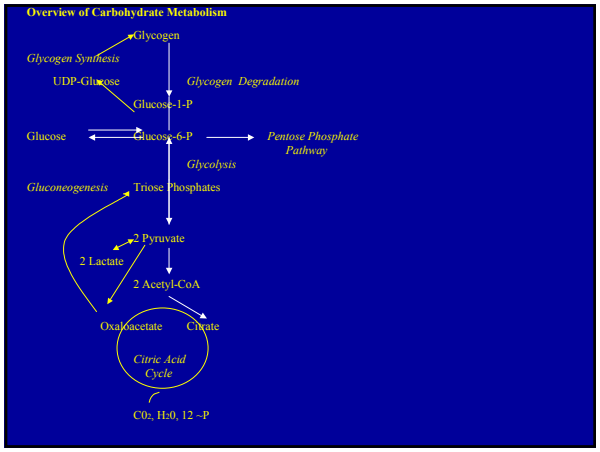
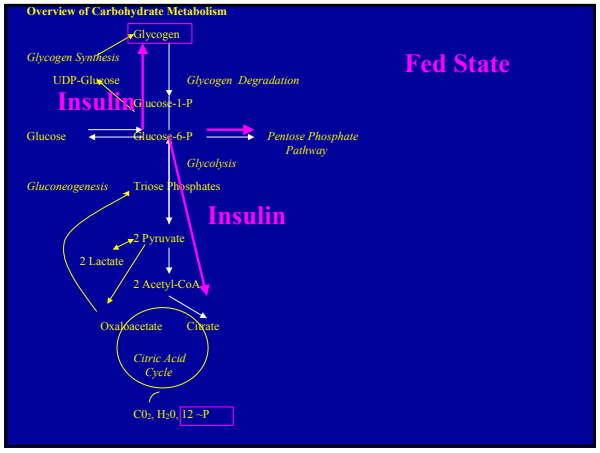
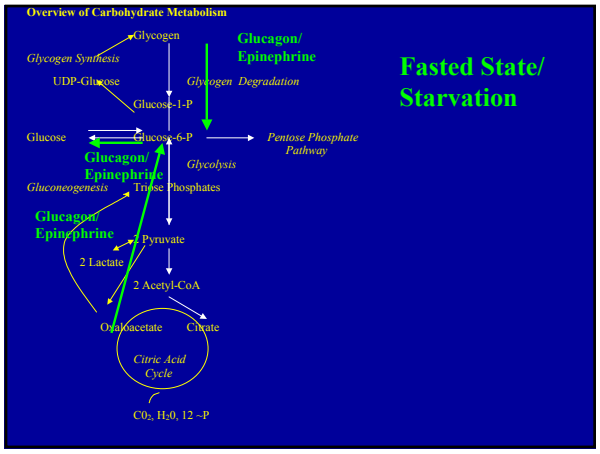
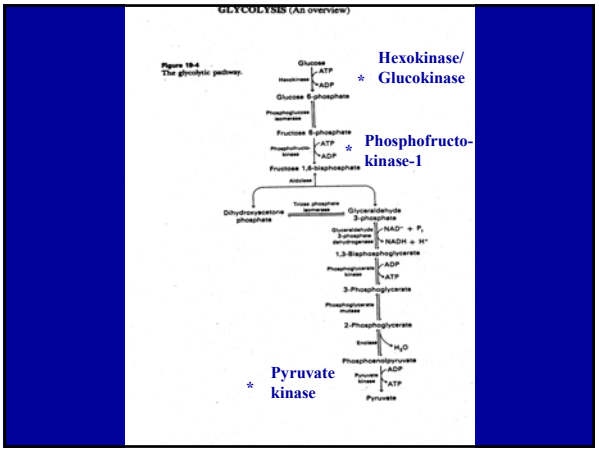
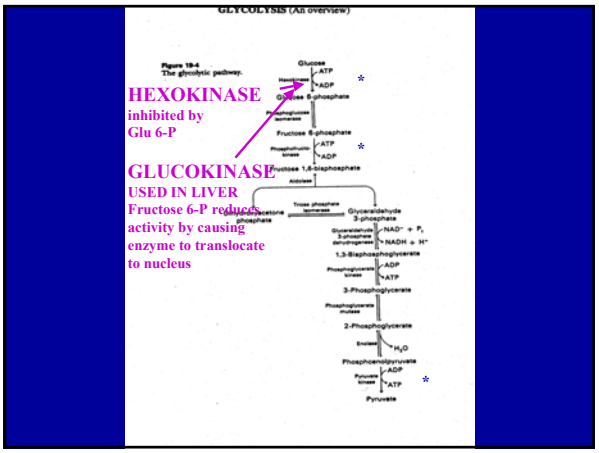
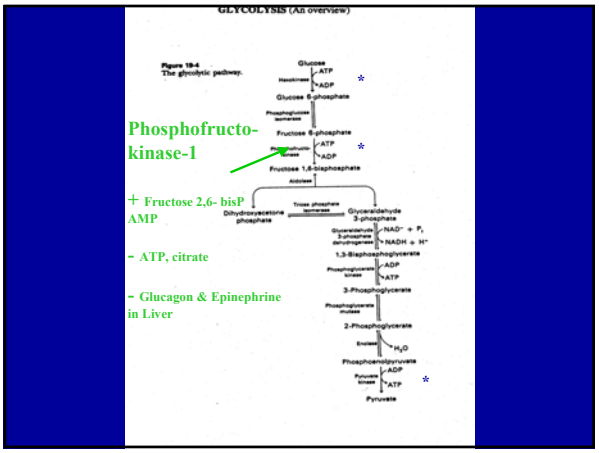

Overview of Carbohydrate Metabolism
Glycogen
Glycogen Synthesis
UDP-Glucose
Glycogen Degradation
Glucose-1-P
Glucose
Glucose-6-P
Pentose Phosphate Pathway
Glycolysis
Gluconeogenesis
Triose Phosphates
2 Pyruvate
2 Lactate
2 Acetyl-CoA
Oxaloacetate
Citrate
Citric Acid Cycle
CO2, H2O, 12 ~P

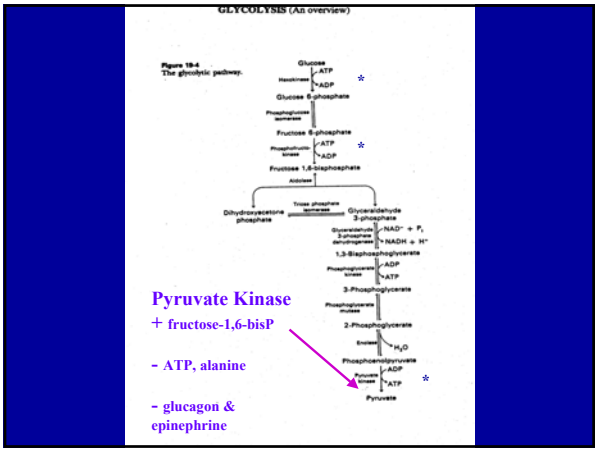

Overview of Carbohydrate Metabolism
Glycogen
Glycogen Synthesis
UDP-Glucose
Glycogen Degradation
Insulin
Glucose-1-P
Glucose
Glucose-6-P
Pentose Phosphate Pathway
Glycolysis
Gluconeogenesis
Triose Phosphates
Insulin
2 Pyruvate
2 Lactate
2 Acetyl-CoA
Oxaloacetate
Citrate
Citric Acid Cycle
CO2, H2O, 12 ~P
Fed State

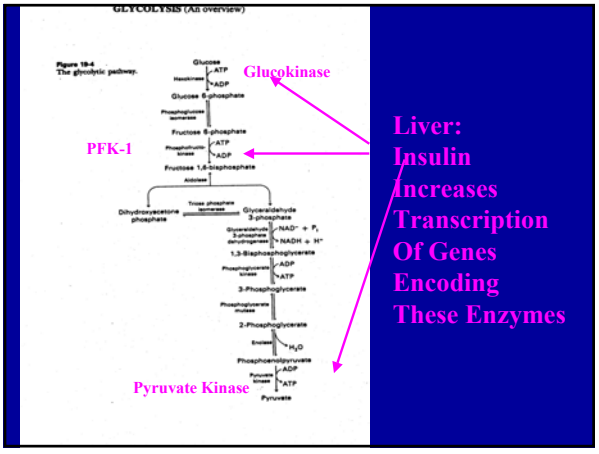

Overview of Carbohydrate Metabolism
Glycogen
Glucagon/ Epinephrine
Glycogen Synthesis
UDP-Glucose
Glycogen Degradation
Glucose-1-P
Glucose
Glucose-6-P
Pentose Phosphate Pathway
Glucagon/ Epinephrine
Glycolysis
Gluconeogenesis
Triose Phosphates
Glucagon/ Epinephrine
2 Pyruvate
2 Lactate
2 Acetyl-CoA
Oxaloacetate
Citrate
Citric Acid Cycle
CO2, H2O, 12 ~P
Fasted State/ Starvation

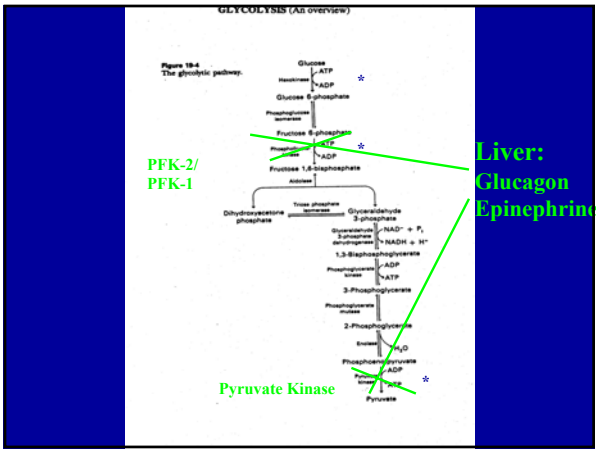

GLYCOLYSIS (An overview)
Figure 19-4
The glycolytic pathway.
Glucose
ATP
ADP
Glucose 6-phosphate
Fructose 6-phosphate
Fructose 1,6-bisphosphate
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate
NAD+ + Pi
NADH + H+
1,3-Bisphosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
H2O
Phosphoenolpyruvate
Pyruvate
Hexokinase/
Glucokinase
Phosphofructo-
kinase-1
Pyruvate
kinase

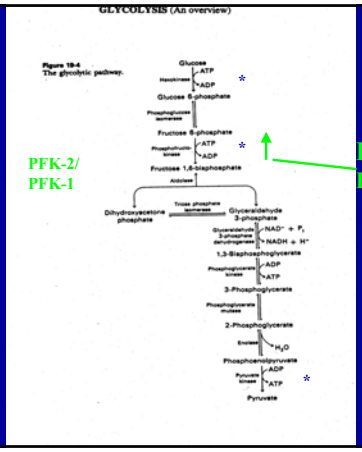

GLYCOLYSIS (An overview)
HEXOKINASE
inhibited by
Glu 6-P
GLUCOKINASE
USED IN LIVER
Fructose 6-P reduces
activity by causing
enzyme to translocate
to nucleus


GLYCOLYSIS (An overview)
Phosphofructo-
kinase-1
+ Fructose 2,6- bisP
AMP
- ATP, citrate
- Glucagon & Epinephrine
in Liver


GLYCOLYSIS (An overview)
Pyruvate Kinase
+ fructose-1,6-bisP
- ATP, alanine
- glucagon &
epinephrine


GLYCOLYSIS (An overview)
Glucokinase
PFK-1
Pyruvate Kinase
Liver:
Insulin
Increases
Transcription
Of Genes
Encoding
These Enzymes

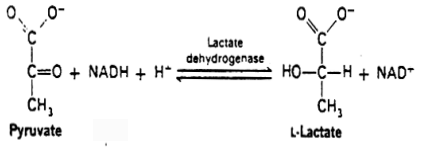

GLYCOLYSIS (An overview)
PFK-2/
PFK-1
Pyruvate Kinase
Liver:
Glucagon
Epinephrine



PFK-2/
PFK-1

Heart:
Epinephrine

Lactate Dehydrogenase



Pyruvate Dehydrogenase (PDH)

Lactate

Alanine

PDH

$$Pyruvate + CoASH + NAD^+ \longrightarrow Acetyl\text{-}CoA + CO_2 + NADH + H^+$$

PDH Gene Deficiency:
- Lactic Acidosis
- Neurological Defects

PDH Activity Low
- Thiamine Deficiency
- Arsenic Poisoning

Treatment – ketogenic diet

Galactosemia

Galactokinase Deficiency	Classical Galactosemia Galactose 1-P Uridyl-Transferase Deficiency
Elevated galactitol Cataracts	Elevated galactitol Cataracts
Galactosemia	Galactosemia
Galactosuria	Galactosuria
	Elevated Galactose 1-P Hepatic Dysfunction Brain Dysfunction (Retardation) Cataracts **Autosomal recessive**

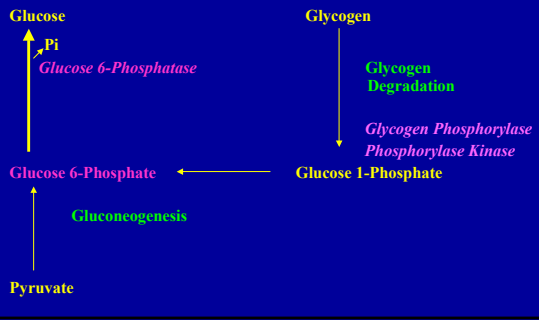
Treatment:
Eliminate galactose/ Lactose MILK

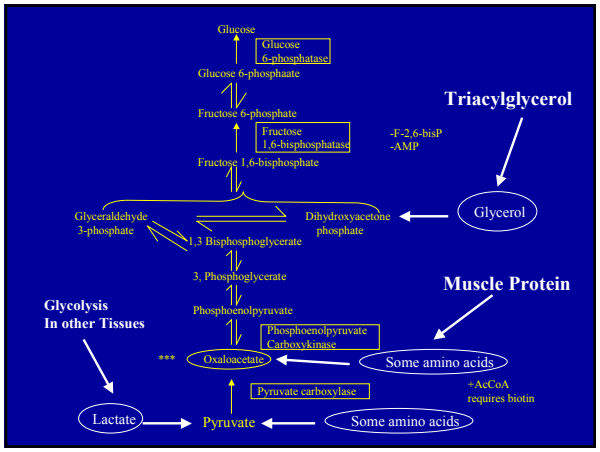
HEREDITARY FRUCTOSE INTOLERANCE
A Deficiency of Aldolase B

Symptoms
Hypoglycemia
Vomiting
Jaundice
Hepatic failure

Treatment: Decrease fructose/sucrose

Glucose Homeostasis is Required for Survival





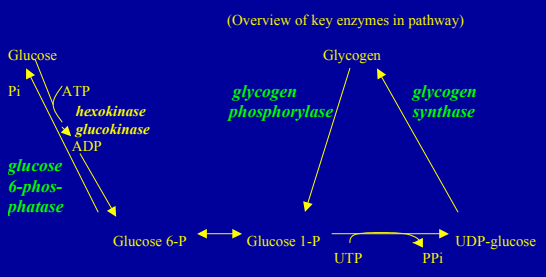
Ethanol metabolism can cause hypoglycemia; the high NADH opposes gluconeogenesis

Ethanol metabolism increases NADH

Increased NADH promotes the conversion of two glucogenic precursors (pyruvate and oxaloacetate) to lactate and malate.

This removes pyruvate and oxaloacetate from the pool of glucogenic precursors.

Glycogen Synthesis and Degradation



Inherited glycogen storage diseases can affect tissue glycogen levels, fasting

Glycogen Storage Diseases

Type	Defective Enzyme	Affected Organ	Glycogen	Clinical Features
I Von Gierke's Disease	Glucose 6-Phosphatase (deficient enzyme or translocase)	Liver & Kidney	Increased Normal Structure	Enlarged liver. Failure to thrive. Severe hypoglycemia, Ketosis. Hyperuricemia, Hyperlipidemia, Mental Retardation
II Pompe's Disease	1,4-Glucosidase (lysosomal)	All organs	Massive increase Normal structure	Cardiorespiratory failure. Death, usually before age 2
III Cori's Disease	Amylo-1,6-debranching	Muscle & Liver	Increased short outer	Like type I, but milder
IV Anderson's Disease	Branching Enzyme	Liver & Spleen	Normal amount; Long Branches	Progressive cirrhosis of liver. Liver failure causes death before age 2.
V McArdle's Disease	Phosphorylase	Muscle	Moderate amount; Normal Structure	Limited ability to perform strenuous exercise; painful muscle cramps.
VI Hers' Disease	Phosphorylase	Liver	Increased amount	Like 1, but milder
VII	PFK-1	Muscle	Increased amount	Like V
VIII	Phosphorylase Kinase	Liver	Increased amount; Normal Structure	Mild liver enlargement; mild hypoglycemia

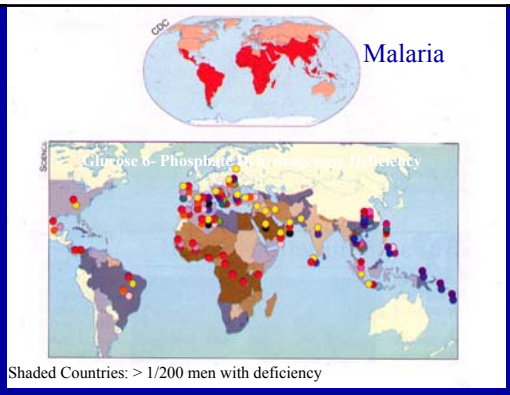
Pentose Phosphate Pathway
(Hexose Monophosphate Shunt)

Generates:

NADPH – Lipid Biosynthesis

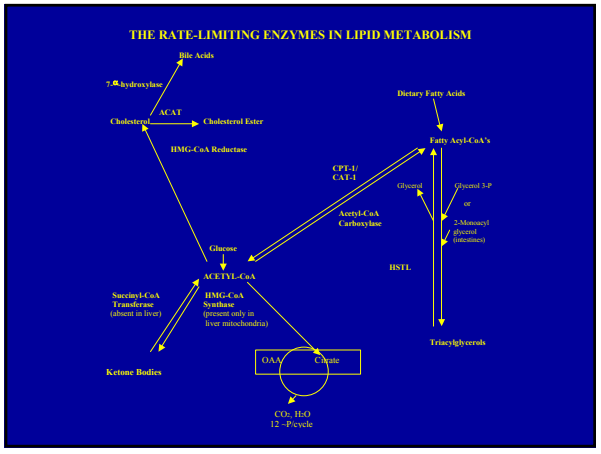
Ribose 5-Phosphate – Purine Biosynthesis – e.g., DNA, RNA, CoA

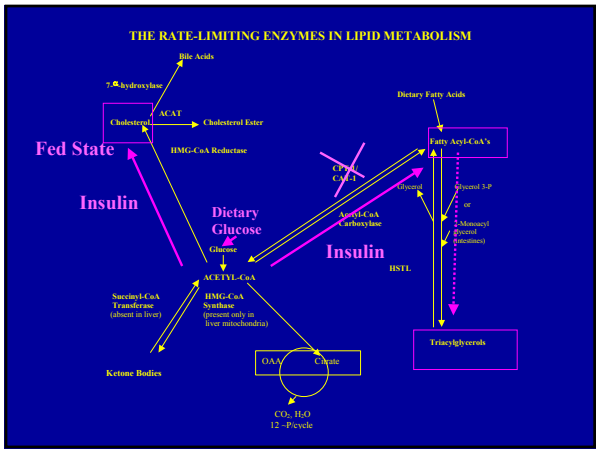
A Genetic ***Deficiency*** of ***Glucose 6-Phosphate Dehydrogenase*** is Associated with Drug-Induced ***Hemolytic Anemia.***

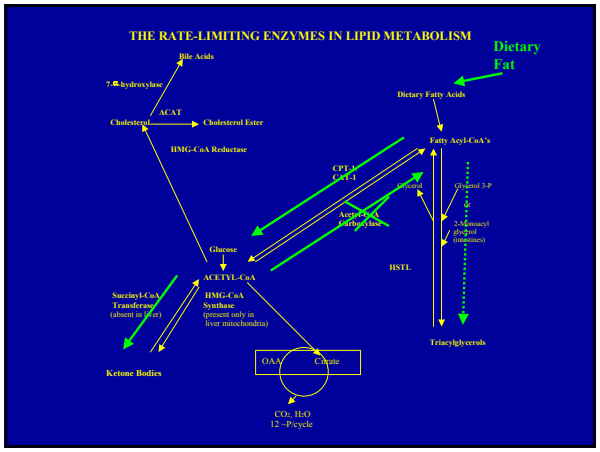


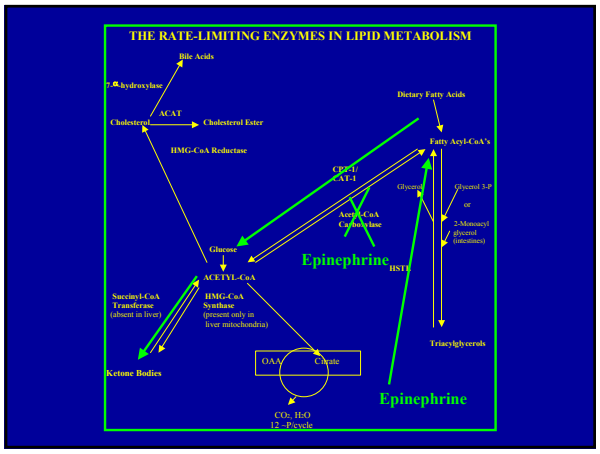
Shaded Countries: > 1/200 men with deficiency

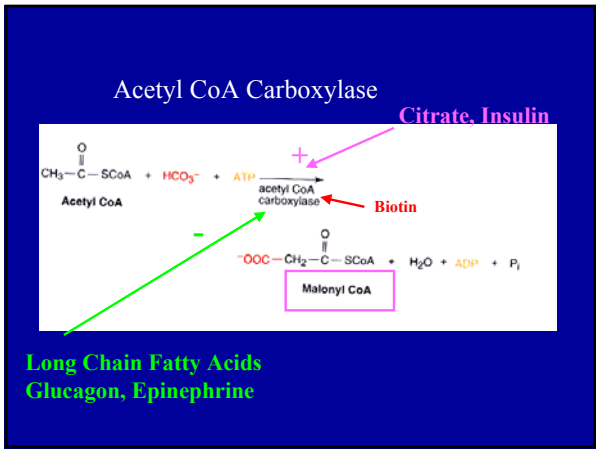
5-25% in Tropical Africa, Middle East, Tropical Asia, Mediterranean

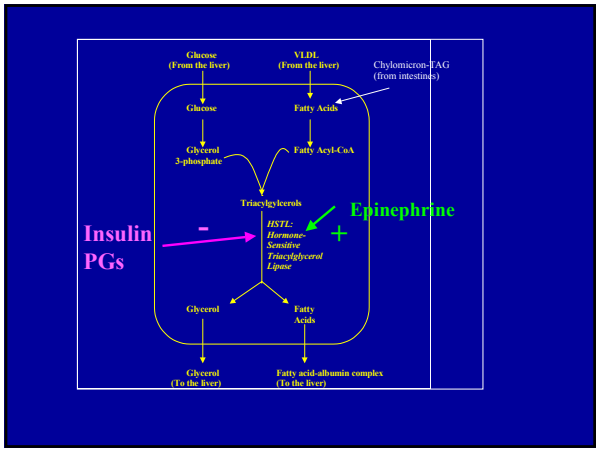


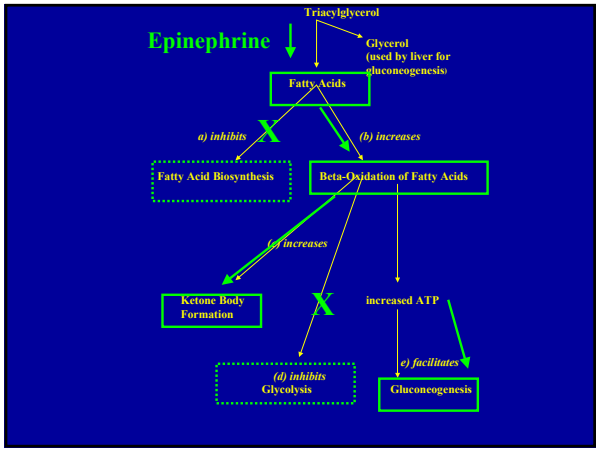



THE RATE-LIMITING ENZYMES IN LIPID METABOLISM
Dietary Fat
Bile Acids
7-α-hydroxylase
ACAT
Cholesterol
Cholesterol Ester
HMG-CoA Reductase
Dietary Fatty Acids
Fatty Acyl-CoA's
CPT-I
CAT-I
Glycerol
Glycerol 3-P
or
2-Monoacyl glycerol (intestines)
Acetyl-CoA Carboxylase
Glucose
ACETYL-CoA
HSTL
Succinyl-CoA Transferase (absent in liver)
HMG-CoA Synthase (present only in liver mitochondria)
Triacylglycerols
Ketone Bodies
OAA
Citrate
CO2, H2O
12 -Picycle


THE RATE-LIMITING ENZYMES IN LIPID METABOLISM
Bile Acids
7-α-hydroxylase
ACAT
Cholesterol
Cholesterol Ester
HMG-CoA Reductase
Dietary Fatty Acids
Fatty Acyl-CoA's
CPT-I
CAT-I
Glycerol
Glycerol 3-P
or
2-Monoacyl glycerol (intestines)
Acetyl-CoA Carboxylase
Glucose
Epinephrine
HSTL
ACETYL-CoA
Succinyl-CoA Transferase (absent in liver)
HMG-CoA Synthase (present only in liver mitochondria)
Triacylglycerols
Ketone Bodies
OAA
Citrate
Epinephrine
CO2, H2O
12 -Picycle

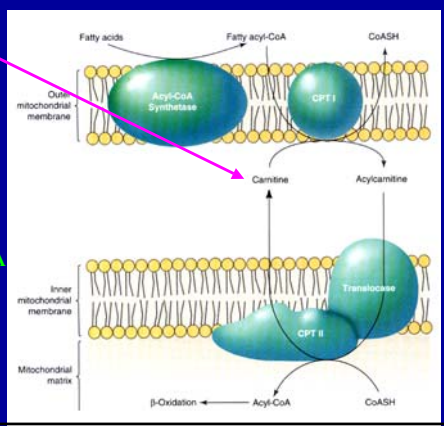

Acetyl CoA Carboxylase
Citrate, Insulin
+
CH3—C—SCoA + HCO3− + ATP
Acetyl CoA
acetyl CoA carboxylase
Biotin
−
−OOC—CH2—C—SCoA + H2O + ADP + Pi
Malonyl CoA
Long Chain Fatty Acids
Glucagon, Epinephrine





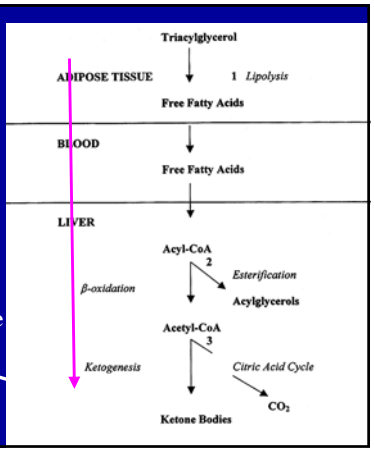
Carnitine transports fatty acids into the mitochondrial matrix.

CPT –1
Only Inhibitor
Is Malonyl-CoA



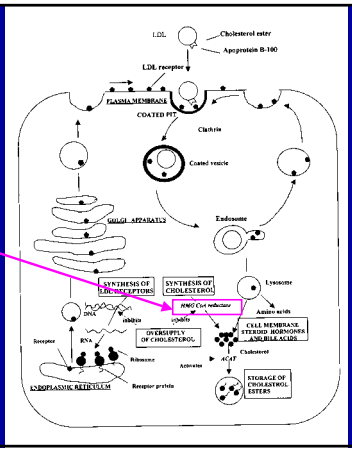
Ketone bodies:

Beta-hydroxybutyrate
Acetoacetate
acetone



LDL Metabolism

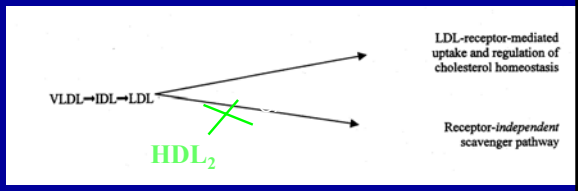
"Statins"
Inhibit
HMC-CoA
Reductase



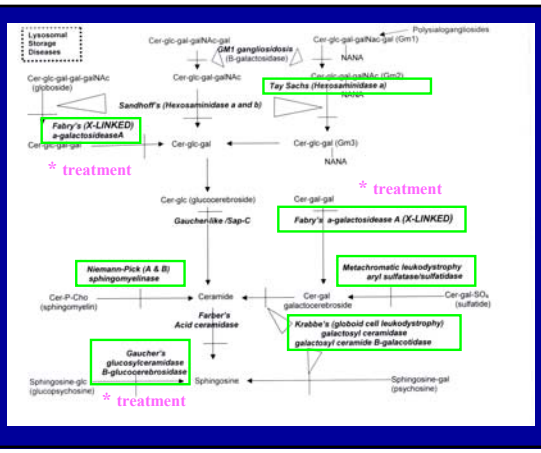
Chemical Composition of Plasma Lipoprotein Class

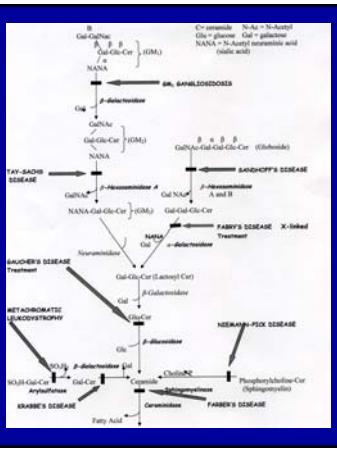
				Percent Composition of Lipid Fraction			
Lipoprotein Class	Function	% Protein	% Lipid	Phospho-lipids	Unesteri-fiedCho-lesterol	Choles-terol Esters	Triacyl-glycerols
HDL	Reverse Cholesterol Transport	40-55	50-55	20-35	12	3-4	3-5
LDL	Cholesterol Transport	20-25	75-80	15-20	35-40	7-10	7-10
IDL	LDL Precursor	15-20	80-85	22	22	8	30
VLDL	Transports Endogenous Fat	5-10	90-95	15-20	10-15	5-10	50-65
Chylo-microns	Transports Exogenous (Dietary) Fat	~2	97-99	7-9	3-5	1-3	84-89

Two Pathways of LDL Clearance



HDL is involved with reverse cholesterol transport

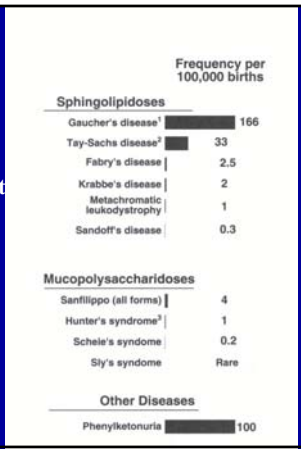




Lysosomal Storage Diseases/Sphingolipidoses

Disease	*Enzyme Deficiency*	*Accumulating Product*	*Results/Characteristics* autosomal recessive unless otherwise noted
Fabry's	alpha-galactocerebrosidase A Alpha-galctosidase A	Ceramide Trihexoside	**X-linked** recessive; renal failure ***Enzyme Replacement Therapy***
Krabbe's	galactosylceramide B-galacto-sdase, Galactosyl ceramidase	galactocerebroside (brain)	optic atrophy, spasticity, early death
Gaucher's	B-glucocerebrosidase Glucocosylceramidase	glucocerebroside (brain, liver, spleen, bone marrow)	"crinkled paper" enlarged cytoplasm ***Enzyme Replacement Therapy*** liver and spleen enlargement **mental retardation in infantile form only**
Niemann-Pick	sphingomyelinase	sphingomyelin & cholesterol (reticuloendothelial & parenchymal cells)	Death by age 3, enlarged liver & spleen **mental retardation**
Tay-Sachs	Hexosaminidase A	GM2 ganglioside	Death by age 3, cherry-red spot on macula Carrier rate: 1/30 Jews of European descent 1/300 for others), **mental retardation**, blindness
Metachromatic Leukodystrophy	arylsulfatase A sulfatidase	sulfatide (brain, kidney, liver, peripheral nerves)	white matter signs, peripheral neuropathy **mental retardation**, demyelination, Nerves stain yellowish brown with cresyl violet
Farber's	Acid ceramidase	ceramide	Painful and progressively deformed joints Subcutaneous nodules, ganulomas, fatal early
Mucopolysaccharidoses – Most Common Forms			
Hurler's	a-L-iduronidase		corneal clouding, **mental retardation**
Hunter's	iduronate sulfatase		Mild form of Hurler's with no corneal clouding **X-linked recessive**

From Lippincott



Type 1 Collagen

Triple-stranded
Gly-X-Y repeat
Glycine – smallest aa
Proline – polyproline helix
OH-pro, OH-lys H-bonding
Lysine aldehydes cross-linking

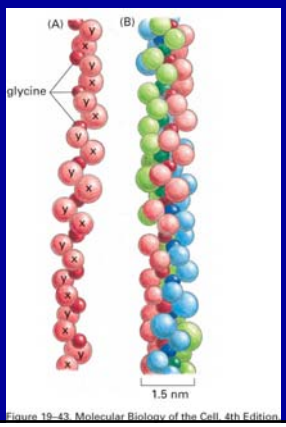


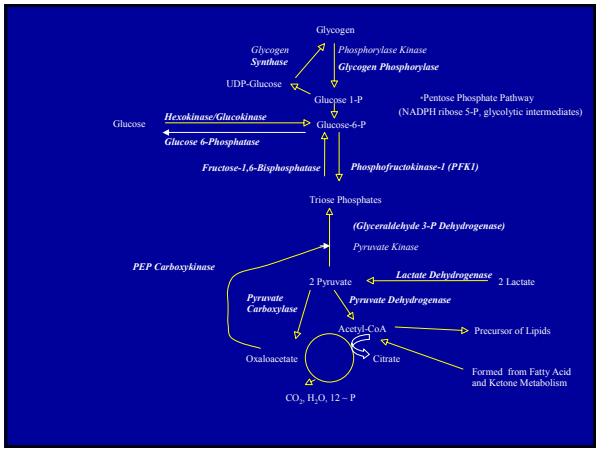
Figure 19–43. Molecular Biology of the Cell, 4th Edition

Selected Collagen Disorders

Disorder	Collagen synthesis	Clinical Manifestations
Osteogenesis Imperfecta 1 **Autosomal Dominant – may act like dominant negative**	Decreased synthesis of type 1 collagen	susceptibility to fractures sometimes confused with child abuse blue sclerae - translucent connective tissue over choroid
Osteogenesis Imperfecta 2 **Autosomal Dominant**	Point mutations & re-arrangement of exons in triple helical regions	Perinatal death; soft, fragile & malformed bones
Ehlers-Danlos	Faulty collagen synthesis	Hyperextensive skin, hypermobility of joints, tendency to bleed

Fibrillin is essential to the integrity of elastin

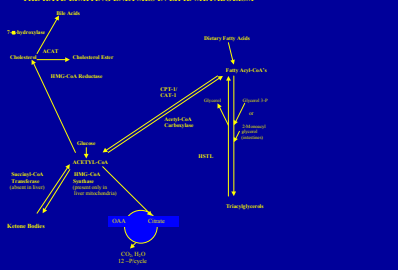
Marfan's Syndrome
mutation in the fibrillin gene



Regulation of Key Enzymes of Carbohydrate Metabolism

Enzyme	Allosteric Activator	Allosteric Inhibitor	Hormonal Activator	Hormonal Inhibitor	Induces Enzyme Synthesis	Comments
Hexokinase –outside liver		Glu 6-P				Low Km for glucose
Glucokinase -liver		Fruc 6-P			Insulin	High Km for glucose
Phosphofructokinase-1, liver	F-2,6-biP, AMP, ADP	ATP Citrate		Glucagon Epinephrine	Insulin	Glucagon & Epinephrine Inhibit PFK-2, which leads to A decrease in F-2,6-biP (the Activator)
Phosphofructokinase-1, muscle	F-2,6-biP AMP, ADP	ATP Citrate	Epinephrine			Epinephrine activates PFK-2, which leads to an increase in F-2,6-biP
Pyruvate Kinase –liver	F-1,6-biP	Alanine ATP		Glucagon Epinephrine	Insulin	
Pyruvate Carboxylase – liver	Acetyl CoA					Requires Biotin
PEP Carboxykinase - liver					Glucagon Epinephrine	Requires GTP hydrolysis
Fructose-1,6-bisphosphatase - liver		F-2,6-biP AMP	Glucagon Epinephrine		Glucagon Epinephrine	Glucagon & Epinephrine Inhibit PFK-2, which leads to A decrease in F-2,6-biP (the Inhibitor)
Glucose 6-phosphatase -liver					Glucagon Epinephrine	
Glycogen Synthase -liver	Glucose 6-P		Insulin	Glucagon Epinephrine		Glucagon & Epi can inhibit Via CAMP system (PKA); Epi can Also inhibit via IP3/DAG (PKC) Ca^{2+} can inhibit via Ca-dep PK
Phosphorylase Kinase -liver	$Ca2+$		Glucagon Epinephrine	Insulin		Calmodulin is a subunit. Ca^{2+} binding directly activates
Glycogen Phosphorylase -liver	AMP	ATP	Glucagon Epinephrine	Insulin		Glucagon & Epi can activate Via CAMP system (PKA); Epi can Also activate via IP3/DAG (PKC) Ca^{2+} can activate via Ca-dep PK
Glucose 6-P Dehydrogenase	$NADP^+$	NADPH			Insulin	
Pyruvate Dehydrogenase		Acetyl CoA NADH				Acetyl-CoA, NADH, & ATP Promote phosphorylation and inhibition. Pyruvate inhibits phosphorylation→ activation In adipose tissue, Insulin promotes dephosphorylation →activation Vitamin Cofactors: thiamine, niacin, riboflavin

THE RATE-LIMITING ENZYMES IN LIPID METABOLISM



ABBREVIATIONS:

ACAT: acyl-CoA acyltransferase
HSTL: hormone sensitive triacylglycerol lipase (adipose tissue)
CPT-1: carnitine palmitoyl transferase-1
CAT-1: carnitine acyl transferase-I

Regulation of Key Enzymes of Lipid Metabolism

Enzyme	Activator	Inhibitor	Hormonal Activator	Hormonal Inhibitor	Induces Enzyme Synthesis	Represses Enzyme Synthesis	Comments
Acetyl CoA -liver Carboxylase	Citrate	Long Chain FattyAcylCoA AMP	Insulin	Glucagon Epinephrine	HighCarbDiet, Fat Free Diet	Glucagon, (Epi) High Fat Diet Fasting	Requires Biotin Synthesizes Malonyl –CoA, The Inhibitor of CPT-1
Carnitine Palmitoyl Transferase – I - liver		Malonyl CoA					
Hormone Sensitive Triacylglycerol Lipase – Adipose Tissue			Epinephrine ACTH	Insulin PGE			
Mitochondrial HMG-CoA Synthase - Liver							
Acetoacetate: Succinyl-CoA CoA Transferase – not liver							
HMG-CoA Reductase - liver		Cholesterol AMP Mevalonate	Insulin	Glucagon			Inhibited by drugs such as Levastatin, mevastatin,etc. Effectiveness of drugs is Dependent on presence of Functional LDL receptors in the liver.
7 –alpha hydroxylase - liver	Cholesterol						
ACAT	Cholesterol						
Lipoprotein Lipase – endothelial	Apo CII						

Note: The regulation of these enzymes in specific tissues is noted. However, many of these pathways take place in several tissues (fatty acid synthesis, fatty acid oxidation, ketone utilization, cholesterol biosynthesis). Ketones are made only in the liver mitochondria and they are not utilized in the liver. Bile acids are made only in the liver. HST Lipase is an adipose tissue enzyme. Lipoprotein lipase is found in the capillary endothelium and is activated by an apoprotein (C-II) found on several lipoproteins.