of relationship with Down Syndrome: 1) patients with trisomy 21 who live to be 40 YOA show Alzheimer's pathology; 2) Alzheimer's patients report a higher incidence than expected of 1st degree relatives with trisomy 21 -- interesting the relationship with 14 and 21: perhaps Robertsonian translocation is involved, here, as well??????
- •
- Although determination of apolipoprotein E₄ levels is available for diagnostic testing, the results are unreliable. To date, the only way to ascertain Alzheimer's is at autopsy by examining brain tissue samples. Death by Alzheimer's is approximately 8-10 years after onset of the disease. The best therapy remains as managing depression and anxiety and other symptoms with symptomatic treatment.

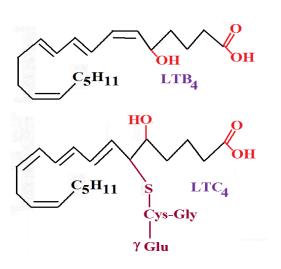
LTA_{A}

Its biological actions are determined primarily by its metabolites.

LTA

LTB_4

chemotactic agent for PMN's (segmented neutrophils); has been proposed to play a role in a variety of acute and chronic inflammatory diseases such as arthritis, dermatoses, inflammatory bowel disease (IBD), and chronic obstructive pulmonary disease (COPD). In particular, LTB₄ seems to play a role in the recruitment of inflammatory cells to the site of tissue injury. (http://ajrccm.atsjournals.org/cgi/content/full/161/2/S1/S25)



LTC₄

involved in allergy and anaphylaxis; more potent than **HISTAMINE** in shutting down airways and increasing swelling; component of SRS-A: bronchoconstrictor and vasodilator



Role of Antileukotriene Agents in Asthma Therapy

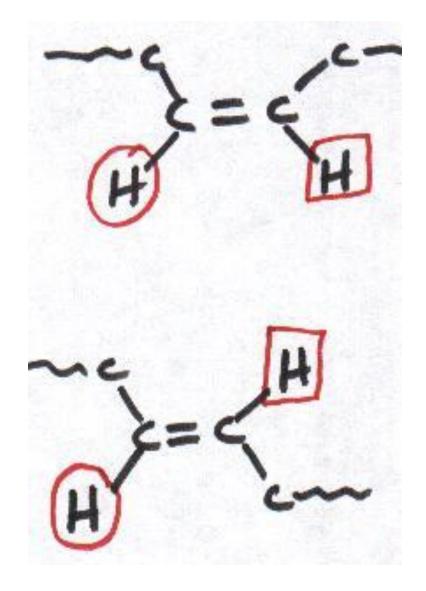
• SM Gawchik; CL Saccar : ABSTRACT: Leukotrienes are proinflammatory mediators

with special significance in asthma. Released by numerous cell types, particularly after exposure to allergens, leukotrienes cause a potent contraction of bronchial smooth muscle, resulting in reduced airway caliber. Further, they cause plasma to leak from the vessels, resulting in edema, and enhance the secretion of mucus--both events that increase airway obstruction. Thus, leukotrienes have been a target of basic research in asthma.

- To date, a number of antileukotriene agents have been developed, and three are currently being used in clinical practice in the United States: *zafirlukast [ACCOLATE]* and *montelukast [SINGULARI]* act by antagonizing the leukotriene receptor, and *zileuton [ZYFLO]* inhibits leukotriene synthesis. Studies have shown that these agents improve asthma symptoms, pulmonary function, and patient quality of life.
- Antileukotriene agents have generally been associated with a low incidence of side effects and good tolerability.
- Currently recommended for mild-to-moderate, persistent asthma, these agents have enabled patients to reduce their use of corticosteroids.

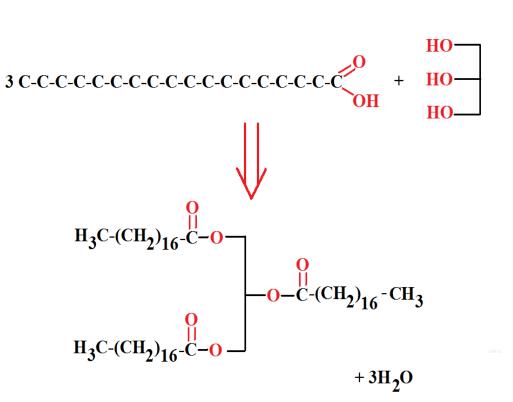
Fatty Acid Anomalies

- When vegetable oils are partially hydrogenated to solidify them, invariably some cis (H's on same side of the double bond) fatty acids are altered (isomerized) to trans (H's on opposite side of double bond) fatty acids.
- Hydrogenated margarine contains 15-40% trans fatty acids.
- Elevated trans fatty acids in one's diet causes hypercholesterolemia which leads to increased coronary artery disease, atherosclerotic heart disease and coronary heart disease.



Triglycerides (TG's or TAG's)

- TG is fairly self explanatory; TAG's are triacyl glycerols the same thing, just a slightly different name. TAG's are made by condensing one molecule of glycerol with three molecules of fatty acids.
- The products are the triglyceride (in this case, tristearin) and 3 moles of water.



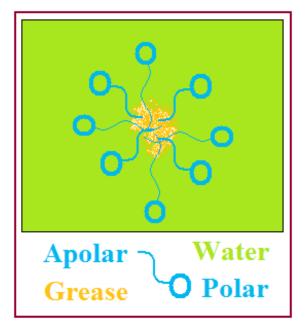
FA's in TG's

• As a general rule, fatty acids align themselves on a glycerol molecule in such a manner that the #1 carbon has a saturated fatty acid bound to it, #2 carbon has an unsaturated fatty acid bound to it and #3 is fair game.

Saponification

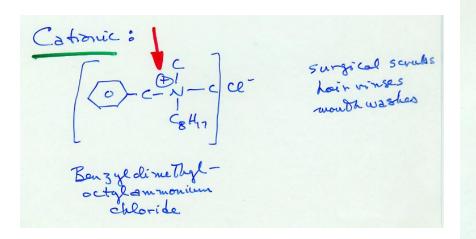
Micelles

$$I = \frac{1}{2} \frac{1}{2}$$



Synthetic Detergents -- Anionic

Synthetic Detergents -- Cationic

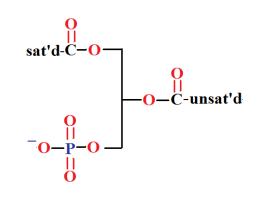


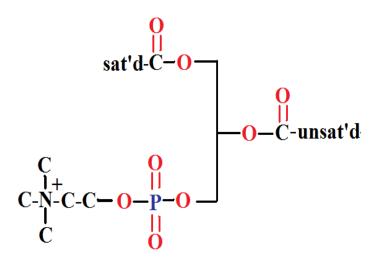
 $H_{3C} - (CH_{2})_{15} - N - C CE^{-1}$ Trime Thyl hexidacyl-zmmore ium chloride

Synthetic Detergents -- Nonionic

- A lipid related to the TAG is the phospholipid (PL).
- Instead of a third fatty acid bound, proper, to the #3 carbon on glycerol, a phosphate is bound there.
- Other groups will bind with the phosphate.
- Figure is representative of phosphatidic acid.
- A representation/illustration of phosphatidyl choline (PC) or lecithin is below.
 - You may know the latter name as it is in non-dairy creamers as an emulsifying agent.
 - PC is also important in cell membranes by assisting in membrane rigidity.
- A related PL, cardiolipin, is a sort of "dimer" of PC.
 - Cardiolipin is found in the inner mitochondrial membrane.
 - This PL causes the inner mitochondrial membrane to be more fluid so that the protein complexes on electron transport will be brought closer together during active cellular respiration.

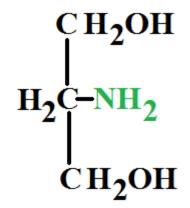
PL's





Sphingolipids

- Differ from phospholipids (aka glycerophospholipids)
- Sphingolipids found in high levels in brain tissue and in myelin sheath around peripheral nerves.
- Sphingomyelin also found in amniotic fluid.

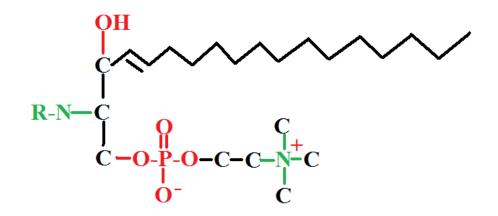


Contained in sphingolipids

Tay-Sachs

- Tay-Sachs is inherited autosomal recessive.
- The protein effected is β -N-acetylhexosaminidase A.
- It is common in eastern European Jews.
- Onset of the disease occurs at about 3-6 months of age.
- The infant develops hypotonia, hyperacusia (abnormally sensitive hearing) and retardation.
- Death usually occurs by age 2-3 years.
- Diagnostic testing is available.
- Therapy seems to be symptomatic.

Sphingomyelin



• Why are PC and sphingomyelin so important?

L/S Ratio

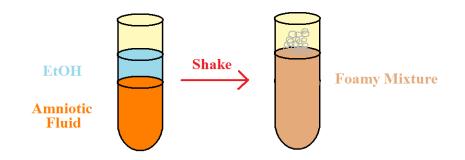
- PC required for surfactant in lung
- Surfactant not important in utero, BUT, is for BREATHING

An increase in PC comes with maturation of the lungs in utero as gestation comes to an end.		
L/S Ratio	Week of Gestation	
< 1	Before 31 st week	
2	34 th week	
4	36 th week	
8	39 th week (term ±)	

- L/S of 2 or greater is ok for C-section
- L/S < 2 NOT uniformly predictive of RDS
- L/S > 2 is associated with absence of RDS

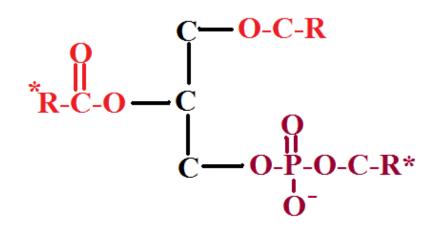
Foam Stability Test

- Fetal surfactant in amniotic fluid "makes" foam in presence of EtOH
- aka "shake test"
- Foam is "USUALLY" indicative of an L/S of about 2



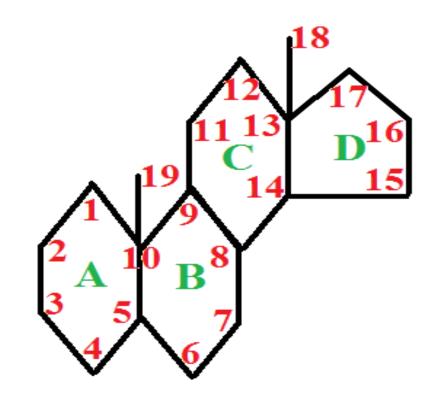
Plasmalogens

- Occur in membranes of nerve cells and muscle cells
- R* in myelin is –C-NH₃+
- R* in cardiac muscle is the N,N,N-trimethylammonium-methyl group (quaternary amine with 4 methyl groups)
- Both R*'s are found in mitochondrial membranes



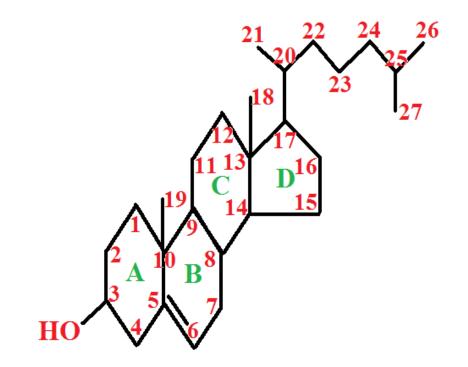
- The steroids are ALL based off of a 4-fused ring system.
- The rings are labeled A thru
 D. Each
 carbon is
 numbered as
 shown in the
 graphic.

The Steroids



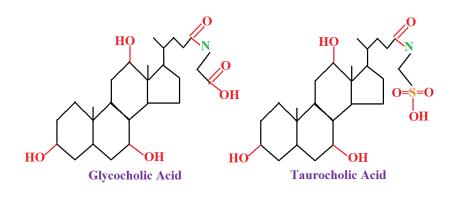
Cholesterol

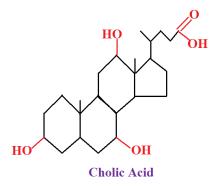
- The primary steroid, i.e., that one compound from which all steroids are derived is cholesterol.
- As you can see, the enumeration of cholesterol (once you are beyond the basic 4 ring system) is different than what one might expect.
- Carbons 18 and 19 are called bridging carbons.
- On carbon #3 is an -OH group and between carbons 5 and 6 is a double bond.
- The hydrocarbon tail off carbon 17 is enumerated for you, above. In addition, the hydrocarbon chain will be modified by the body as necessary for the synthesis of specific steroids.



- Cholesterol also plays an important role in digestion.
- The manner in which this occurs is that a derivative of cholesterol (cholic acid) reacts with one of two amino acids or derivatives to form detergents.
- Detergents emulsify fat in the small bowel as small particles so that the enzymes in our small bowels may begin digesting the lipid.
- The two big bile salts, as these detergents are called, are glycocholic acid and taurocholic acid.
- Glycocholic acid is formed by the reaction of gly with cholic acid.
- Taurocholic acid is formed by reacting the oxidized product of cys, taurine, with cholic acid.
- Note that there is a polar, charged end and a nonpolar, uncharged, lipid-like end.
- It is due to these features that detergents work, i.e., the lipid-like end binds the lipid-like molecules and the polar end interacts with the water, in effect lifting the grease into the water.

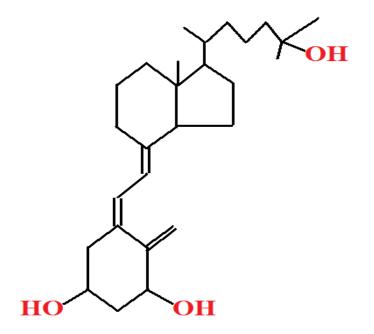
Digestive Detergents





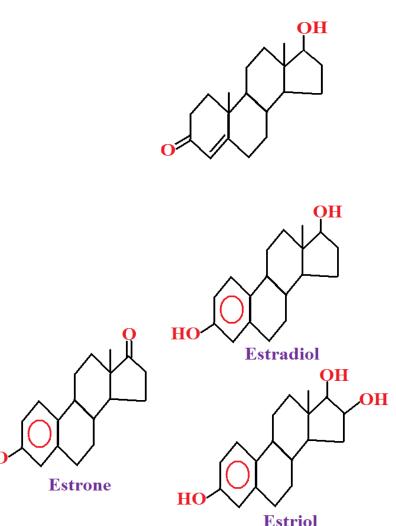
Important Steroid Hormones

- The first is Vitamin D₃.
- This steroid is necessary for proper bone uptake of calcium and for adequate calcium metabolism in the body.
- The synthesis of this steroid begins in the skin with the photolysis of a cholesterol metabolite called 7-dehydrocholesterol.
- The synthesis of this "vitamin" is completed in the liver and kidney, respectively.



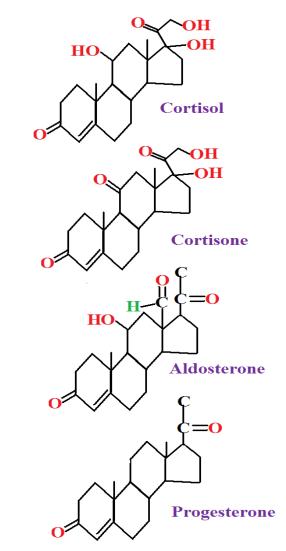
Sex Hormones

- Cholesterol is also the precursor for the steroid sex hormones.
- Note that each estrogen (estriol, estradiol and estrone) has an aromatic ring A.
- This is due to an enzyme found in the biological fat layer in females called aromatase.
- Aromatase aromaticizes testosterone to the estrogens.



Other Steroid Hormones of Importance

- Cortisol is known as the muscle wasting hormone.
- This hormone kicks in as a stress hormone during starvation and causes muscle protein to be catabolized in such a manner that the carbon back bone of the individual amino acids is used to synthesize glucose.
- Cortisone we're familiar with as an anti-inflammatory agent.
- Aldosterone is a mineralocorticoid that is responsible for directly regulating sodium/potassium ion regulation and indirectly with water balance and chloride ion regulation.
- Progesterone is the last female sex steroid hormone and is also the precursor for the synthesis of testosterone in the male.



The Most Complex Lipids: The Lipoproteins of The Blood

Lipid Complexed with Water-Soluble Proteins We are interested in 4 categories of lipoproteins: Chylomicrons, VLDL's, LDL's and HDL's (very low density lipoproteins, low density lipoproteins and high density lipoproteins). The table below describes the characteristics of the lipoproteins:

Classes of Lipoproteins					
	% Protein	% TAG	% PL	% Cholesterol esters	
Chylomicrons	1-2	85-95	3-6	2-4	
VLDL	6-10	50-65	15-20	16-22	
LDL	18-22	4-8	18-24	45-50	
HDL	45-55	2-7	26-32	15-20	

Lipoproteins \equiv lipid complexed with water-soluble proteins

Comments

- Chylomicrons, by and large, are artifactual in the sense that they appear after we've eaten or if we have some sort of lipid metabolizing disease, e.g. diabetes mellitus, and are usually rapidly cleared from the blood stream under normal circumstances.
- The LDL's are the cholesterol forms we hear about as the "bad" cholesterol.
 - This portion is true as when we get too many LDL's, the cholesterol plates out in our arteries and forms atherosclerotic plaques.
- While the HDL's are touted as the "good" cholesterol, it is important to remember that it is ONE form of the HDL that is the good cholesterol.
- ASIDE: Not all cholesterol is "bad" cholesterol.
 - Remember, we need some cholesterol in our diets to synthesize steroid hormones.
 - While our bodies WILL synthesize steroids from smaller molecules, they
 prefer cholesterol as the starting molecule.
- Note that LDL-cholesterol runs about half cholesterol.

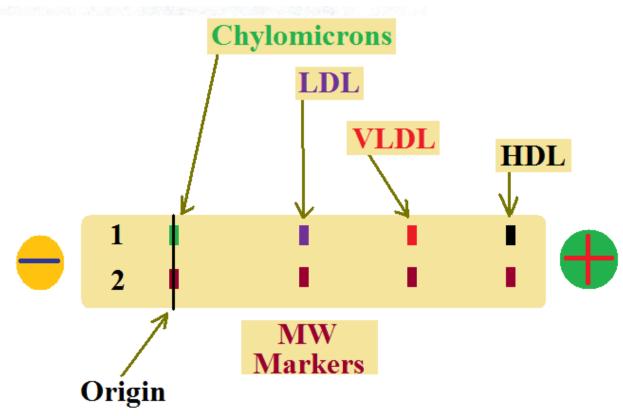
LDL-Cholesterol

 In many instances, it is difficult to obtain an actual lab analysis of the LDL-cholesterol. In that case, it may be calculated in one of two ways:

Method 1:

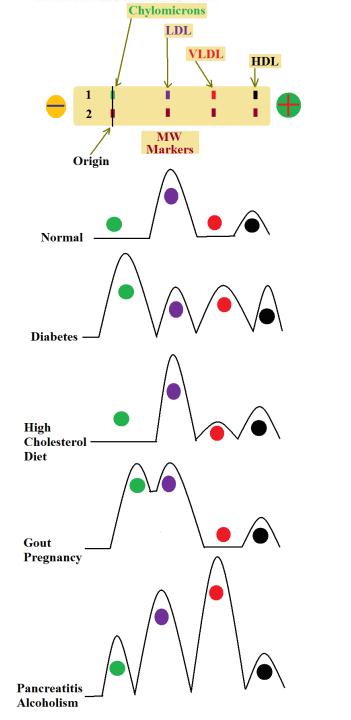
- LDL = Cholesterol_(total) (VLDL + HDL) Method 2:
- LDL = Cholesterol_(total) [(0.2*TAG) + HDL] where TAG are the triglycerides in your blood

- These lipoproteins may be separated in a polyacrylamide gel or on paper that is in an appropriate buffer by applying an electrical current.
- This is called electrophoresis.
- As the molecules migrate into the gel under the influence of the current, they "are looking" for the region of the gel at that particular pH and charge where the medium is most "like themselves".
- Once these molecules reach that region, they stop migrating and may be analyzed.
- Below is a representative graphic that demonstrates the separation of these lipoproteins at a pH of 8.6



- Note that with the exception of the Chylomicrons, the other lipoproteins are attracted to the positive side of the gel (or paper), indicating that their charges are more negative.
- The origin is the place where the samples are place in tiny wells in the gel.
- The Chylomicrons did not move from the origin.
- Information like this is very useful, clinically.

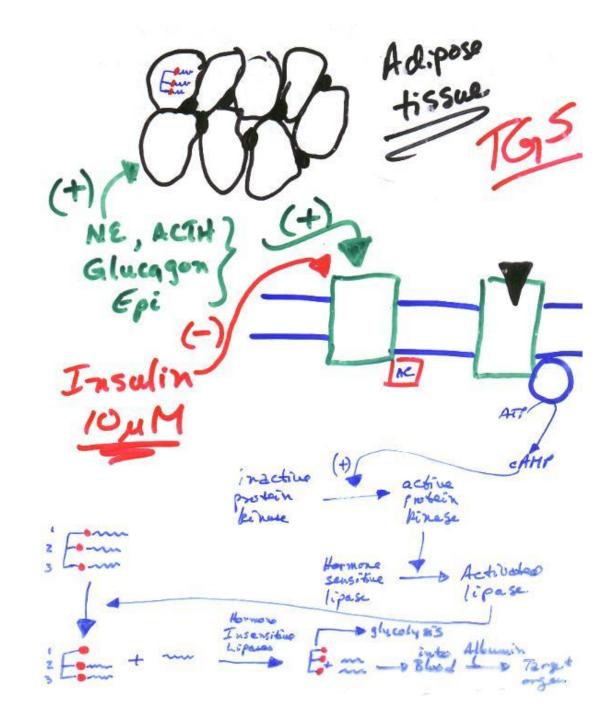
- Information like this is very useful, clinically. Patterns of lipoproteins may be detected by utilizing a gel scanner that uses light to detect how much of a particular lipoprotein is present. Some sample scans and their associated disease states are presented to the right.
- Note that
 - diabetics have elevated Chylomicrons and VLDL's with lowered LDLcholesterol;
 - those eating a high cholesterol diet have elevated LDL's and VLDL's;
 - those with gout have elevated LDL's and VLDL's, as do pregnant women;
 - those with pancreatitis or alcoholism have elevated Chylomicrons, LDL's and VLDL's.

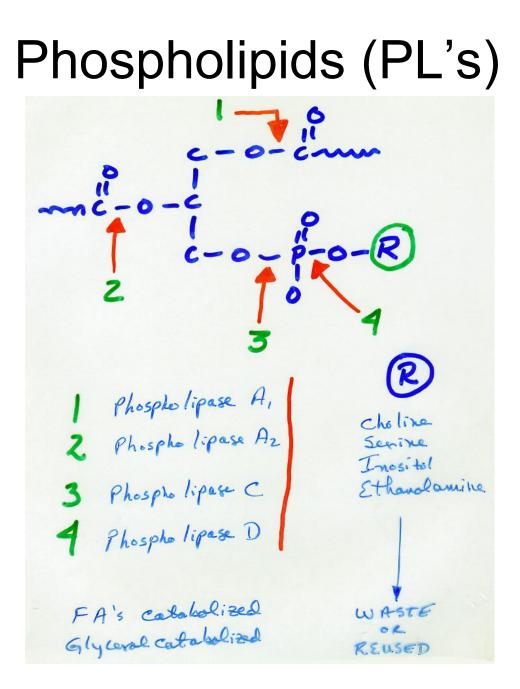


Lipid Metabolism

The Nickel Tour

Lipids

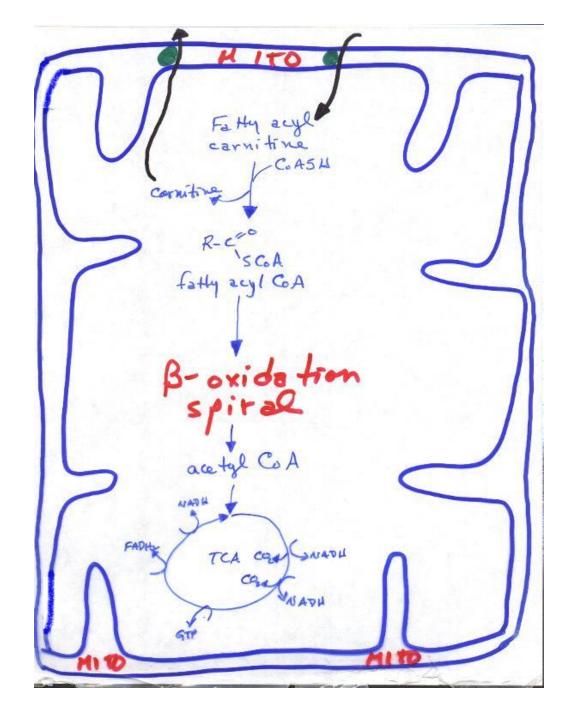




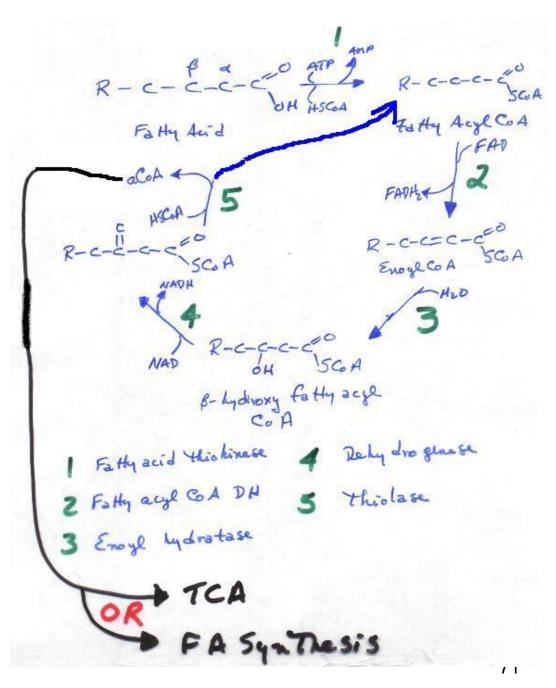
Fatty Acid Catabolism

ATP FA COASH >2Pi AMP . Ac five ted R-40 0-SCOA à fatty acyl Cod 2 04 carniti 45GA Carnitine -0H Vacyeles C-N-C fatty 200 MITO HITO fatty acyl carnitine

Fatty Acid Catabolism



β-Oxidation of Fatty Acids



β-Oxidation of Fatty Acids

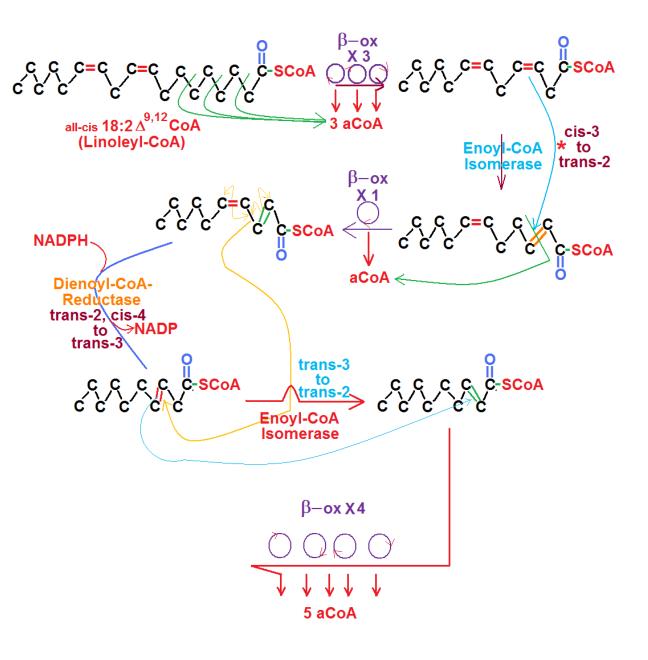
- H3C(CHS)14 SGA aGA CA a CoA CA
- Note that for 16 carbons, you only have to go through 7 turns of β-oxidation
- For 22 carbons, 10 turns
- For 30 carbons, 14 turns
- Why???

Oxidation of Odd-Numbered Fatty Acid Chains HSCoA C-C-C-C-SCoA C-C-C-SCoA aCoA D/L-methylmalonylCoA TCA Succiny CoA

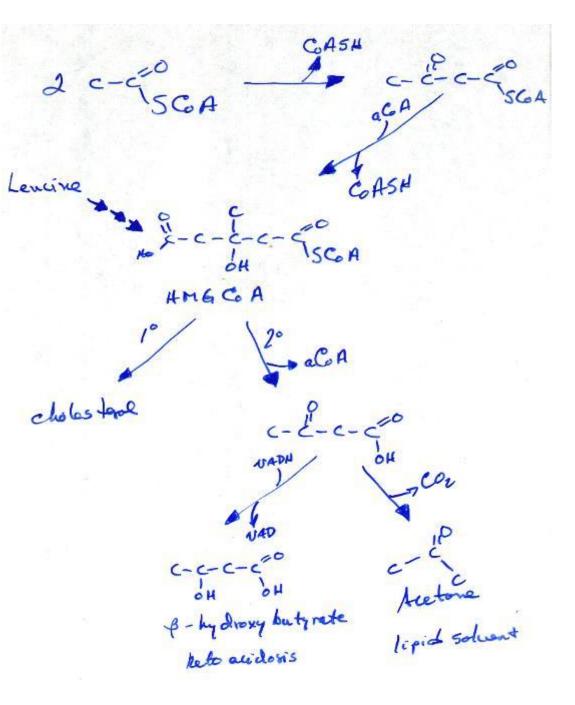
- The oxidation of fatty acids with an odd number of carbon atoms in its chain follows normal β-oxidation UNTIL there are 5 carbons left in the CoA derivative.
- At that time, one aCoA is cleaved AND a molecule of propionyl CoA is released by thiolase INSTEAD of the usual last molecule of aCoA.
- Details in above graphic.

Oxidation of Unsaturated Fatty Acids

- Unsaturation in fatty acids adds a bit of complexity to these kinds of fatty acids.
- "cis" double bonds must be isomerized to "trans" isomers for proper βoxidation.
- NADPH is used to reduce and rearrange adjacent "trans" and "cis" double bonds to perpetuate normal β-oxidation
- NADPH comes from intramito sources, e.g., GDH and/or iCDH



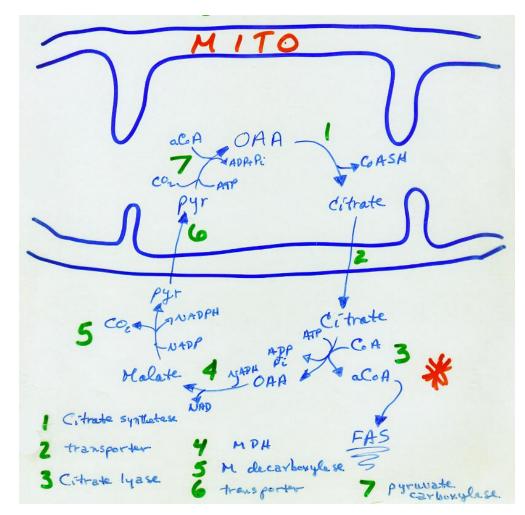
Acetyl CoA



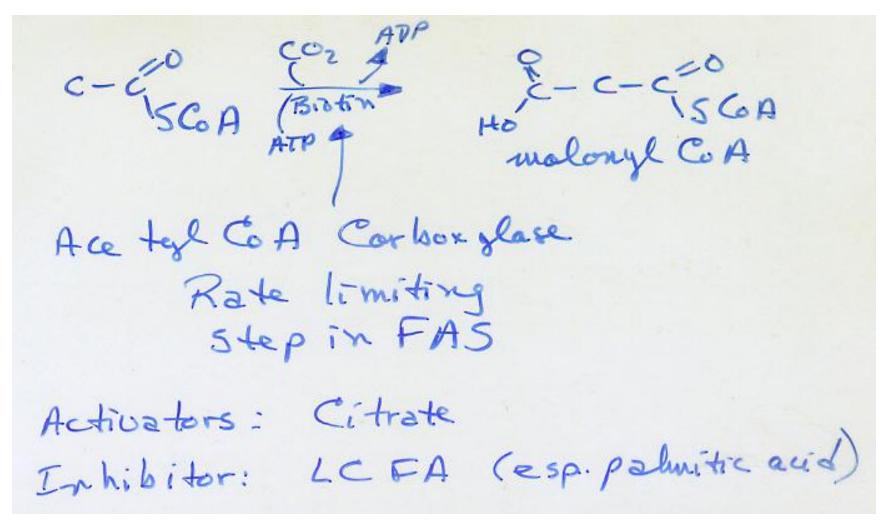
Fatty Acid Synthesis (Synthetase)

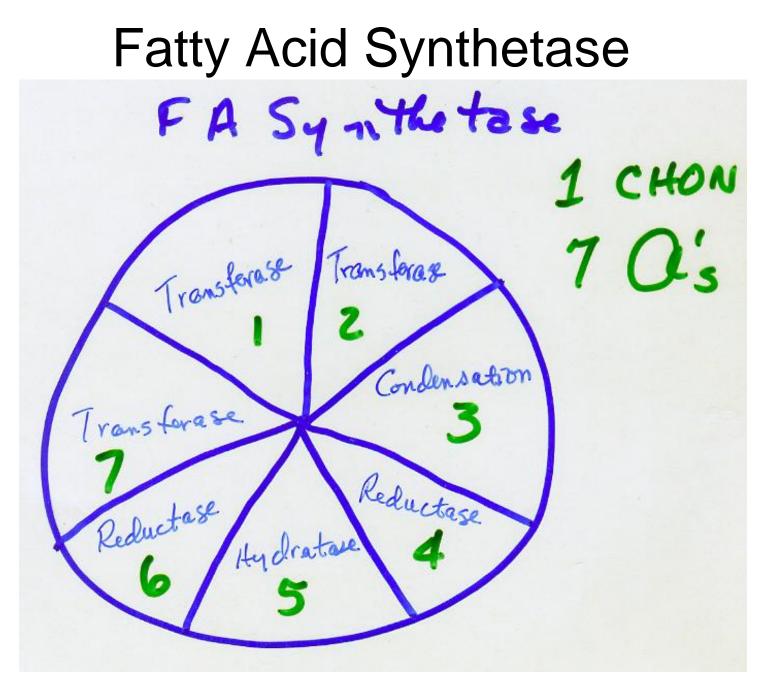
- 1. Citrate synthetase
- 2. Transporter
- 3. Sitrate lyase
- 4. MDH
- 5. M decarboxylase
- 6. Transporter
- 7. Pyruvate carboxylase

FAS occurs primarily in cytosol of liver Are some steps in the mito



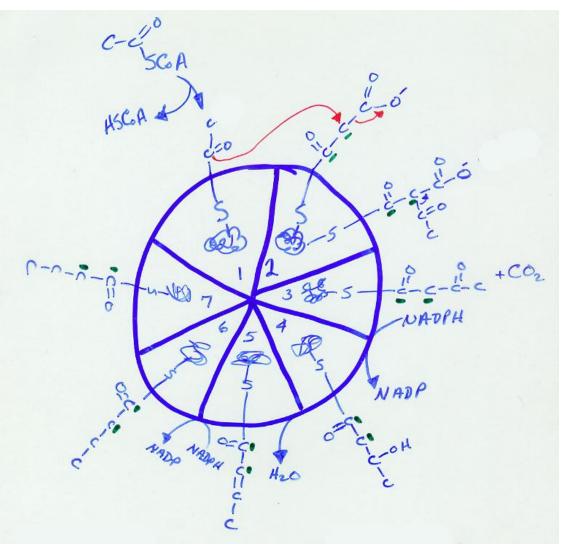
Acetyl CoA Carboxylase





"Rotary Synthesis"

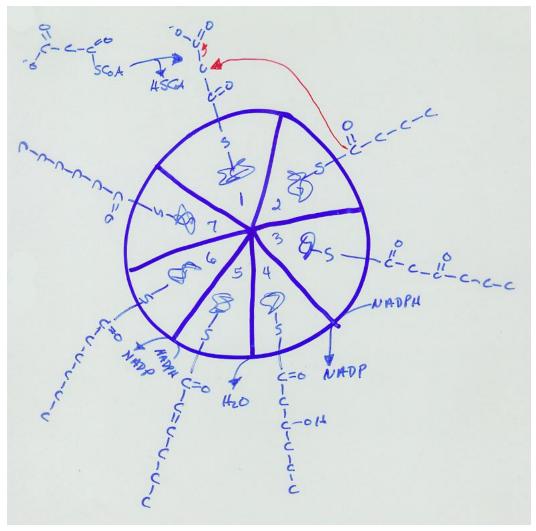
1.Transferase 2.Transferase **3.**Condensation 4.Reductase 5.Hydratase 6.Reductase 7.Transferase C-C from malonate



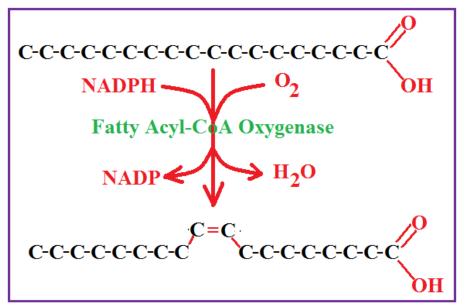
Second Rotation

1.Transferase
 2.Transferase
 3.Condensation
 4.Reductase
 5.Hydratase
 6.Reductase
 7.Transferase
 C-C from malonate

 And continues until C₁₆ which is hydrolyzed.



18:1, n-9 Biosynthesis



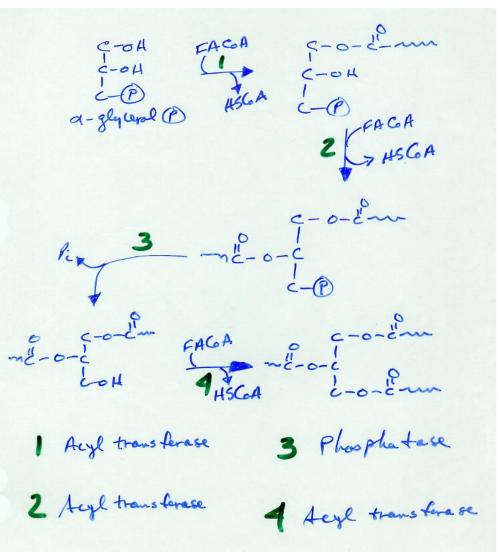
Elongation of 18:1, n-9 in vertebrates does not seem to occur commonly: mammals (excepting herbivores and non-seafood eating animals) lack the enzymes to unsaturate FA's beyond the #9 position; plants don't seem to elongate 18:1, n-3 to 20:5, n-3, although it seems that herbivores, et al, do.

LOTS of confusing data on MUFA to PUFA (n-3) conversion

Elongation of 18:1, n-9 in plants DOES occur in the synthesis of ALA (18:3, n-3) $^{81}_{81}$

TGS Synthesis

- 1. Acyl transferase
- 2. Acyl transferase
- 3. Phosphatase
- 4. Acyl transferase



Cholesterol Biosynthesis

HMGCoA Reductase and Inhibitors (β -hydroxy- β -methyl glutaryl coenzyme A) HMGCOA HONG COA - c- c- c- c=0 0H 156A - 2 NADPH Meuzstatin 2NADP & > HSGA Mevalonate Prava statin

84

Fluvastat

Cholesterol Synthesis

2-c-c-c-0H develorate

Squalene

soprene subunits

Uit D

1-dHC

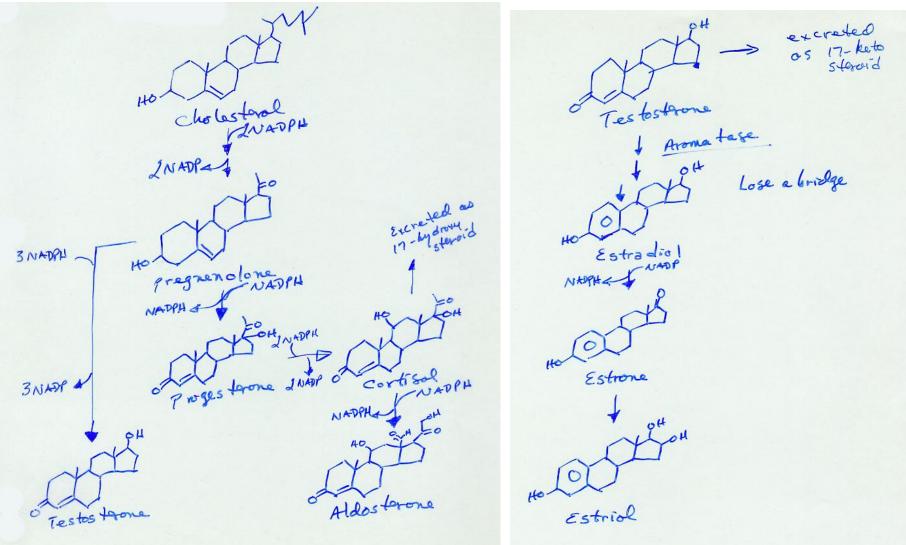
| Rear rangement

Squalance

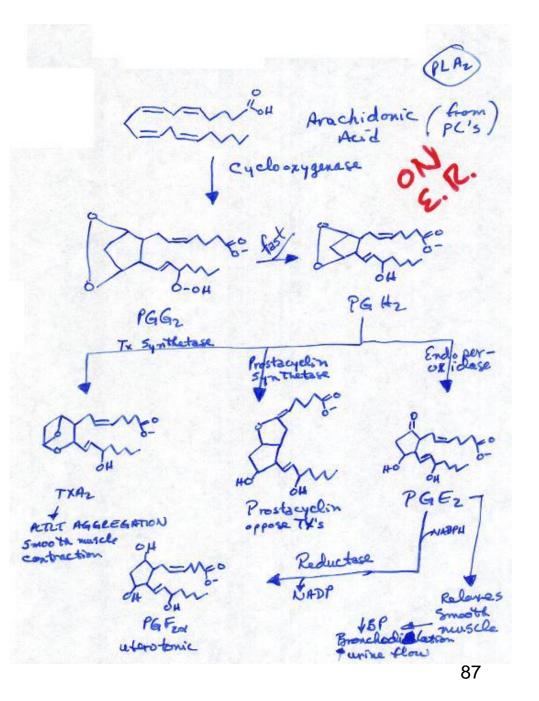
" Zips Up"

cholesteral

Steroid Hormone Synthesis

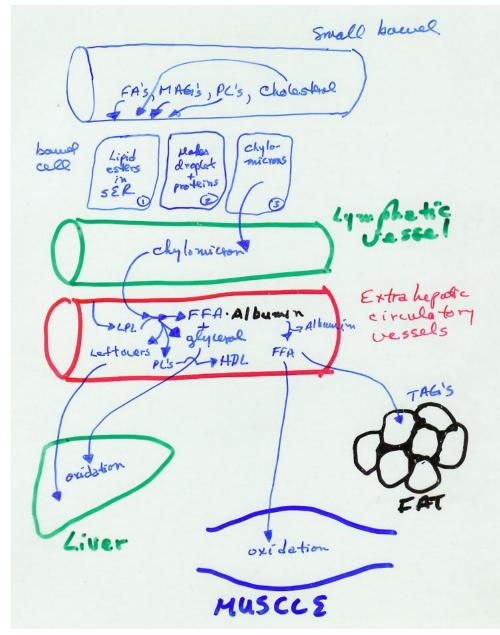


Prostaglandins



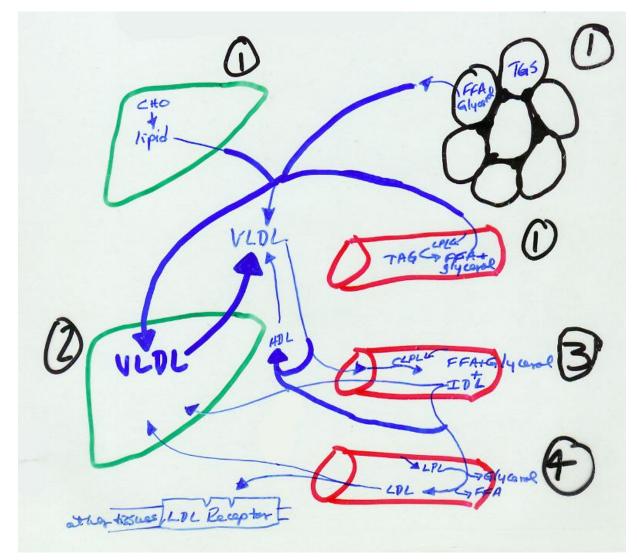
Chylomicron Metabolism

•Chylomicrons are exclusively from the diet (exogenous)

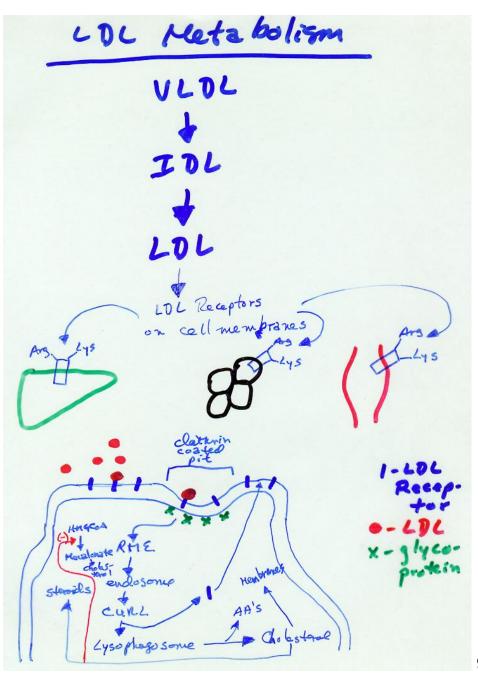


Exogenous Lipid Metabolism

\bigcirc = endogenous lipid sources

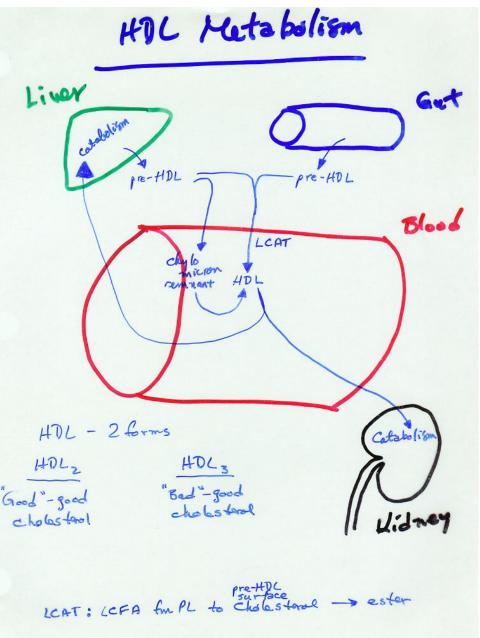


LDL Metabolism



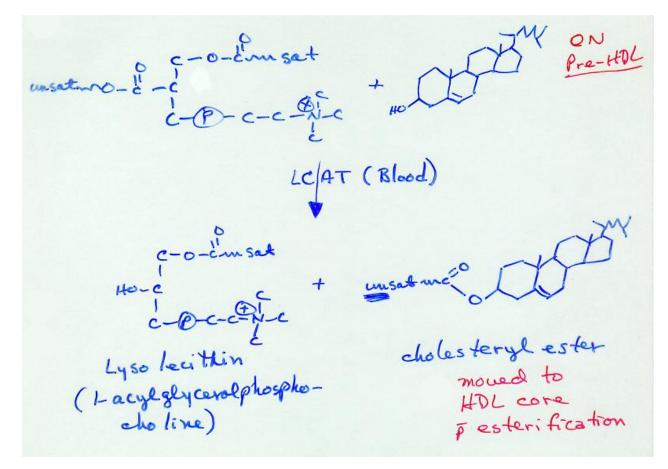
HDL Metabolism

LCAT: LCFA from PL to pre-HDL surface cholesterol to form ester



Lecithin-Cholesterol Acyl Transferase: "LCAT"

Used in lipid TRANSPORT



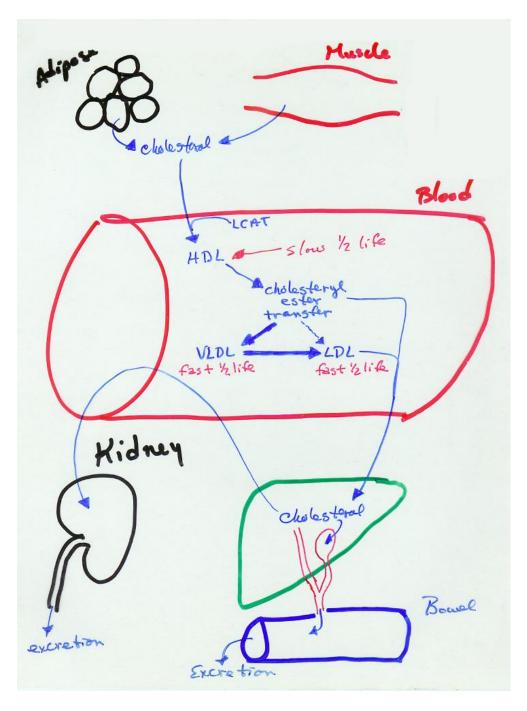
Acyl CoA: Cholesterol Acyl Transferase: "ACAT"

Prepares cholesterol for intracellular STORAGE

Murley + ACAT (intra cellular) TY m choles terye ester

HDL Protective Role

 Accelerates cholesterol excretion



Clinical Applications of Lipids:

Metabolic Syndrome

Cardiac Disease Risk Factors

Reduced HDL Contributors

- Male gender
- Obesity
- Physical inactivity
- Cigarette smoking
- Hypertriglyceridemia
- Children of someone with CHD

Elevated HDL Contributors

- Female gender
- Vigorous exercise
- NOT a child of someone with CHD

Arithmetic Lipoprotein Relationships

$$VLDL_{Cholesterd} = \frac{TAG}{5}$$

When no chylomicrons or remnants are present

$$LDL_{Cholesterd} = Cholesterol_T - (VLDL_{Cholesterd} + HDL_{Cholesterd})$$

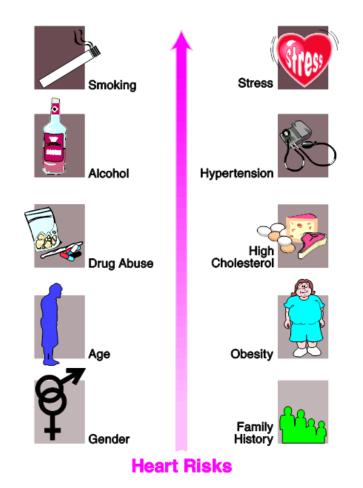
$$\Leftrightarrow C_T - (0.2_{TAG} + HDL_{Cholesterd})$$

$$>\uparrow$$
 HDL_{2-Cholesterd} \rightarrow < risk of CHD

$$> \uparrow LDL_{Cholesterd} \rightarrow > risk of CHD$$

Risk Factors

- Metabolic syndrome is characterized by a group of metabolic risk factors in one person. They include:
- Abdominal obesity (excessive fat tissue in and around the abdomen)
- Atherogenic dyslipidemia (blood fat disorders — high triglycerides, low HDL cholesterol and high LDL cholesterol — that foster plaque buildups in artery walls)
- Elevated blood pressure
- Smoking
- Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor–1 in the blood)
- Proinflammatory state (e.g., elevated C-reactive protein in the blood)



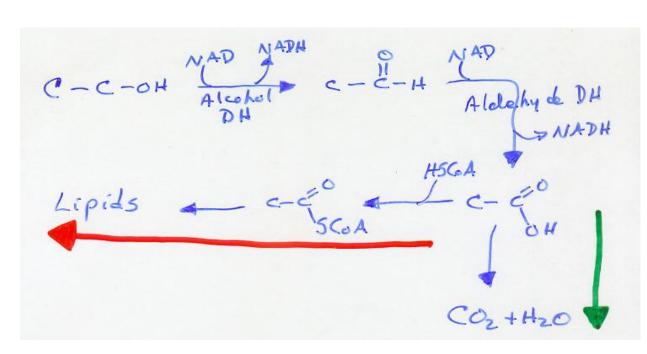
Risk Factors

- age the incidence of metabolic syndrome increases with age
- ethnicity African Americans and Mexican Americans are more prone to metabolic syndrome. African-American women are about 60 percent more likely than African-American men to have the syndrome.
- body mass index (BMI; kg/m²) greater than 25 the BMI is calculated as a measure of body fat compared to height and weight.
- Insulin resistance or glucose intolerance (the body can't properly use insulin or blood sugar)
 - personal or family history of diabetes there is a greater risk for metabolic syndrome for those who have experienced diabetes during pregnancy (gestational diabetes) or who have a family member with type 2 diabetes.
- history of heavy drinking
- Stress
- post-me
- high-fat diet
- Post-menopausal status
- sedentary lifestyle



Heart Risks

Ethyl Alcohol Metabolism



- Makes mito an incredibly REDUCED environment
- With lots of NADH, this inhibits ALL NAD-requiring enzymes
- Therefore, EtOH is typically used in fat synthesis rather than in oxidation

Diagnostic: Apple or Pear?

There are no well-accepted criteria for diagnosing metabolic syndrome.

Abdominal obesity (excessive fat tissue in and around the abdomen)

Shape determined by measuring your true waist to widest hip ratio. A ratio greater than 0.8 indicates that you are an apple shape. A ratio less than 0.8 means you are a pear shape.

The National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) says:

Women with waist-to-hip ratios of more than 0.8 are at increased health risk because of their fat distribution.

Men with waist-to-hip ratios of more than 1.0 are at increased health risk because of their fat distribution .

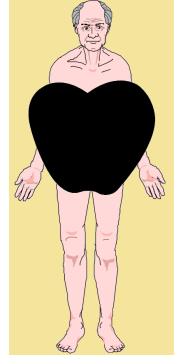
Dx: Elevated waist circumference:

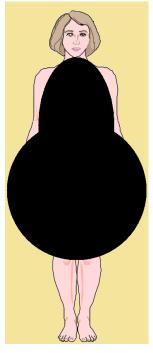
Men — Equal to or greater than 40 inches (102 cm)

Women — Equal to or greater than 35 inches (88 cm)

More sensitive than BMI

National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III); The American Heart Association; The National Heart, Lung, and Blood Institute World Health Organization (WHO) American Association of Clinical Endocrinologists (AACE)





Diagnostics

 People with metabolic syndrome are at increased risk of coronary heart disease and other diseases related to plaque buildups in artery walls (e.g., stroke and peripheral vascular disease) and type 2 diabetes. Metabolic syndrome has become increasingly common in the United States. It's estimated that over 50 million Americans have it.

Diagnostics

- The dominant underlying risk factors for this syndrome appear to be abdominal obesity and insulin resistance.
- Insulin resistance is a generalized metabolic disorder, in which the body can't use insulin efficiently.
- This is why metabolic syndrome is also called the insulin resistance syndrome.
- Other conditions associated with the syndrome include physical inactivity, aging, hormonal imbalance and genetic predisposition.

Diagnostics

- Elevated triglycerides: Equal to or greater than 150 mg/dL
- Reduced HDL ("good") cholesterol: Men — Less than 40 mg/dL Women — Less than 50 mg/dL
- Elevated blood pressure: Equal to or greater than 130/85 mm Hg Or use of antihypertensive medication (medication used to lower blood pressure)
- Elevated fasting glucose: Equal to or greater than 100 mg/dL

Management

- For managing both long- and short-term risk, lifestyle therapies are the first-line interventions to reduce the metabolic risk factors. These lifestyle interventions include:
- Weight loss to achieve a desirable weight (BMI less than 25 kg/m²)
- Increased physical activity, with a goal of at least 30 minutes of moderate-intensity activity on most days of the week
- Healthy eating habits that include reduced intake of saturated fat, trans fat and cholesterol
 - <u>http://www.atherotech.com/images/vapliterature/pdfs/Chol</u> <u>esterolTest.pdf</u> <-- assigned reading!

Management

 The primary goal of clinical management of metabolic syndrome is to reduce the risk for cardiovascular disease and type 2 diabetes. Then, the first-line therapy is to reduce the major risk factors for cardiovascular disease: stop smoking and reduce LDL cholesterol, blood pressure and glucose levels to the recommended levels.

Approaches to Lowering Lipid Levels

- ω-3 FA's (DHA and EPA (ALA??))
 - Reduce VLDL
 - Reduce platelet aggregation
- Water soluble fibers (pectins, gumns, hemicelluloses, legumes)
 - Reduce cholesterol levels
- Cholestyramine
 - Bile binding resin that reduces cholesterol uptake from the diet
- Nicotinic ACID NOT the AMIDE or the inositol salt
 - Inhibits VLDL from liver (i.e., secretion) and inhibits FA release from adipose tissue
 - Increases HDL₂ levels
- HMGCoA Reductase inhibitors
 - Inhibit de novo cholesterol synthesis
- Dietary Restrictions
- Exercise (Stress Reduction)