



Step 1 High-Yield

Course Pack

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- Reproductive
- Neurology and Psychiatry
- Behavioral Medicine

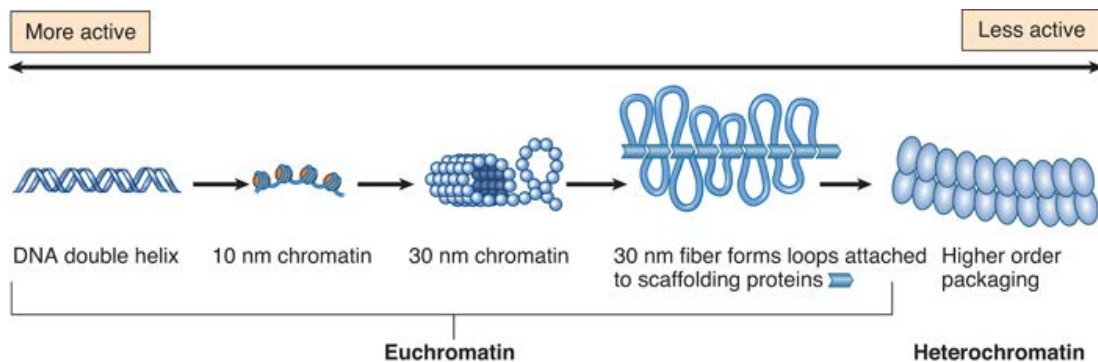


Intro to Biochemistry & Molecular Biology – Part I

Jonathan Faiwischewski, M4, UMDNJ.

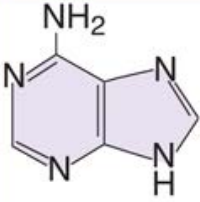
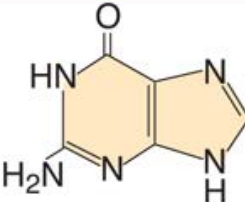
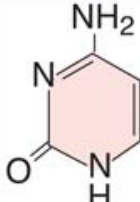
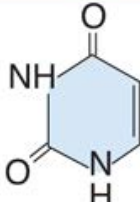
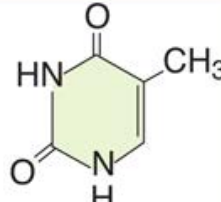
x1.5

BC01-1



x1.5

BC01-2

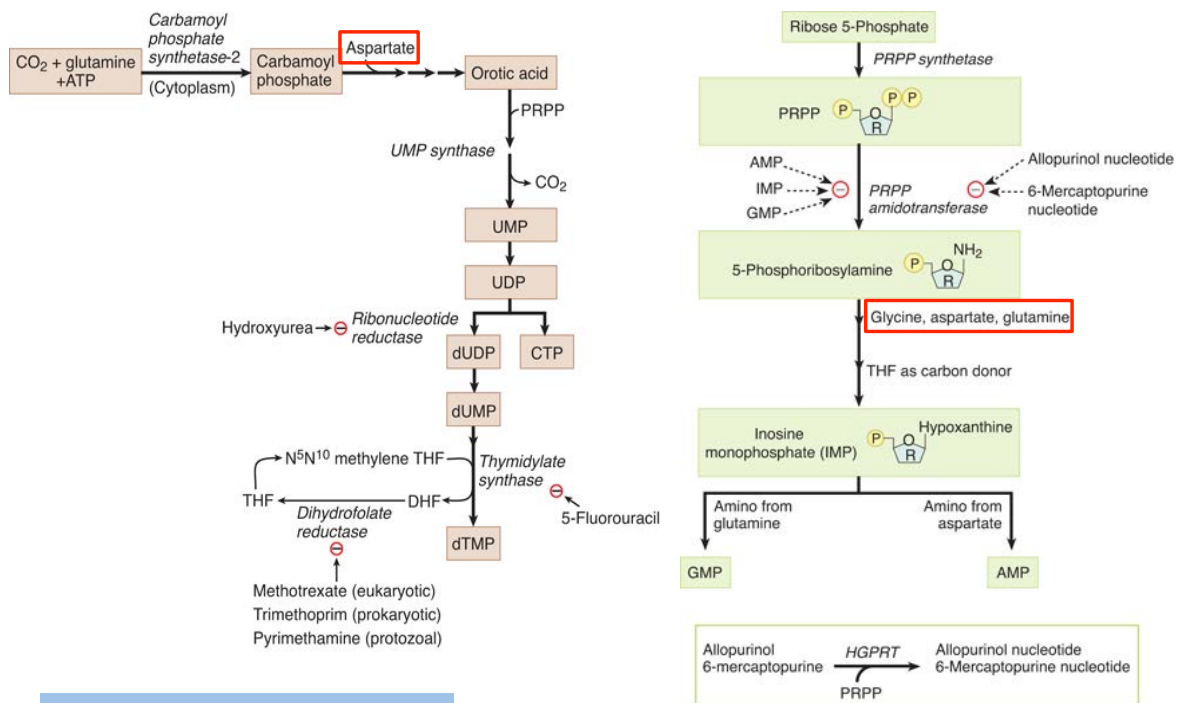
Purines		Pyrimidines		
				
Adenine	Guanine	Cytosine	Uracil	Thymine

A = T, G = C, 2 : 3

FA 2012: 68.2 • FA 2011: 67.1 • FA 2010: 67
ME 3e: 60

x1.5

BC01-3



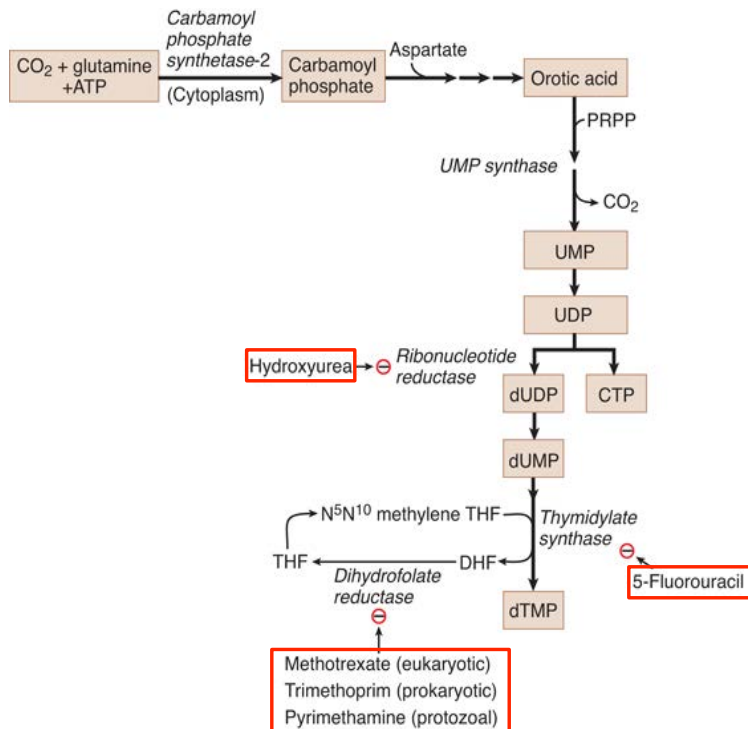
Pyrimidine Synthesis Pathway

Purine Synthesis Pathway

FA 2012: 69.1 • FA 2011: 68.1 • FA 2010: 68
ME 3e: 61

x1.5

BC01-4



OTC deficiency

- ↑ orotic acid
- Hyperammonemia
- No megaloblastic anemia

Orotic aciduria

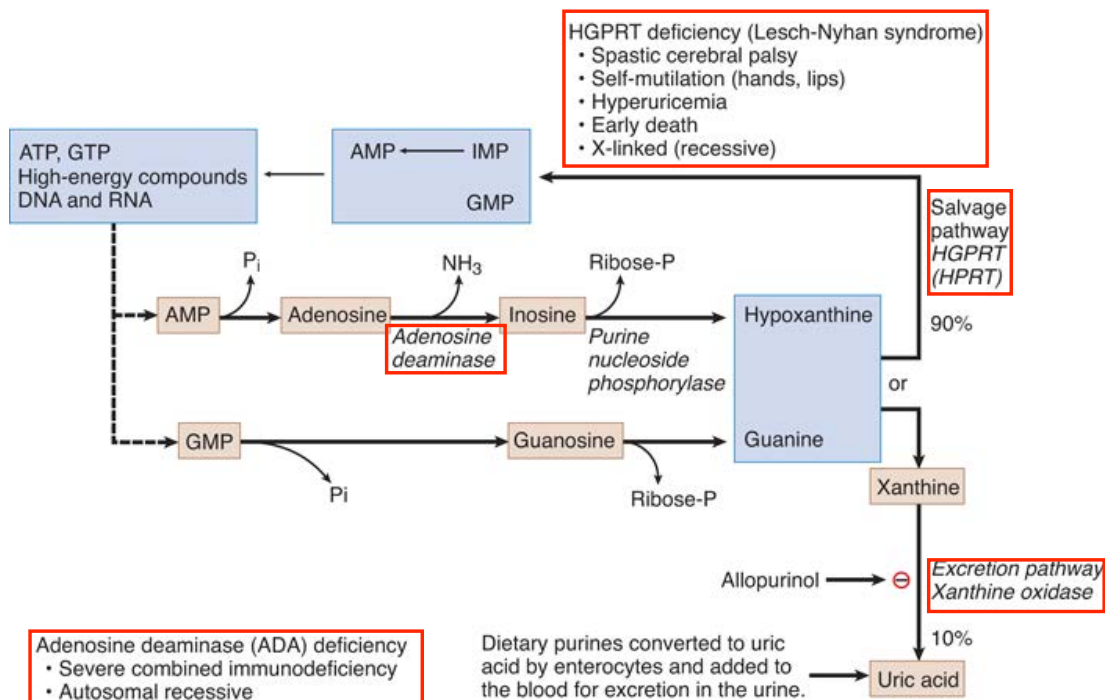
- UMP synthase deficiency
- ↑ orotic acid
- No hyperammonemia
- Megaloblastic anemia

Pyrimidine Synthesis Pathway

FA 2012: 69.2 • FA 2011: 68.2 • FA 2010: 68
ME 3e: 61

x1.5

BC01-5



FA 2012: 70.1 • FA 2011: 69.1 • FA 2010: 69
ME 3e: 61

x1.5

BC01-6

First Position (5' End)	Second Position				Third Position (3' End)
	U	C	A	G	
U	UUU } Phe UUC } UUA } Leu UUG }	UCU } Ser UCC } UCA } UCG }	UAU } Tyr UAC } UAA } Stop UAG }	UGU } Cys UGC } UGA } Stop UGG } Trp	U C A G
C	CUU } Leu CUC } CUA } CUG }	CCU } Pro CCC } CCA } CCG }	CAU } His CAC } CAA } Gln CAG }	CGU } Arg CGC } CGA } CGG }	U C A G
A	AUU } Ile AUC } AUA } Met AUG }	ACU } Thr ACC } ACA } ACG }	AAU } Asn AAC } AAA } Lys AAG }	AGU } Ser AGC } AGA } Arg AGG }	U C A G
G	GUU } Val GUC } GUA } GUG }	GCU } Ala GCC } GCA } GCG }	GAU } Asp GAC } GAA } Glu GAG }	GGU } Gly GGC } GGA } GGG }	U C A G

- The code is unambiguous
- The code is degenerate
- The code is commaless
- The code is universal

*Exceptions: mitochondria, mycoplasma, archaebacteria

Figure I-4-1. The Genetic Code

FA 2012: 70.2 • FA 2011: 69.2 • FA 2010: 69
ME 3e: 60

x1.5

BC01-7

Normal	ATGGCAATTCGTTTTTACCTATAGGG...DNA	coding strand
	Met Ala Ile Arg Phe Leu Pro Ile Gly	Amino Acid
Silent Mutation	ATGGCAATTCGTTTTTGCCTATAGGG...DNA	coding strand
	Met Ala Ile Arg Phe Leu Pro Ile Gly	Amino Acid
Missense Mutation	ATGGCAATTCGTTTTTCACCTATAGGG...DNA	coding strand
	Met Ala Ile Arg Phe Ser Pro Ile Gly	Amino Acid
Nonsense Mutation	ATGGCAATTCGTTTTTGACCTATAGGG...DNA	coding strand
	Met Ala Ile Arg Phe Stop	Amino Acid
Frameshift Mutation (1bp deletion)	ATGGCAATTCGTTTTTACCTATAGGG...DNA	coding strand
	Met Ala Ile Arg Phe Tyr Leu Stop	Amino Acid

Figure I-4-2. Some Common Types of Mutations in DNA

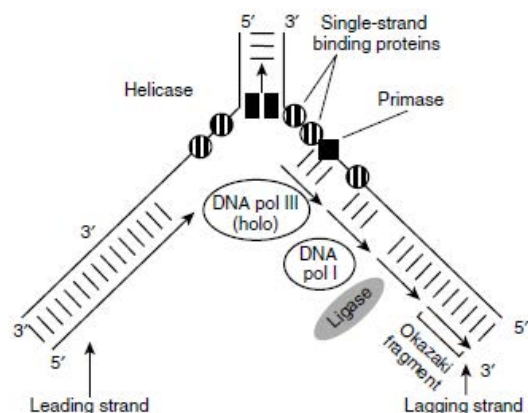
FA 2012: 71.1 • FA 2011: 69.3 • FA 2010: 70
ME 3e: 64

x1.5

BC01-8

Step in Replication	Prokaryotic Cells
Origin of replication (ori)	One ori site per chromosome
Unwinding of DNA double helix	Helicase
Stabilization of unwound template strands	Single-stranded DNA-binding protein (SSB)
Synthesis of RNA primers	Primase
Synthesis of DNA Leading strand Lagging strand (Okazaki fragments)	DNA polymerase III DNA polymerase III
Removal of RNA primers	DNA polymerase I (5'→3' exonuclease)
Replacement of RNA with DNA	DNA polymerase I
Joining of Okazaki fragments	DNA ligase
Removal of positive supercoils ahead of advancing replication forks	DNA topoisomerase II (DNA gyrase)
Synthesis of telomeres	Not required

Events at the Replication Fork

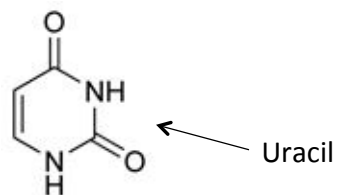
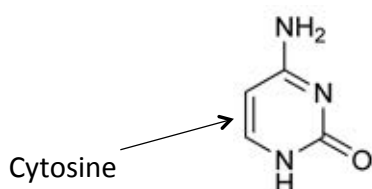


FA 2012: 72.1 • FA 2011: 70.1 • FA 2010: 70
ME 3e: 63

x1.5

BC01-9

Recognition/Excision Enzyme	Repair Enzymes	Damaged DNA target	Cause of DNA mutations	Condition
Excision endonuclease	DNA polymerase DNA ligase	Thymine dimers (G1)	UV radiation	Xeroderma pigmentosum
Base excision repair	Glycosylase AP endonuclease DNA polymerase DNA ligase			
Mismatch repair	DNA polymerase DNA ligase	Mismatched base (G2) Microsatellite instability	DNA replication errors (mutations in hMSH2, hMLH1)	Hereditary nonpolyposis colorectal cancer (HNPCC)
Double-stranded repair (non-homologous end-joining)	DNA ligase			

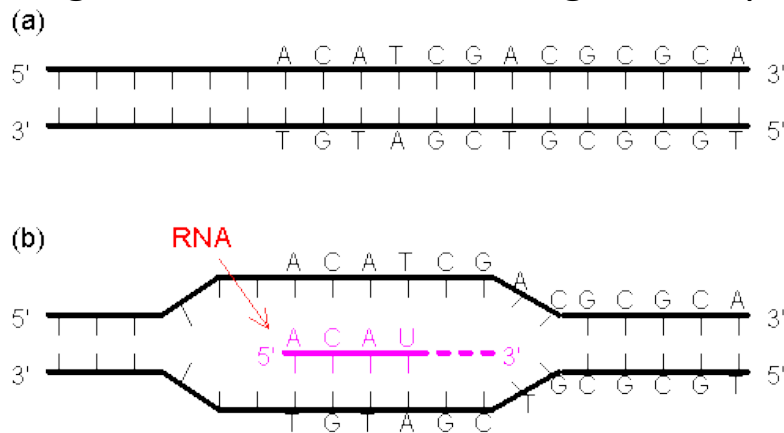


FA 2012: 73.1 • FA 2011: 71.1 • FA 2010: 71
ME 3e: 64

x1.5

BC01-10

- The newly synthesized strand is made in the 5' → 3' direction
- The template strand is scanned in the 3' → 5' direction
- The template strand is used during the transcription
- The coding strand is not used during transcription



FA 2012: 74.1 • FA 2011: 71.2 • FA 2010: 71
ME 3e: 60

x1.5

BC01-11

- Question:
 - A 3-week-old boy is brought to the physician because of lethargy. He has an uncomplicated birth history. He appears lethargic, and his mother says that he does not interact very much with her. He weighed 3.2 kg (7 lbs) at birth but weighs only 2.72 kg (6 lbs) at this visit. Small yellow crystals are found in the patient's diaper. Laboratory studies show megaloblastic anemia. What is the most likely treatment for this patient's disorder?

FA 2012: 74.1 • FA 2011: 71.2 • FA 2010: 71
ME 3e:

x1.5

BC01-12

Answer:

This child most likely has Orotic Aciduria, an autosomal recessive disease caused by a defect in either Orotic acid phosphoribosyltransferase or oritidine 5' - phosphate decarboxylase. Findings include orotic aciduria, megaloblastic anemia, and failure to thrive. The treatment is oral uridine administration.



Molecular Biology – Part II

Jonathan Faiwischewski, M4, UMDNJ.

x1.5

BC02-1

mRNA	Messenger RNA carries sequence info from DNA to ribosomes to be translated
rRNA	Ribosomal RNA is a component of ribosomes
tRNA	Transfer RNA carries amino acids to ribosomes for protein synthesis

- Rampant, Massive, Tiny
- rRNA = rampant
- mRNA = massive
- tRNA = tiny

x1.5

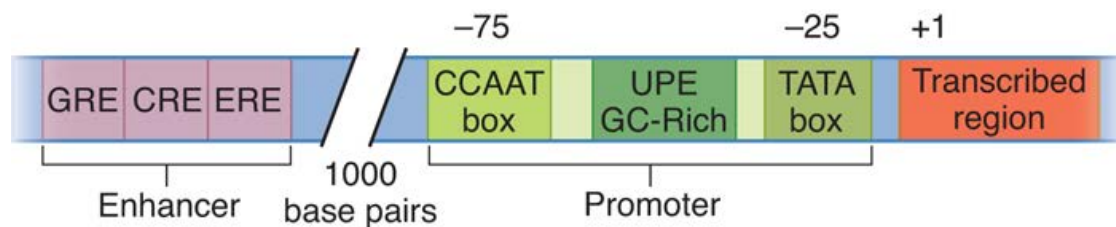
BC02-2

- mRNA start codon (initiation codon) – AUG
 - Eukaryotes – methionine (Met)
 - Prokaryotes – formylmethionine (fMet)
- mRNA stop codons – UAA, UAG, UGA
 - UAA – U Are Away
 - UAG – U Are Gone
 - UGA – U Go Away

FA 2012: 74.3 • FA 2011: 72.2 • FA 2010: 72
ME 3e: 66

x1.5

BC02-3



- Promoters:
 - Bind the transcription factors
 - Located upstream
- Enhancers:
 - Located anywhere
 - Binding sites for activator proteins
- Silencers:
 - Binding sites for repressors proteins

FA 2012: 75.1 • FA 2011: 72.3 • FA 2010: 72
ME 3e: 65

x1.5

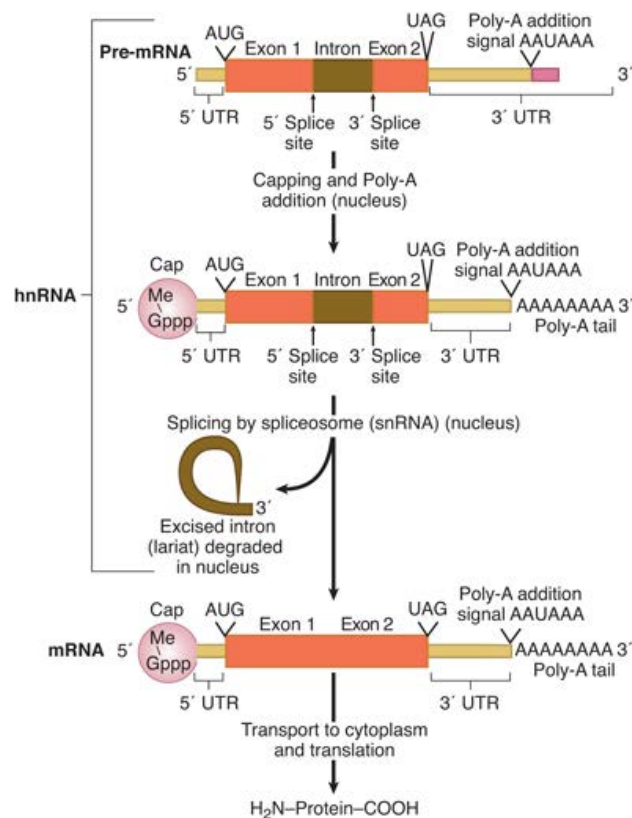
BC02-4

Prokaryotic	Eukaryotic
Single RNA polymerase (a2 bb')	3 types of RNA polymerase -Remember rampant, massive, tiny -RNAP 1: makes 45S (cleaved into 28S, 18S, and 5.8S) rRNA (in the nucleolus) -RNAP 2: makes hnRNA/mRNA and some snRNA -RNAP 3: makes tRNA, 5S rRNA
Inhibited by rifampin	RNAP 2 is inhibited by α -amanitin (mushrooms)
Actinomycin D inhibits both types of RNA	

FA 2012: 75.3 • FA 2011: 72.5 • FA 2010: 72
ME 3e: 65

x1.5

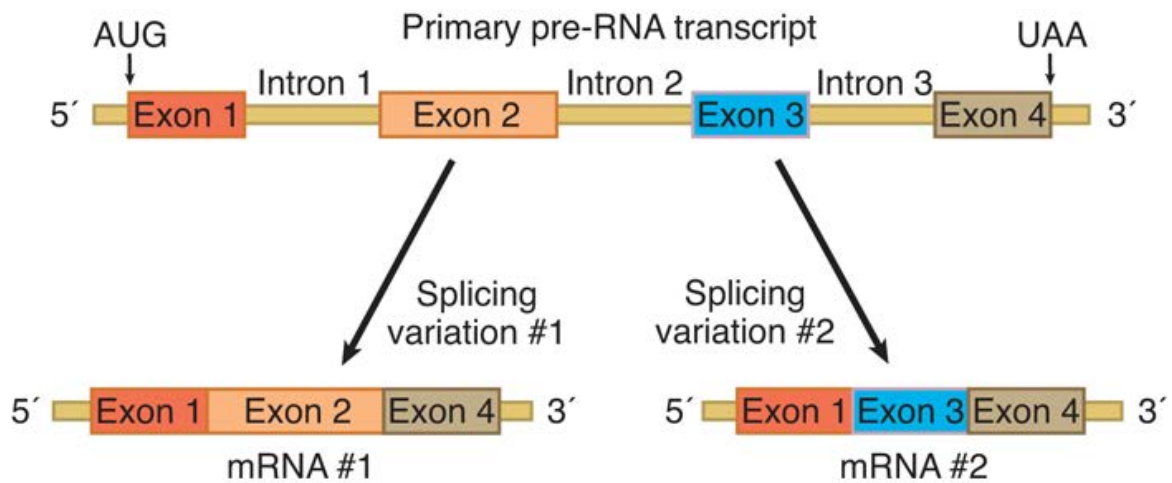
BC02-5



FA 2012: 75.4 • FA 2011: 72.6 • FA 2010: 72
ME 3e: 65

x1.5

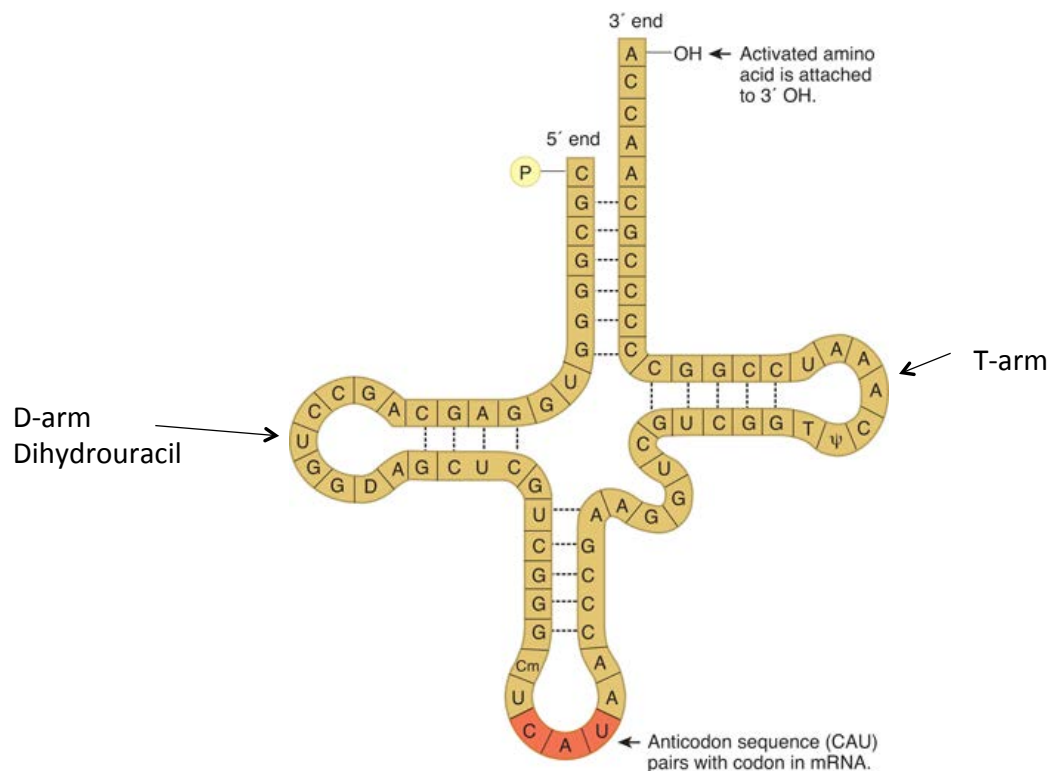
BC02-6



FA 2012: 77.1 • FA 2011: 73.2 • FA 2010: 73
ME 3e: 65

x1.5

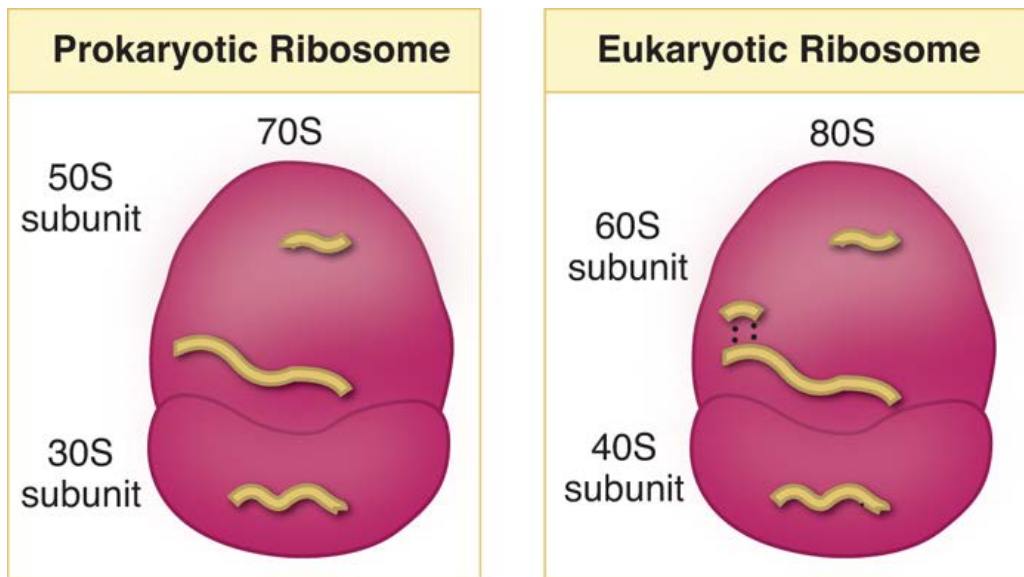
BC02-7



FA 2012: 77.2 • FA 2011: 74.1 • FA 2010: 74
ME 3e: 66

x1.5

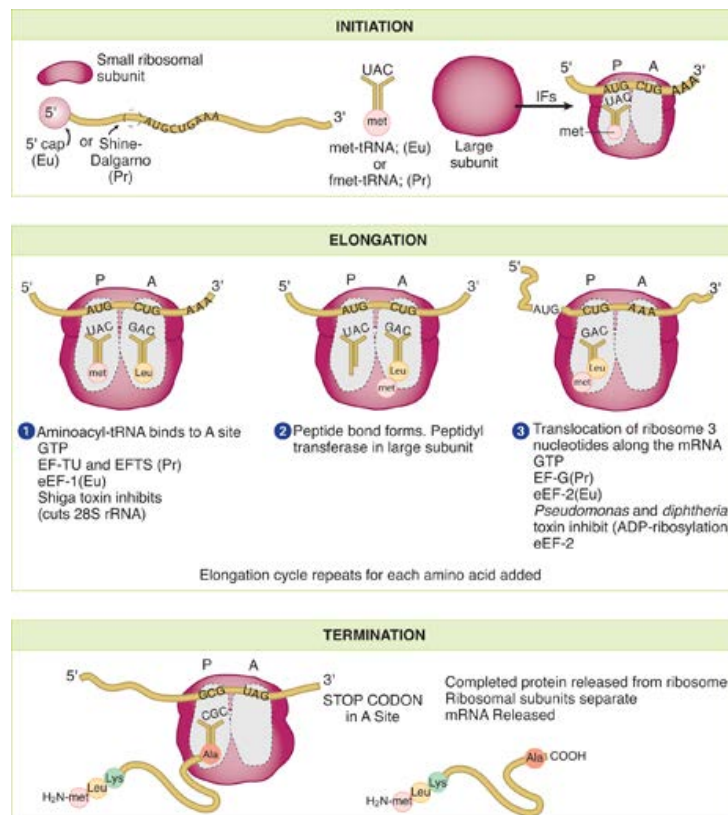
BC02-8



FA 2012: 78.1 • FA 2011: 75.1 • FA 2010: 75
ME 3e: 66

x1.5

BC02-9



FA 2012: 78.1 • FA 2011: 75.1 • FA 2010: 75
ME 3e: 66

x1.5

BC02-10

Posttranslational Modifications

Proteolysis	Cleavage of peptide bonds
Glycosylation	Addition of oligosaccharides
Phosphorylation	Addition of phosphate by protein kinase
γ -carboxylation	Creation of Ca^{2+} binding sites
Ubiquitin	Destroys misfolded proteins
Ubiquitination	Labeling and destruction of misfolded proteins

FA 2012: 78.2 • FA 2011: 75.2 • FA 2010: 75
ME 3e: 67

x1.5

BC02-11

Table V-1-3. Summary of Mechanisms of Protein Synthesis Inhibition

Event	Antibiotic(s) and Binding Site(s)	Mechanism(s)
1. Formation of initiation complex	Aminoglycosides (30S) Linezolid (50S)	Interfere with initiation codon functions—block association of 50S ribosomal subunit with mRNA-30S (static); misreading of code (aminoglycosides only)—incorporation of wrong amino acid (–cidal)
2. Amino-acid incorporation	Tetracyclines (30S) Dalfopristin/ quinupristin (50S)	Block the attachment of aminoacyl tRNA to acceptor site (–static)
3. Formation of peptide bond	Chloramphenicol (50S)	Inhibit the activity of peptidyltransferase (–static)
4. Translocation	Macrolides and clindamycin (50S)	Inhibit translocation of peptidyl-tRNA from acceptor to donor site (–static)

FA 2012: 78.1 • FA 2011: 75.1 • FA 2010: 75
ME 3e: 66

x1.5

BC02-12

- Question

- An 8-year-old girl of Greek descent presents to her pediatrician's office with complaint of poor exercise tolerance in her gym class at school. Her mother states that she had similar problems as a child and has needed blood transfusions several times in her life. On exam she appears normal for her stated age. She is found to have pale conjunctiva and oral mucosa and is mildly tachycardic. A CBC reveals WBC 8.2, Hgb 7.2, Hct 28.9, Plt 168, MCV 62. The defect in this patient is found at what level of the cell?

- A. DNA synthesis
 - B. Transcription
 - C. Translation
 - D. Post-translational modification

FA 2012: 78.2 • FA 2011: 75.2 • FA 2010: 75

x1.5

BC02-13

- Answer:

- This presentation of a severely microcytic anemia (MCV < 70) with family history is suspicious for a hemoglobinopathy. Beta-thalassemia is common in people of Greek descent. Beta-thalassemia is an autosomal recessive disease caused by a mutation in a splice acceptor site, causing an exon to be missed in the mRNA coding for the beta-hemoglobin chain. Thus, the answer is B: transcription.

FA 2012: 78.2 • FA 2011: 75.2 • FA 2010: 75

x1.5

BC02-14

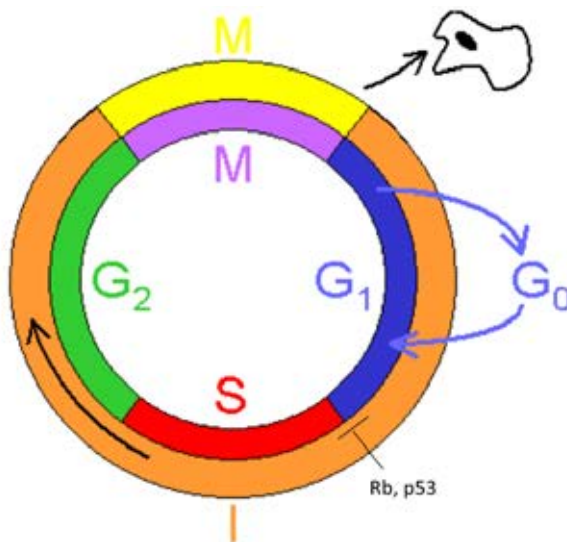


Cell Biology – Part I

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x1.5

BC03-1



Phases of the cell cycle:

- **G₁**: cell growth; checkpoint ensures that the cell is ready for DNA synthesis
- **S**: synthesis phase; DNA replication occurs
- **G₂**: continued growth, duplication of organelles; G₂ checkpoint ensures that the cell is ready to enter the M phase
- **M**: mitosis
- **G₀**: quiescent stage; cells not actively dividing

Cell_cycle.png, commons.wikimedia.org, used with permission

x1.5

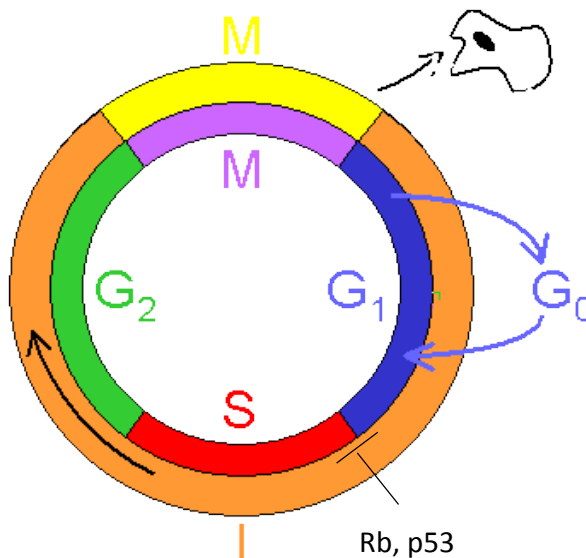
BC03-2

Regulators of the Cell Cycle		
Cyclins	Phase-specific proteins that activate cyclin-dependent kinases (CDKs)	Cyclin levels rise and fall depending on the stage of the cell cycle
CDKs	Regulate the cell cycle and transcription, among other things	CDKs bound to various substrates such as cyclin promote cell-cycle progression via phosphorylation
Rb	Tumor suppressor that inhibits the G1 to S transition	Mutation of both alleles results in development of retinoblastoma
p53	Tumor suppressor that inhibits the G1 to S transition	Mutations lead to Li-Fraumeni syndrome

FA 2012: 79.1 • FA 2011: 76.1 • FA 2010: 76
ME 3e: 83

x1.5

BC03-3



Cell_cycle.png, commons.wikimedia.org,
used with permission

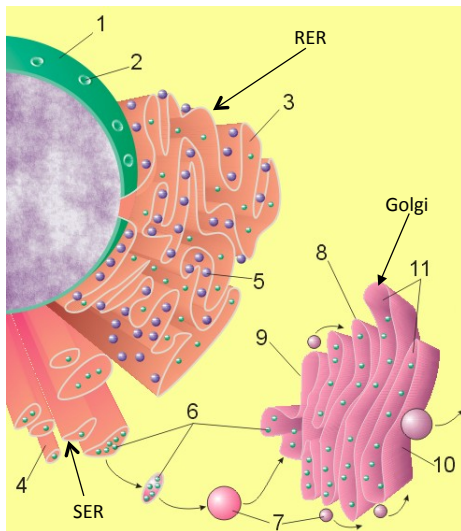
Cell types:

- Permanent – remain in phase G_0 (neurons, RBCs)
- Stable – enter G_1 from G_0 when stimulated. (Hepatocytes, lymphocytes)
- Labile – never go to G_0 . (Bone marrow, intestinal mucosa, skin, hair follicles)

FA 2012: 79.1 • FA 2011: 76.1 • FA 2010: 76
ME 3e: 83

x1.5

BC03-4



- 1-Nuclear membrane
- 2-Nuclear pore
- 3-Rough endoplasmic reticulum (RER)
- 4-Smooth endoplasmic reticulum (SER)
- 5-Ribosome attached to RER
- 6-Macromolecules
- 7-Transport vesicles
- 8-Golgi apparatus
- 9-Cis face of Golgi apparatus
- 10-Trans face of Golgi apparatus
- 11-Cisternae of Golgi apparatus

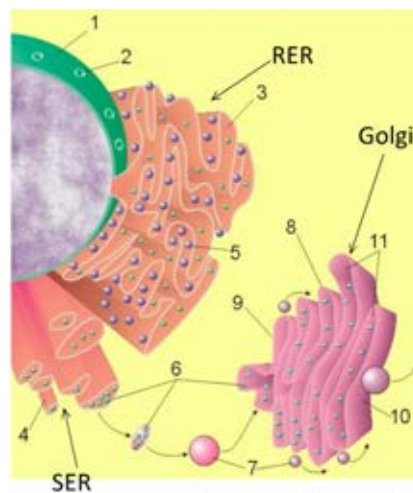
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- N-terminal hydrophobic sequence: added to proteins to signify to the ribosome to bring them to the ER
 - N-terminus is translated first
- Cells rich in RER: endocrine cells, neurons, plasma cells (antibody production)
 - Important for secretory protein products
- Nissl bodies: important for making neurotransmitters

FA 2012: 79.2 • FA 2011: 76.2 • FA 2010: 76
ME 3e: 78

x1.5

BC03-5



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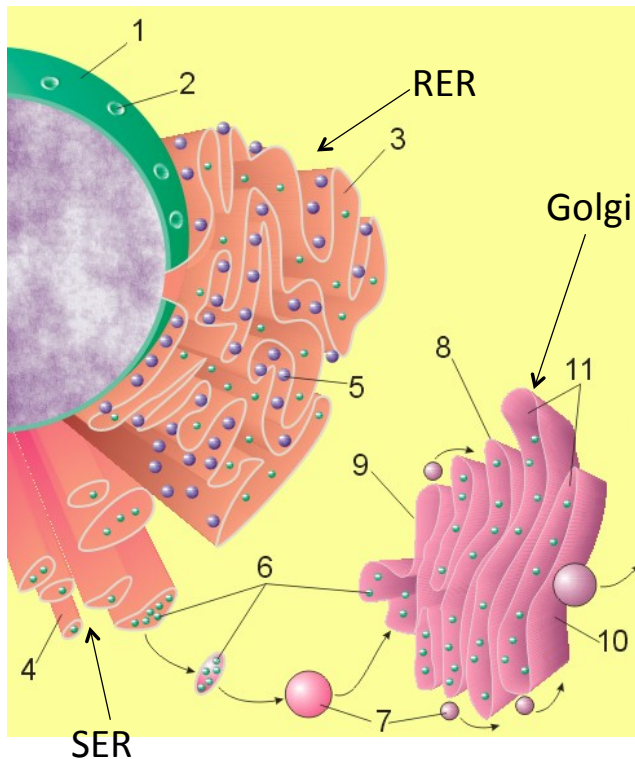
- 1-Nuclear membrane
- 2-Nuclear pore
- 3-Rough endoplasmic reticulum (RER)
- 4-Smooth endoplasmic reticulum (SER)
- 5-Ribosome attached to RER
- 6-Macromolecules
- 7-Transport vesicles
- 8-Golgi apparatus
- 9-Cis face of Golgi apparatus
- 10-Trans face of Golgi apparatus
- 11-Cisternae of Golgi apparatus

- N-terminal hydrophobic sequence: added to proteins to signify to the ribosome to bring them to the ER
 - N-terminus is translated first
- Cells rich in RER: endocrine cells, neurons, plasma cells (antibody production)
 - Important for secretory protein products
- Nissl bodies: important for making neurotransmitters

FA 2012: 79.2 • FA 2011: 76.2 • FA 2010: 76
ME 3e: 78

x1.5

BC03-6



commons.wikimedia.org, used with permission

Functions of SER:

- Detoxification reactions (Liver)
- Steroid synthesis (Adrenal cortex)

FA 2012: 79.3 • FA 2011: 76.3 • FA 2010: 76
ME 3e: 79

x1.5

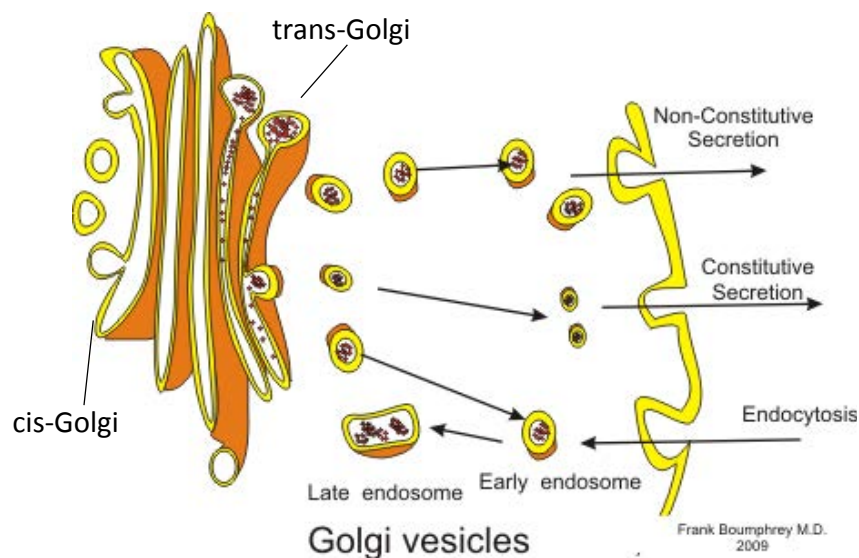
BC03-7

- Post-translational modification of proteins as addresses for organelles:
 - N-terminal hydrophobic sequence for RER
 - Mannose-6-P for lysosomal storage
 - C-terminal palmitoylation for membrane anchoring (transmembrane receptors)

FA 2012: 79.3 • FA 2011: 76.3 • FA 2010: 76
ME 3e: 79

x1.5

BC03-8



- COP I functions in retrograde (backward) movement (trans-Golgi to cis-Golgi)
- COP II functions in anterograde (forward) movement
- Clathrin plays a role in the formation of coated vesicles; especially important in endosome formation

Golgi_secretions.jpg, commons.wikimedia.org, used with permission

FA 2012: 80.1 • FA 2011: 77.1 • FA 2010: 77
ME 3e: 79

x1.5

BC03-9

• I-cell disease

- Named for the intracytoplasmic inclusions
- Deficiency of N-acetylglucosamine-phosphotransferase
- Failure of addition of mannose-6-phosphate to lysosome proteins
- Characterized by inclusion bodies in the cell
- Symptoms: skeletal abnormalities, coarse features, restricted joint movement, psychomotor retardation, corneal clouding and cataracts
- Laboratory findings include high levels of lysosomal enzymes in the blood
- Life span is less than 10 years

FA 2012: 80.1 • FA 2011: 77.1 • FA 2010: 77
ME 3e: 79

x1.5

BC03-10

- Microtubules: cell “motors”
 - Polymerization of small spherical molecules (dimers of alpha and beta tubulin with 2 GTP molecules) arranged in a long cylinder
 - Function in:
 - Mitosis – mitotic spindle
 - Flagella, cilia, axonal transport
 - Target for antibiotics – e.g. antihelmintics, paclitaxel, Vinca alkaloids, colchicine
 - Associated proteins:
 - Dynein – retrograde movement along microtubules (e.g. axonal transport)
 - Kinesin – anterograde movements
 - Mnemonic – You can Dine In or Take Out

FA 2012: 81.2 • FA 2011: 78.1 • FA 2010: 78
ME 3e: 81

x1.5

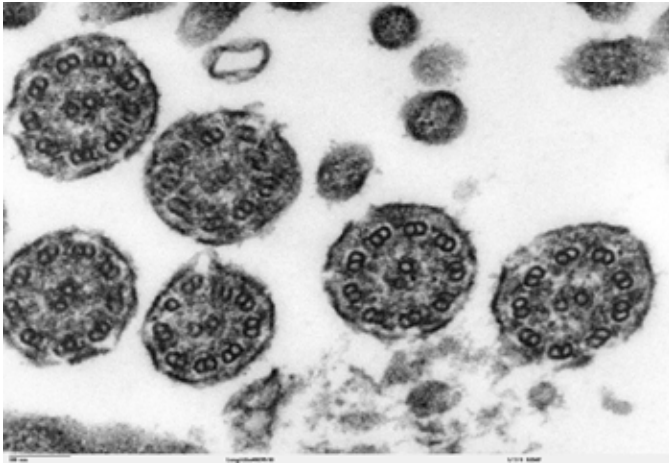
BC03-11

- Drugs that act on microtubules
 - Mebendazole: antihelmintic that inhibits synthesis of parasitic microtubules
 - Griseofulvin: antifungal that binds to tubulin and interferes with microtubule function
 - Vinca alkaloids: antineoplastic anti-mitotic and anti-microtubule agents
 - Colchicine: binds to tubulin and inhibits mitosis
- Chediak-Higashi syndrome:
 - Disease in which microtubules do not correctly polymerize or depolymerize
 - Triad of partial albinism, peripheral neuropathy, and chronic pyogenic infections

FA 2012: 81.2 • FA 2011: 78.1 • FA 2010: 78
ME 3e: 81

x1.5

BC03-12



Bronchiolar_area_cilia_cross-sections_1.jpg, commons.wikimedia.org, used with permission.

Kartagener Syndrome

- Autosomal recessive condition
- Caused by defect in dynein, which leads to immotile cilia
- Chronic cough, rhinitis, sinusitis
- Male and female infertility
- Associated with situs inversus

FA 2012: 81.3 • FA 2011: 78.2 • FA 2010: 78
ME 3e: 81

x1.5

BC03-13

- Cytoskeleton: cell scaffolding
 - Actin and myosin – for “movement” of the skeleton (like little cell muscles)
 - Microtubules
 - Intermediate filaments – the “beams” of the scaffolding
 - Stains for intermediate filaments in various tissues:
 - Vimentin (connective tissue)
 - Desmin (muscle)
 - Cytokeratin (epithelium)
 - Glial fibrillary acidic protein (GFAP) (glial cells)
 - Neurofilaments (neurons)

FA 2012: 81.4 • FA 2011: 78.3 • FA 2010: 78
ME 3e: 81

x1.5

BC03-14

- Plasma membrane
 - More cholesterol -> less fluidity, higher melting temp.
 - Integral membrane proteins are labeled with C-terminal palmylation, and have glycine-rich region in the transmembrane segment (remember, glycine is a non-polar AA)

FA 2012: 81.5 • FA 2011: 78.4 • FA 2010: 78
ME 3e: 80

x1.5

BC03-15

- Question:
 - An 8-year-old girl presents to the emergency room with chief complaint of difficulty breathing for 1 day. Her parents tell the physician that she has been feverish and has been coughing up profuse, malodorous sputum and has been hospitalized several times in the past for “pneumonia”. On physical exam she appears in moderate respiratory distress, but is an otherwise normal-appearing 8-year-old girl. On lung exam she is found to have wheezes and rhonchi diffusely, and her heart sounds are normal at the second parasternal intercostals spaces but are not audible in the fourth parasternal intercostals space or at the fifth intercostals space in the left midclavicular line. Which of the following is true?
 - A. This patient is in need of emergent pericardiocentesis.
 - B. A chest X-ray of this patient will reveal an absent thymus shadow.
 - C. This patient is unlikely to be able to sustain a viable pregnancy in the future.
 - D. This disease is associated with pancreatic insufficiency.

FA 2012: 82.1 • FA 2011: 78.5 • FA 2010: 78
ME 3e:

x1.5

BC03-16

- **Answer**

The finding of non-audible left-sided heart sounds, which is suspicious for dextrocardia, as well as recurrent respiratory infections should make you think of a genetic disease such as Kartagener Syndrome. This condition is a genetic disorder caused by a defect in dynein, which results in paralysis of cilia in the respiratory and reproductive tracts, resulting in recurrent infections and infertility. Failure of ciliary movement during development is also associated with situs inversus. Therefore, the answer is C – this patient is unlikely to be able to sustain a viable pregnancy in the future.

FA 2012: 82.1 • FA 2011: 78.5 • FA 2010: 78
ME 3e:

x1.5

BC03-17

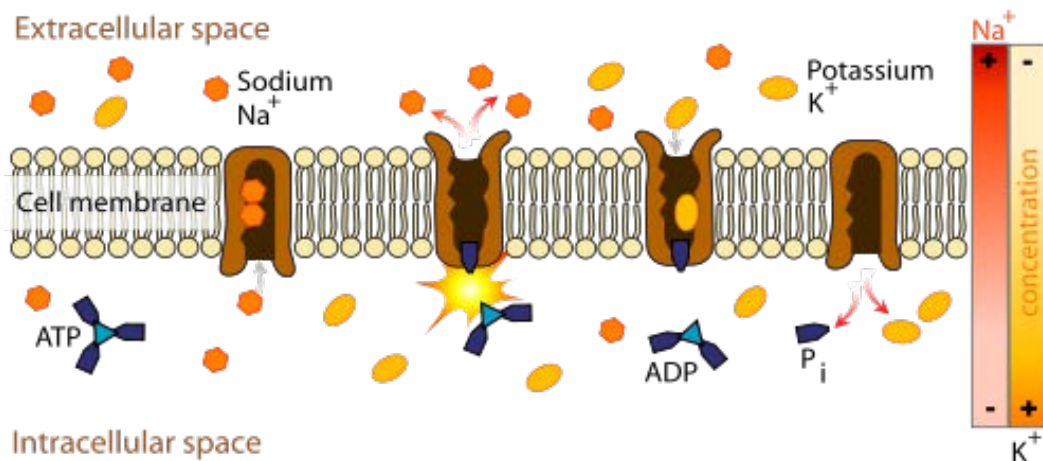


Cell Biology - Part II: Lab Techniques

Jonathan Faiwischewski, M4, UMDNJ.

x1.5

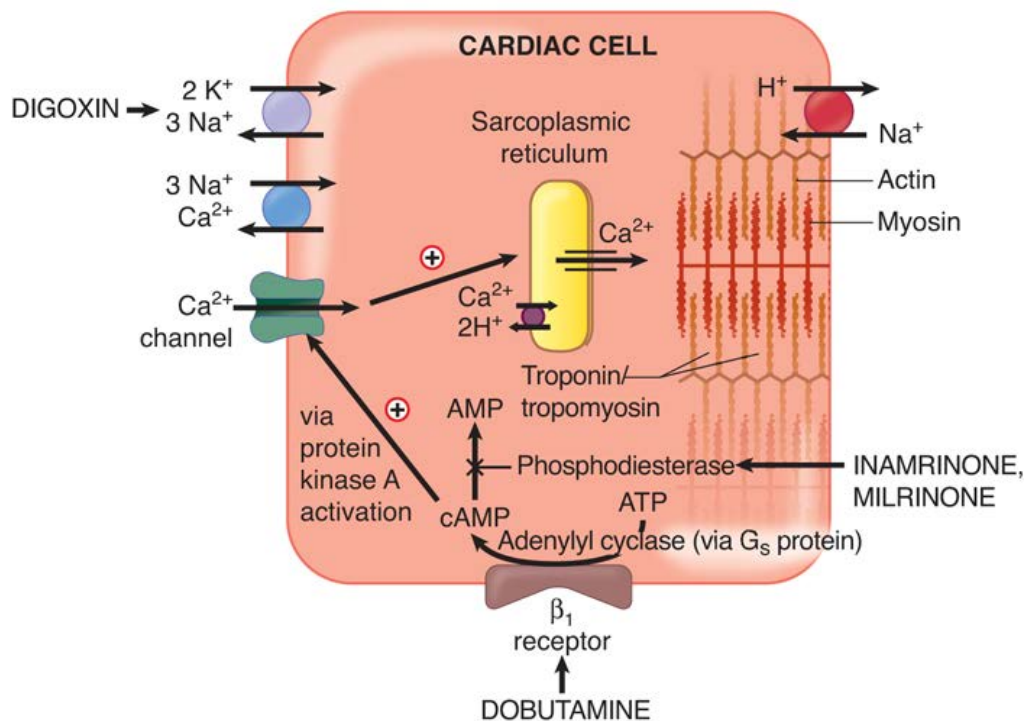
BC04-1



commons.wikimedia.org, used with permission.

x1.5

BC04-2



FA 2012: 82.2 • FA 2011: 79.1 • FA 2010: 79
ME 3e: 271

x1.5

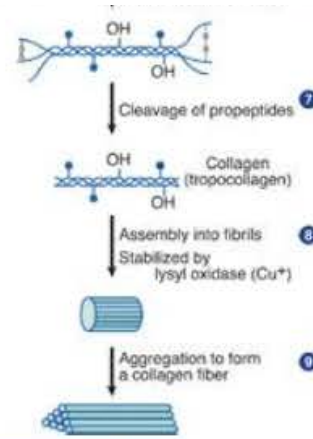
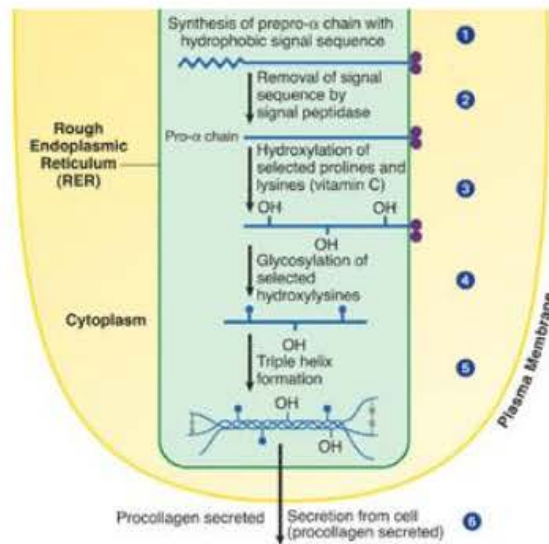
BC04-3

- Major types of collagen
 - Type I – bone, skin, fascia, tendons, cornea, teeth, mature scars
 - Type II – cartilage, vitreous humor, nucleus pulposus
 - Type III – reticular fibers
 - Type IV – basement membrane
- Mnemonic
 - Type ONE = bONE
 - Type TWO = carTWOlage
 - Type four in the floor

FA 2012: 82.3 • FA 2011: 79.2 • FA 2010: 79
ME 3e: 68

x1.5

BC04-4



FA 2012: 83.1 • FA 2011: 79.3 • FA 2010: 79
ME 3e: 68

x1.5

BC04-5

- Menkes disease
 - Deficient collagen cross-linking due to copper deficiency
 - Characterized by depigmented hair, osteoporosis, anemia, cerebral degeneration, and arterial tortuosity and rupture
- Ehlers-Danlos syndrome
 - Hereditary deficiency of collagen synthesis
 - Most commonly involves type 3 collagen
 - Clinical triad of stretchy skin, bruising, hypermobile joints
 - Associated with berry aneurysm and possible subarachnoid hemorrhage; also with mitral valve prolapse

FA 2012: 83.3 • FA 2011: 80.1 • FA 2010: 80
ME 3e: 68

x1.5

BC04-6



- Osteogenesis imperfecta
 - Autosomal dominant inheritance
 - Abnormality in type I collagen
 - Characterized by blue sclerae, multiple fractures, hearing loss, and dental imperfections

FA 2012: 83.2 • FA 2011: 80.2 • FA 2010: 80
ME 3e: 68

x1.5

BC04-7

- Alport's Syndrome:
 - X-linked recessive
 - Defect in type IV collagen
 - Hereditary nephritis (involvement of glomerular basement membrane)
 - Deafness (involvement of basement membrane in Organ of Corti)

FA 2012: 86.2 • FA 2011: 82.3 • FA 2010: 82
ME 3e: 68

x1.5

BC04-8

- Elastin
 - Elastic protein found in connective tissue
 - Lung, arteries, ligaments, vocal cords
 - Similarly to collagen but with no separate steps for hydroxylation and glycosylation
 - Rich in proline and lysine
 - Cross-linked by fibrillin

FA 2012: 84.2 • FA 2011: 80.4 • FA 2010: 80
ME 3e: 68

x1.5

BC04-9

- Trypsin and elastase degrade elastin
- α_1 -antitrypsin protects elastin
- Deficiency of α_1 -antitrypsin:
 - Can be hereditary or due to cigarette smoking
 - Causes degradation of elastin
 - Characterized by hepatic cirrhosis and emphysema

FA 2012: 84.2 • FA 2011: 80.4 • FA 2010: 80
ME 3e: 293

x1.5

BC04-10

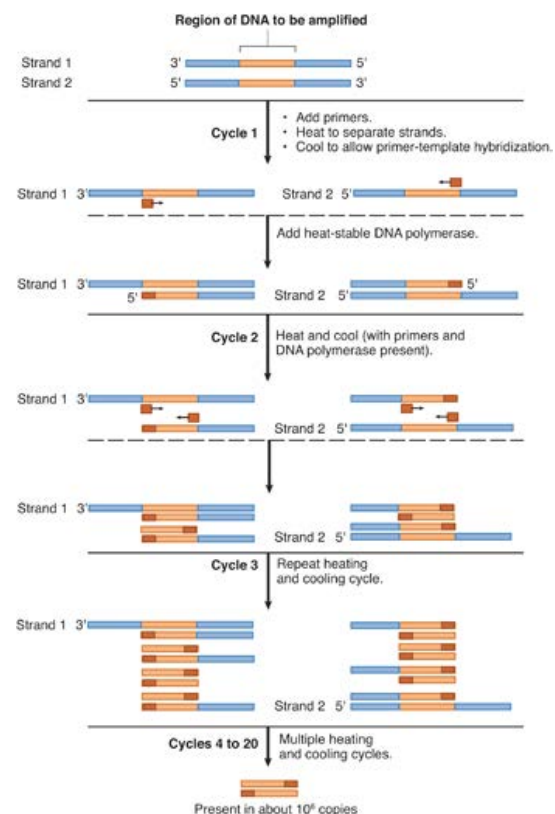
- Marfan syndrome
 - Caused by a defect in fibrillin
 - Characterized by:
 - Tall, thin, long extremities
 - Arachnodactyly
 - Hyperextensible joints
 - Eye abnormalities (ectopia lentis)
 - Associated with aortic dissection

FA 2012: 84.2 • FA 2011: 80.4 • FA 2010: 80
ME 3e: 73

x1.5

BC04-11

- PCR is used to amplify and study DNA
- Steps:
 - Denaturation: heat used to split the DNA
 - Annealing: primers anneal to single-stranded DNA template
 - Elongation: nucleotides are added to template strand and cooled for reannealing



FA 2012: 84.3 • FA 2011: 81.1 • FA 2010: 81
ME 3e: 69

x1.5

BC04-12

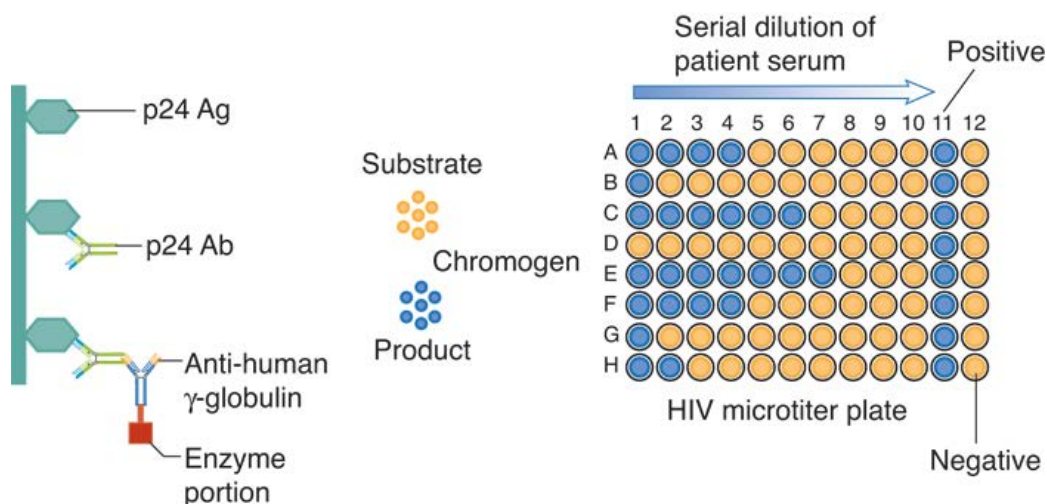
- Blotting
 - Southern blot: first blotting technique; introduced by Dr. Southern
 - Mnemonics
 - Southern blot is most fundamental, so it is used to detect DNA
 - The opposite of Southern is Northern, and this is used to detect RNA
 - The remaining blot is the Western, which is used to detect protein
- Microarrays
 - Used to detect the presence of SNPs

FA 2012: 85.1 • FA 2011: 81.2 • FA 2010: 81
ME 3e: 71

x1.5

BC04-13

- ELISA: to identify a specific antibody or antigen
 - Can be performed using a known antigen to find its antibody
 - Can also be performed using a known antibody to find its antigen



FA 2012: 85.3 • FA 2011: 81.4 • FA 2010: 81
ME 3e: 71

x1.5

BC04-14

- FISH
 - Fluorescent DNA is used to look for the presence/absence of a gene in tissue.
 - Specifically, this technique is used to look for deletions (FISH does not bind so it doesn't light up)
 - e.g. Loss of tumor suppressors in a tumor.

FA 2012: 85.4 • FA 2011: 82.1 • FA 2010: 82
ME 3e: 71

x1.5

BC04-15

- Cloning: Making Recombinant DNA
 - Technique uses restriction enzymes to open up a plasmid, creating “sticky ends”
 - The gene of choice and an additional gene for antibiotic resistance are inserted
 - The plasmid is closed and selectively grown by introducing the antibiotic so that all bacteria without the antibiotic resistance gene die
 - The gene product of interest is extracted
 - We can do this now with other animal species

FA 2012: 86.1 • FA 2011: 82.2 • FA 2010: 82
ME 3e: 69

x1.5

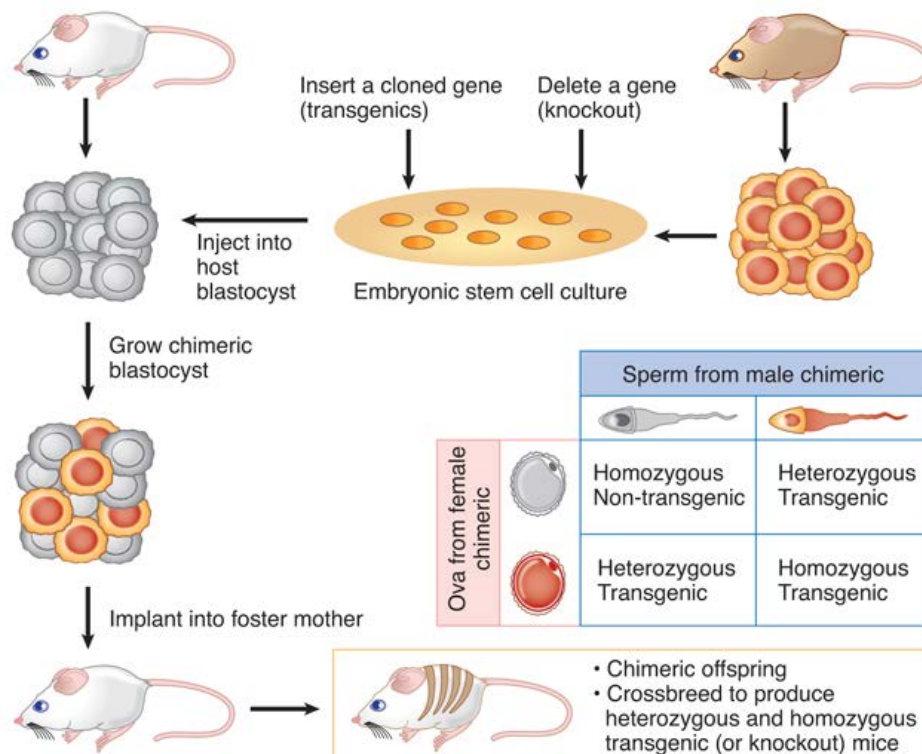
BC04-16

- Sanger Sequencing:
 - Use dideoxynucleotides to cause chain termination (just like we do in antiviral drugs)
 - Electrophorese the different DNA strains of various lengths to determine the original DNA strand's sequence.

FA 2012: 86.2 • FA 2011: 82.3 • FA 2010: n/a
ME 3e: 70

x1.5

BC04-17

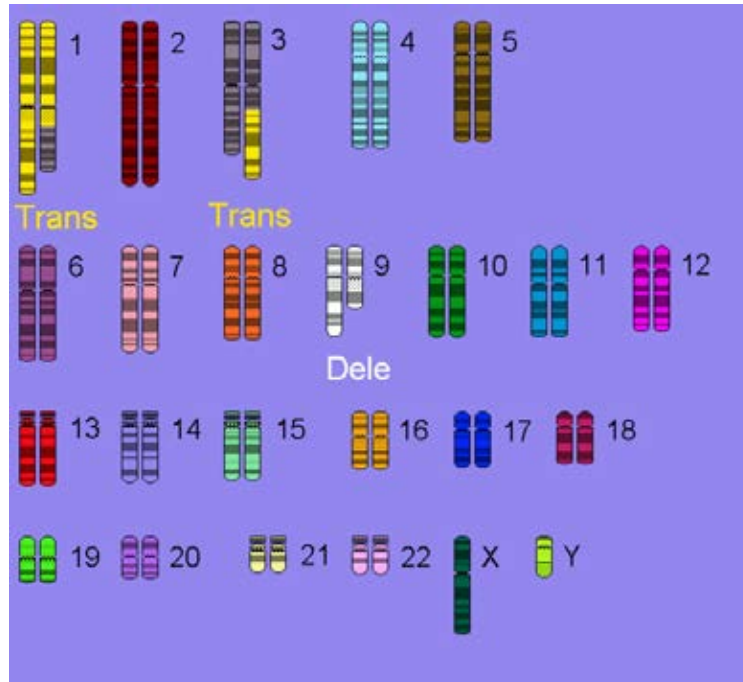


FA 2012: 86.3 • FA 2011: 82.4 • FA 2010: 82
ME 3e: 70

x1.5

BC04-18

- Look at the chromosomes in a cell



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FA 2012: 86.2 • FA 2011: 82.3 • FA 2010: 82
ME 3e: 71

x1.5

BC04-19

Questions

- If you want to determine if a baby's infection is caused by adenovirus, which method would you use?
- If you suspect trisomy 21 in a baby with a congenital heart defect, which method would you use?
- If you want to study the effect of L-dopa on Parkinson's disease, which method would you use?
- If you want to determine the sequence of an unknown gene, which method would you use?

x1.5

BC04-20



Medical Genetics

Jonathan Faiwischewski, M4, UMDNJ.

x1.5

BC05-1

- Codominance – multiple alleles that are expressed simultaneously
- Variable expression – same allele, different severity
- Incomplete penetrance – an allele may or may not cause disease
- Pleiotropy – single disease mutation affects multiple organ systems
- Imprinting – symptoms depend on whether mutant gene was inherited from father or mother
- Anticipation – earlier age of onset and increased disease severity with each generation

x1.5

BC05-2

- Loss of heterozygosity – loss of normal function of one allele when the other allele was already inactivated
- Dominant negative – mutation found in only one copy leads to inactivation of other copy
- Linkage disequilibrium – association of alleles at two or more loci
- Mosaicism – different cell lines present in one organism
- Locus heterogeneity – same disease phenotype from mutations in different loci
- Uniparental disomy – both copies of a chromosome come from a single parent

FA 2012: 87.1 • FA 2011: 83.1 • FA 2010: 83
ME 3e: 73

x1.5

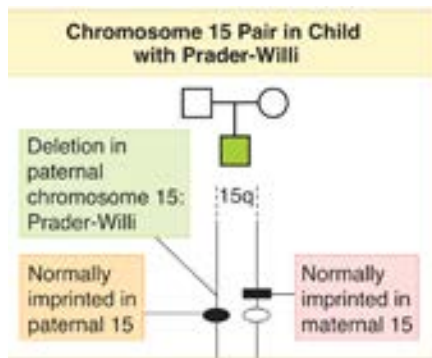
BC05-3

- Hardy-Weinberg equilibrium
 - Allele and genotype frequencies in a population remain constant if these conditions are met:
 - Random mating
 - No mutations
 - No natural selection
 - No migration in or out of the population
 - No genetic drift
 - For any single given chromosome, $p + q = 1$
 - For two chromosomes, $(p + q = 1)^2 = p^2 + 2pq + q^2 = 1$
 - p = normal allele
 - q = diseased allele

FA 2012: 88.1 • FA 2011: 84.1 • FA 2010: 84
ME 3e: 77

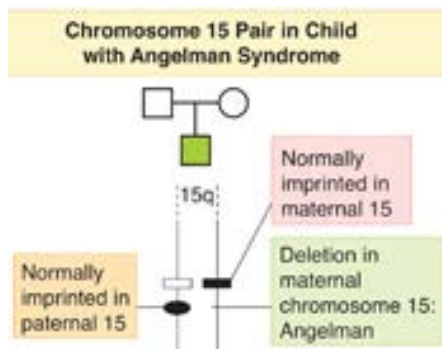
x1.5

BC05-4



Prader-Willi syndrome

- Deletion in paternal chromosome
- Characteristics
 - Short stature and obese
- Hyperphagia
 - Mental retardation



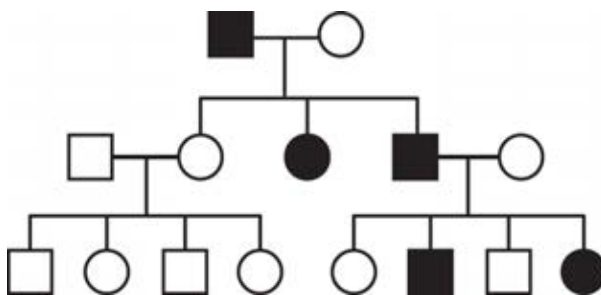
Angelman syndrome

- Deletion in maternal chromosome
- Characteristics
 - “Happy puppet” appearance
 - Always smiling
 - Hyperactivity
 - Mental retardation, seizures

FA 2012: 88.2 • FA 2011: 84.2 • FA 2010: 84
ME 3e: 77

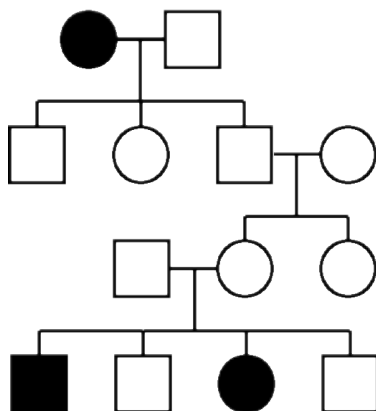
x1.5

BC05-5



Autosomal dominant

- See disease in every generation
- Affects both sexes



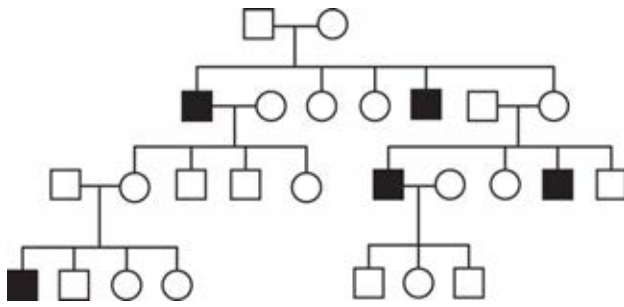
Autosomal recessive

- Disease skips generations
- Affects both sexes

FA 2012: 89.1 • FA 2011: 85.1 • FA 2010: 85
ME 3e: 72

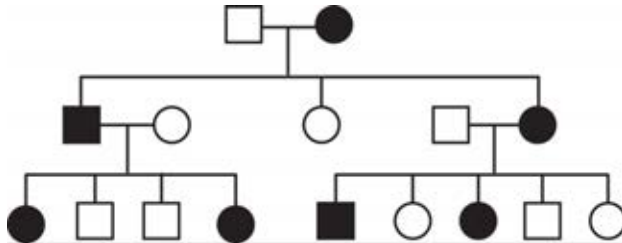
x1.5

BC05-6



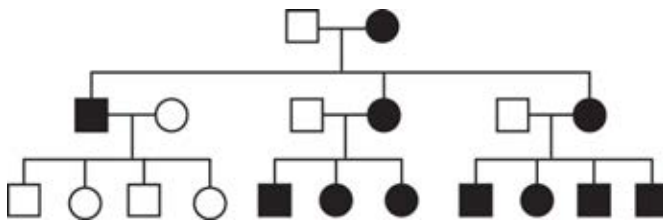
X-linked recessive

- Usually affects males only
- No male-to-male transmission



X-linked dominant

- Usually affects both sexes
- No male-to-male transmission



Mitochondrial inheritance

- Inherited only maternally
- Transmitted to all children

FA 2012: 89.1 • FA 2011: 85.1 • FA 2010: 85
ME 3e: 72

x1.5

BC05-7

General rules

- If the disease only affects males, it is most likely X-linked recessive
- If the mutation is in an enzyme, the disease is most likely autosomal recessive
- If the mutation is in a structural protein, oncogene, or tumor suppressor gene, the disease is most likely autosomal dominant

FA 2012: 89.1 • FA 2011: 85.1 • FA 2010: 85
ME 3e: 72

x1.5

BC05-8

- Autosomal dominant diseases
 - Achondroplasia (dwarfism): FGF-receptor 3 defect
 - Adult/Autosomal Dominant Polycystic Kidney: bilateral massive polycystic kidneys; involves chromosome 16
 - Hematuria, flank pain, end-stage renal disease, mitral valve prolapse, berry aneurysm
 - Familial adenomatous polyposis (FAP): many colon polyps; high risk of colon cancer; deletion of APC gene on chromosome 5
 - Familial hyperlipidemia IIA: loss of LDL receptor;
 - Atherosclerosis, xanthomas, MI, stroke; more severe in heterozygotes
 - Osler-Weber-Rendu syndrome: telangiectasias, bleeding, arteriovenous malformations
 - Spherocytosis: spectrin/ankyrin defect causes loss of normal RBC shape, hemolytic anemia
 - Treated with splenectomy, with associated complications
 - Huntington disease: CAG repeat on chromosome 4
 - Progressive dementia; caudate atrophy causes choreic movement

FA 2012: 90.1 • FA 2011: 86.1 • FA 2010: 86
ME 3e: 72

x1.5

BC05-9

- Autosomal Dominant diseases (cont'd)
 - Marfan's disease: fibrillin mutation
 - Tall, lanky body habitus; long limbs; pectus excavatum; cystic medial necrosis of aorta → aortic dissection, aortic insufficiency, mitral valve regurgitation
 - Multiple endocrine neoplasia (MEN):
 - Type 1: 3 P's – cancers of the pituitary, pancreas, parathyroid
 - Type 2A: Parathyroid cancer, pheochromocytoma, medullary cancer of thyroid
 - Type 2B: pheochromocytoma, medullary cancer of thyroid, neuromas
 - Neurofibromatosis
 - Type 1 (NF1; von Recklinghausen's): associated with chromosome 17, café-au-lait spots, neurofibromas, Lisch nodules
 - Type 2: associated with chromosome 22, bilateral acoustic neuromas (schwannomas), juvenile cataracts.

FA 2012: 90.1 • FA 2011: 86.1 • FA 2010: 86
ME 3e: 73

x1.5

BC05-10

- Autosomal Dominant diseases (cont'd)
 - Tuberous sclerosis: facial lesions, hypopigmented ash leaf spots, cortical and renal hamartomas, mental retardation, renal cysts and angiomyolipomas, cardiac rhabdomyomas, astrocytomas.
 - TS vs NF1: WTF, dude? (WTFD)
 - White (ash leaf) lesions = Tuberous; Fibromas (NF1) = Dark (café-au-lait spots)
 - Von Hippel-Lindau syndrome (VHL): deletion of tumor suppressor on chromosome 3 leads to overgrowth of blood vessels; risk of renal cell carcinoma
 - Hemangioblastomas of retina, cerebellum and medulla

FA 2012: 90.1 • FA 2011: 86.1 • FA 2010: 86
ME 3e: 73

x1.5

BC05-11

- Autosomal recessive diseases
 - Albinism
 - AR polycystic kidney disease
 - Cystic fibrosis
 - Glycogen storage diseases
 - Hemochromatosis
 - Mucopolysaccharidosis
 - Phenylketonuria
 - Sickle cell disease
 - Sphingolipidosis
 - Thalassemias

FA 2012: 91.1 • FA 2011: 87.1 • FA 2010: 87
ME 3e: 72

x1.5

BC05-12

- Cystic Fibrosis
 - Autosomal recessive defect in CFTR gene (delta-F508 deletion) on chromosome 7
 - CFTR codes for a chloride channel
 - Inability to lubricate lungs leads to recurrent pneumonia, bronchiectasis
 - Important organisms: *Staphylococcus aureus*, *Pseudomonas aeruginosa*
 - Inability to lubricate pancreatic ducts leads to pancreatic insufficiency
 - Characterized by steatorrhea, malabsorption of fat-soluble vitamins
 - Can also lead to diabetes
 - Inability to dilute sweat causes salty sweat, positive sweat test, “salty baby”

FA 2012: 91.2 • FA 2011: 87.2 • FA 2010: 87
ME 3e: 73

x1.5

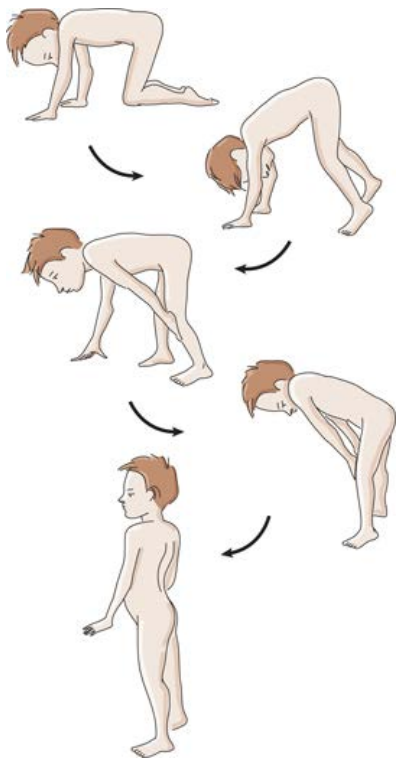
BC05-13

- X-linked recessive diseases
 - Bruton’s agammaglobulinemia
 - Wiskott-Aldrich syndrome
 - Fabry’s disease
 - G6PD deficiency
 - Ocular albinism
 - Lesch-Nyhan syndrome
 - Muscular dystrophies
 - Hunter’s syndrome
 - Hemophilia A and B

FA 2012: 91.3 • FA 2011: 87.3 • FA 2010: 87
ME 3e: 72

x1.5

BC05-14



- **Duchenne's muscular dystrophy**
 - Most common and severe muscular dystrophy
 - Caused by a defect of the deletion of dystrophin gene
 - Characteristics
 - Progressive muscle weakness
 - Calf pseudohypertrophy
 - Proximal weakness of shoulder and pelvic girdles
 - Gower's sign (see left)
 - Cardiomyopathy
 - Onset of symptoms by age 5 years

FA 2012: 91.4 • FA 2011: 87.4 • FA 2010: 87
ME 3e: 72

x1.5

BC05-15

- **Trinucleotide repeat expansion diseases**
 - Huntington disease = CAG repeat (chromosome 4)
 - Myotonic dystrophy = CTG repeat (chromosome 19)
 - Muscular dystrophy with myotonia
 - Delayed development, low IQ, behavioral problems
 - Fragile X = CGG repeat (X chromosome)
 - Mnemonic: Big Balls, Big Jaw, Big Ears
 - 2nd most common genetic cause of MR after Down Syndrome
 - Physical exam: MVP murmur (mid-systolic snap, late systolic murmur at apex, radiates to axilla)
 - Friedrich's ataxia = GAA repeat (chromosome 9)
 - Loss of neurons in the spinocerebellar tract, dorsal columns, and corticospinal tract

FA 2012: 92.2 • FA 2011: 88.1 • FA 2010: 88
ME 3e: 72

x1.5

BC05-16

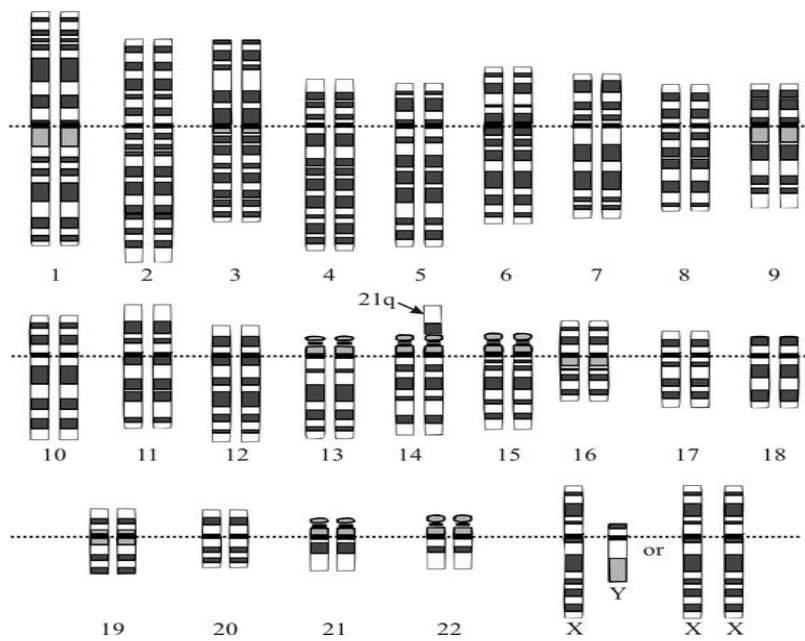
- Down Syndrome (trisomy 21)
 - Flat facies, epicanthal folds, simian crease
 - Risk of acute lymphoblastic leukemia, early Alzheimer's disease
 - $\uparrow\beta$ -HCG, $\uparrow$ inhibin, $\downarrow$ AFP, $\downarrow$ estriol
- Edwards syndrome (trisomy 18)
 - Rockerbottom feet, micrognathia, clenched hands
- Patau's syndrome (trisomy 13)
 - Cleft lip, holoprosencephaly, polydactyly



FA 2012: 93.1 • FA 2011: 88.2 • FA 2010: 88
ME 3e: 74

x1.5

BC05-17



t(21q:14q)
producing a third
“chunk” of Cr.
21, causing the
phenotype of
Down Syndrome

FA 2012: 93.2 • FA 2011: 89.1 • FA 2010: 89
ME 3e: 76

x1.5

BC05-18

- Cri-du-chat syndrome
 - Microdeletion of short arm of chromosome 5
 - Characterized by microcephaly, mental retardation, high-pitched crying (cri-du-chat, or cat-like cry), cardiac abnormalities
- Williams syndrome
 - Microdeletion of long arm of chromosome 7
 - Characterized by “elfin” facies, mental retardation, hypercalcemia, extreme friendliness with strangers, cardiovascular abnormalities

FA 2012: 94.1 • FA 2011: 89.2 • FA 2010: 89
ME 3e: 77

x1.5

BC05-19

- 22q11 deletion syndromes
 - Cleft palate, abnormal facies
 - Thymic aplasia – T- cell deficiency
 - Cardiac defects
 - Parathyroid aplasia - hypocalcemia
 - DiGeorge syndrome - thymic, parathyroid, and cardiac defects
 - Velocardiofacial syndrome - palate, facial, and cardiac defects

FA 2012: 94.3 • FA 2011: 89.4 • FA 2010: 89
ME 3e: 77

x1.5

BC05-20

- Question

- A 12-year-old boy presents to the emergency room after having a seizure at school. He is accompanied by a teacher who is unable to give any medical history, but can explain that she saw his left leg start to shake in his chair, then his left arm, then his whole body started to convulse and he fell to the floor, shaking. She says the episode lasted 8 minutes, during which time EMS was called and he was transported immediately. On exam, he appears confused and slow to respond but knows his name and where he is. Neurologic exam reveals a right gaze preference, but is otherwise normal. He is noted to have a patch of hypopigmented skin on his right lower extremity. Which is true of the patient's prognosis?
 - A. The patient likely has renal cysts.
 - B. This is a benign childhood epilepsy, he will outgrow it.
 - C. He should be started on broad-spectrum antibiotics for meningitis.
 - D. The patient is at risk for pheochromocytoma.

FA 2012: 94.3 • FA 2011: 89.4 • FA 2010: 89
ME 3e:

x1.5

BC05-21

- Answer:

- The presentation of a Jacksonian March (explain) and Todd's Paralysis (gaze preference) suggest a grand mal seizure originating in the right frontal lobe. The physical finding of a hypopigmented patch of skin (ash leaf spot) is suggestive of tuberous sclerosis, a disease of hamartomatous growths of the cortex and retina, seizures, MR/learning disability, renal cysts and angiomyolipomas, cardiac rhabdomyomas, and risk of astrocytomas.

FA 2012: 94.2 • FA 2011: 89.3 • FA 2010: 89
ME 3e:

x1.5

BC05-22



Vitamins and Nutrition

Jonathan Faiwischewski, M4, UMDNJ.

x1.5

BC06-1

- Fat-soluble vitamins
 - A, D, E, K
 - Excreted primarily by the liver
 - Can accumulate to toxic levels because it can be stored in fatty tissue
 - Absorption is dependent on the pancreas and terminal ileum
- Water-soluble vitamins
 - All others
 - Excreted primarily in the urine
 - Toxicity is very rare

x1.5

BC06-2

- Vitamin A (retinol)
 - Precursor for rhodopsin in the eye
 - Involved in epithelial differentiation and maintenance
 - Needed for WBC function
 - Supplement in measles infection
- Deficiency: night blindness, dry skin
- Toxicity: teratogenic, arthralgias, headaches (pseudotumor cerebri), hepatosplenomegaly

FA 2012: 95.1 • FA 2011: 90.4 • FA 2010: 90
ME 3e: 57

x1.5

BC06-3

- B vitamins mnemonic:
 - The River is North of the Pretty Pacific California (vitamins 1, 2, 3, 5, 6, 12)
- Vitamin B1
 - Precursor for the coenzyme thymine pyrophosphate
 - Important in glycolysis, TCA cycle, HMP shunt, and AA-metabolism
- Vitamin B1 deficiency
 - Wernicke-Korsakoff syndrome
 - Advanced dementia seen in chronic alcoholics
 - Involves infarcts of the mamillary bodies of the hypothalamus
 - Characterized by confabulation, making up answers (not lying)
 - Beriberi
 - Dry: neuropathy
 - Wet: high-output heart failure

FA 2012: 95.2 • FA 2011: 91.1 • FA 2010: 91
ME 3e: 56

x1.5

BC06-4

- Vitamin B2 (riboflavin)
 - FAD and FMN (cofactors in oxidation and reduction)
- Vitamin B2 deficiency
 - Magenta tongue
 - Cheilosis
 - Corneal neovascularization

FA 2012: 95.3 • FA 2011: 91.2 • FA 2010: 91
ME 3e: 56

x1.5

BC06-5

- Vitamin B3 (niacin)
 - Precursor for NAD and NADP
 - Derived from tryptophan
 - Lack of tryptophan may cause deficiency, such as that seen in Hartnup disease, corn diet
 - Used to lower LDL and raise HDL levels
- Vitamin B3 deficiency
 - Pellagra: triad of diarrhea, dermatitis, dementia, and death (in order of increasing severity)
 - Causes of pellagra: Hartnup disease, corn diet, carcinoid syndrome, prolonged isoniazid use
- Vitamin B3 excess
 - May cause dyspepsia and facial flushing due to prostaglandin-mediated histamine synthesis
 - Aspirin can help alleviate this

FA 2012: 96.1 • FA 2011: 91.3 • FA 2010: 91
ME 3e: 56

x1.5

BC06-6

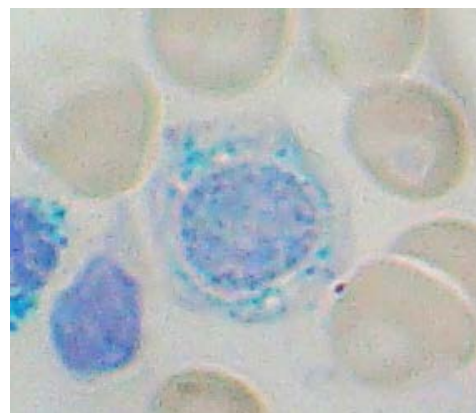
- Vitamin B5 (pantothenic acid)
 - Part of CoA
 - Used in fatty acid metabolism, glycolosis
- Vitamin B5 deficiency
 - Dermatitis
 - Enteritis
 - Adrenal insufficiency

FA 2012: 96.2 • FA 2011: 91.4 • FA 2010: 91
ME 3e: 56

x1.5

BC06-7

- Vitamin B6 (pyridoxine)
 - Involved in transamination and decarboxylation of amino acids, gluconeogenesis, conversion of tryptophan to niacin, spingolipid synthesis, neurotransmitter synthesis, immune function, and steroid hormone modulation
- Vitamin B6 deficiency
 - Sideroblastic anemia, peripheral neuropathy, seizures



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FA 2012: 96.3 • FA 2011: 91.5 • FA 2010: 91
ME 3e: 56

x1.5

BC06-8

- Vitamin B12 (cobalamin)

- Needed for the following:

B12

- Homocystiene + met-THF → Methionine + THF

B6

B12

- Prioponyl CoA → Methylmalonyl CoA → Succinyl CoA

- Vitamin B12 deficiency

- Seen in patients with: alcoholism, pernicious anemia, gastric bypass, diseases of terminal ileum, celiac disease

FA 2012: 97.1 • FA 2011: 92.1 • FA 2010: 92
ME 3e: 56

x1.5

BC06-9

- Vitamin B12 deficiency, cont'd

- Characterized by

- Macrocytic anemia (MCV > 105)
 - Polysegmented PMN (6 or greater segments)
 - Subacute combined degeneration: dysfunction of the lateral and dorsal spinal tracts (fine touch, conscious proprioception, and motor)

- Diagnosis: Schilling test is used to detect the etiology of the deficiency

FA 2012: 97.1 • FA 2011: 92.1 • FA 2010: 92
ME 3e: 56

x1.5

BC06-10

- Folate
 - Needed for nucleic acid synthesis
- Folate deficiency
 - Can be caused by: drugs (sulfonamides, MTX), alcoholism, pregnancy
 - Deficiency in early pregnancy causes neural tube defects in fetus
 - Deficiency looks like B12 deficiency, with key differences
 - Macrocytic anemia (MCV > 100)
 - Polysegmented PMN (5 lobes or more)
 - NO NEUROLOGIC INVOLVEMENT

FA 2012: 97.2 • FA 2011: 92.2 • FA 2010: 92
ME 3e: 56

x1.5

BC06-11

- Biotin
 - Cofactor for carboxylation enzymes:
 - Pyruvate carboxylase – gluconeogenesis
 - Acetyl-CoA carboxylase – fatty acid synthesis
 - Propionyl-CoA carboxylase – odd-carbon fatty acids
 - Methylcrotonyl-CoA carboxylase
- Biotin deficiency
 - Caused by excessive consumption of raw eggs
 - Characterized by: alopecia, bowel inflammation, muscle pain

FA 2012: 98.2 • FA 2011: 93.1 • FA 2010: 93
ME 3e: 56

x1.5

BC06-12

- Vitamin C (ascorbate)
 - Function:
 - Keeps iron in the reduced state
 - Iron absorption in GI tract
 - Collagen synthesis
 - Catecholamine synthesis
- Vitamin C deficiency
 - Scurvy:
 - Pirates get it (favorite letter of the alphabet?)
 - *Swollen, bleeding gums*, bruising, anemia, slow wound healing, perifollicular hemorrhage, corkscrew hairs

FA 2012: 98.3 • FA 2011: 93.2 • FA 2010: 93
ME 3e: 56

x1.5

BC06-13

- Vitamin D
 - Important for calcium homeostasis
 - Not found in breast milk! Supplement for nursing babies
 - Precursor converted in skin by UV light
 - Hydroxylation
 - 25-hydroxylation occurs in the liver
 - Kidney hydroxylate at 1- or 24- position (1,25- form is active, 24,25- form is inactive)
- Vitamin D deficiency
 - Rickets in children (bent bones)
 - Osteomalacia (brittle bones) in adults
 - Hypocalcemia (Chvostek's sign – spasm of facial nerve when tapped – and Trousseau's sign – spasm of the hand and forearm upon application of a BP cuff and compression of the brachial artery)
- Vitamin D excess
 - Seen in sarcoid
 - Causes hypercalcemia, with confusion, polyuria, polydipsia, anorexia, vomiting, and muscle weakness

FA 2012: 99.1 • FA 2011: 93.3 • FA 2010: 93
ME 3e: 57

x1.5

BC06-14

- Vitamin E
 - Important for erythrocytes
 - Antioxidant properties
- Vitamin E deficiency
 - Deficiency causes:
 - Hemolytic anemia following oxidative stress (like G-6PD deficiency)
 - Muscle weakness/neurodysfunction (looks like Friedrich's Ataxia)
 - Accelerated atherosclerosis

FA 2012: 99.2 • FA 2011: 93.4 • FA 2010: 93
ME 3e: 57

x1.5

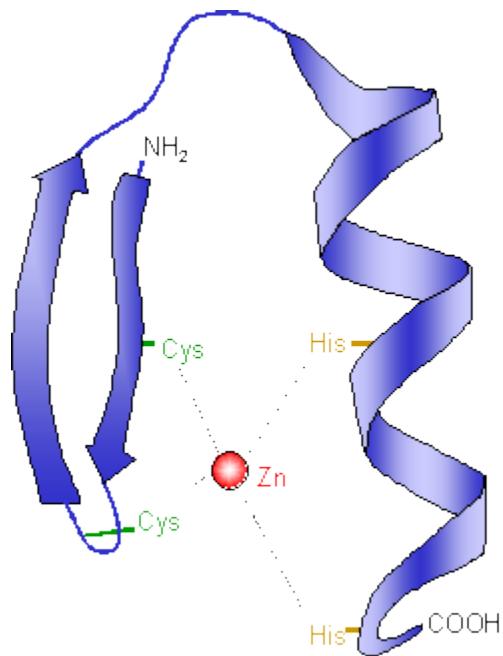
BC06-15

- K is for Koagulation
 - Causes Kamma Karboxylation of Klutamic acid
 - Comes from Kritters in our Kolon
 - Kids are Klean – Kive them some!
 - Can Cause Crazy PT/PTT if its deficient (bleeding problems)

FA 2012: 99.3 • FA 2011: 94.1 • FA 2010: 94
ME 3e: 57

x1.5

BC06-16



Zinc Deficiency

- Delayed wound healing
- Hypogonadism
- ↓ adult hair
- Anosmia

Author: Mgnus Manske,
Common.wikimedia used with permission

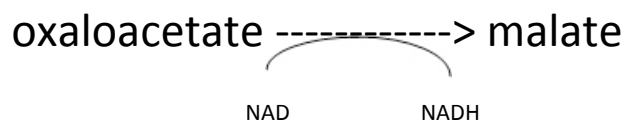
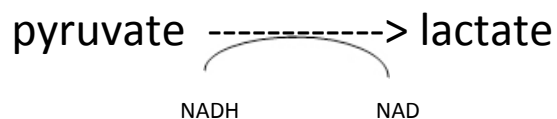
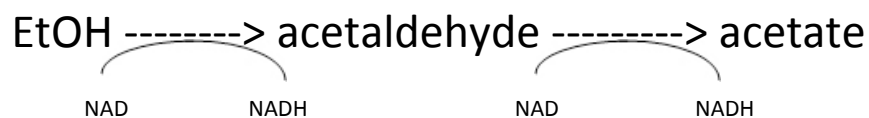
FA 2012: 99.4 • FA 2011: 94.2 • FA 2010: 94
ME 3e: 57

x1.5

BC06-17

alcohol dehydrogenase (fomepizole -)

aldehyde dehydrogenase (disulfiram)



FA 2012: 100.1 • FA 2011: 94.3 • FA 2010: 94
ME 3e: 57

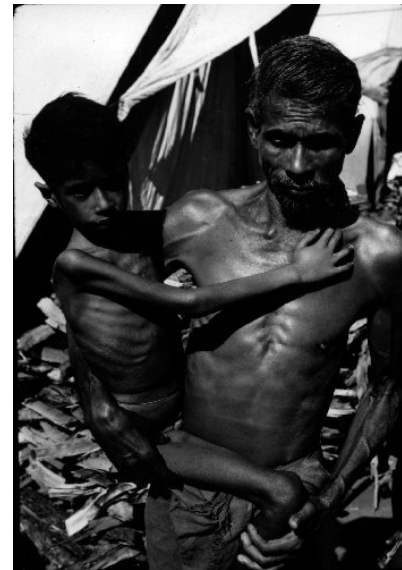
x1.5

BC06-18



Kwashiorkor

- Protein deficiency
- Edema, anemia, fatty liver



Marasmus

- Calorie deficiency
- Tissue and muscle wasting

Commons.wikimedia.org

FA 2012: 100.2 • FA 2011: 94.4 • FA 2010: 94
ME 3e: 57

x1.5

BC06-19

• Question 1

- A 38-year-old homeless man is brought to the emergency department after he is found unresponsive. Laboratory studies show a serum glucose of 42 mg/dL. He is given a bolus of 50% dextrose and seems to improve and is admitted for observation. The next day, he is interviewed by a medical student who asks him if he knows where he is, to which he responds “I am in Disney world, and it’s a beautiful day outside.” What is the most likely diagnosis?

• Answer:

- Korsakoff’s syndrome

FA 2012: 100.3 • FA 2011: 94.5 • FA 2010: 94
ME 3e:

x1.5

BC06-20

- Question 2

- A 42-year-old woman comes to the physician 6 months after undergoing a gastric bypass procedure for severe obesity. Before the procedure, her BMI was 55, and today it is 34. She has vague symptoms such as fatigue, poor exercise tolerance, and paresthesias in her feet. She has a history of type 2 diabetes, and last hemoglobin A1c was 5.8%. What findings are most likely on peripheral blood smear?

- Answer:

- Megaloblastic anemia and polysegmented PMNs



Metabolism: Aerobic Respiration

Jonathan Faiwischewski, M4, UMDNJ.

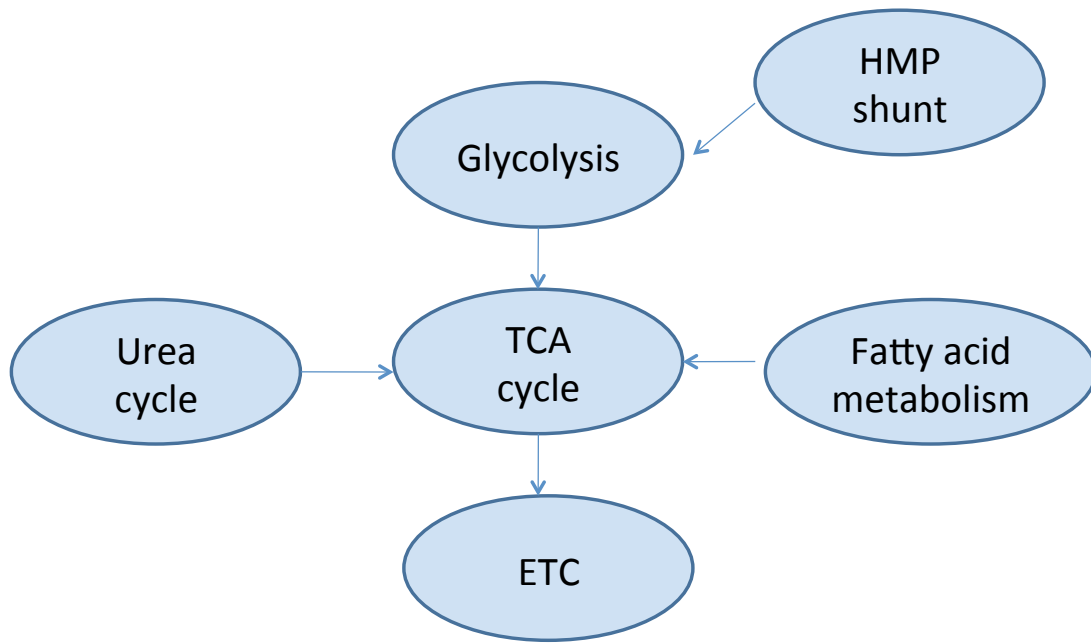
x1.5

BC07-1

- Sites of metabolism
 - Specific types of cells
 - Some metabolic processes take place in all cells (e.g. glycolysis)
 - Others occur in particular cells (e.g. the urea cycle, which takes place primarily in the liver)
 - Cellular locations
 - Mitochondria – electron transport chain
 - Cytoplasm – glycolysis
 - Mitochondria and cytoplasm - gluconeogenesis

x1.5

BC07-2



FA 2012: 102.1 • FA 2011: 96.1 • FA 2010: 96
ME 3e: 38

x1.5 BC07-3

- Glycolysis
 - Generates ATP through the oxidation (burning) of sugar.
- ATP
 - A highly energetic molecule
 - Highly unstable → used up almost immediately
- Glycolysis
 - Takes place in the cytoplasm
 - Electron carriers that it generates there need to be transported to the mitochondria so they can be used for the ETC.

FA 2012: 103.1 • FA 2011: 97.1 • FA 2010: 97
ME 3e: 38

x1.5 BC07-4

- The main electron carriers are NADH, NADPH and FADH.
 - NADH and FADH are used in the catabolic pathways
 - NADPH is used in anabolic pathways
- NADH and FADH are used in several pathways, including glycolysis and the citric acid cycle
- NADPH is produced in the HMP shunt
 - Used in respiratory burst and by glutathione reductase

FA 2012: 103.3 • FA 2011: 97.3 • FA 2010: 97
ME 3e: 38

x1.5

BC07-5

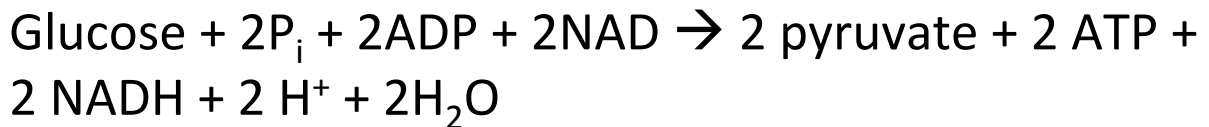
- Hexokinase and glucokinase phosphorylate glucose to trap it in the cell.

Hexokinase	Glucokinase
Most tissues	Hepatocytes and pancreatic b-islet cells (along with GLUT-2, acts as the glucose sensor)
Low K_m (0.05 mM in erythrocytes)	High K_m (10 mM)
Low V_{max}	High V_{max}
Inhibited by glucose-6-phosphate	Induced by insulin in hepatocytes

FA 2012: 103.4 • FA 2011: 97.4 • FA 2010: 97
ME 3e: 38

x1.5

BC07-6

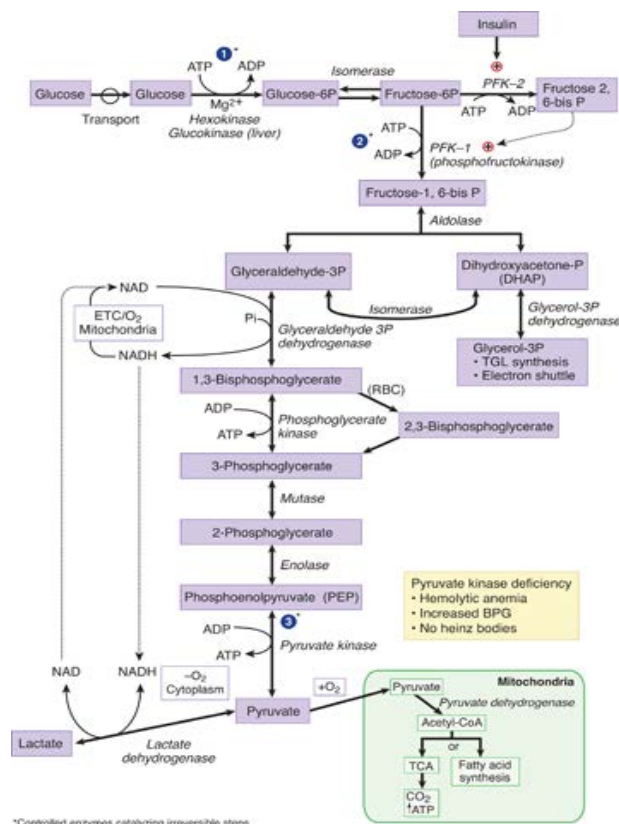


- One glucose molecule is converted into two pyruvate molecules
 - Pyruvate is used in the TCA cycle
- Generates two ATP molecules
- Generates two NADH molecules
 - NADH is used in the electron transport chain

FA 2012: 104.1 • FA 2011: 98.1 • FA 2010: 98
ME 3e: 38

x1.5

BC07-7



*Controlled enzymes catalyzing irreversible steps

PFK-1	PFK-2
→ F-1,6-BP	→ F-2,6-BP
Rate-limiting step of glycolysis	Glycolysis regulator: ↑ glycolysis ↓ gluconeogenesis
⊕ AMP ⊕ F-2,6-BP [†] ⊖ ATP ⊖ Citrate	⊕ Insulin ⊖ Glucagon

Pyruvate kinase	
⊕ F-1,6-BP ⊕ Insulin [†]	⊖ ATP ⊖ Acetyl-CoA ⊖ Alanine [†] ⊖ Glucagon [†]

FA 2012: 104.1 • FA 2011: 98.1 • FA 2010: 98
ME 3e: 38

x1.5

BC07-8

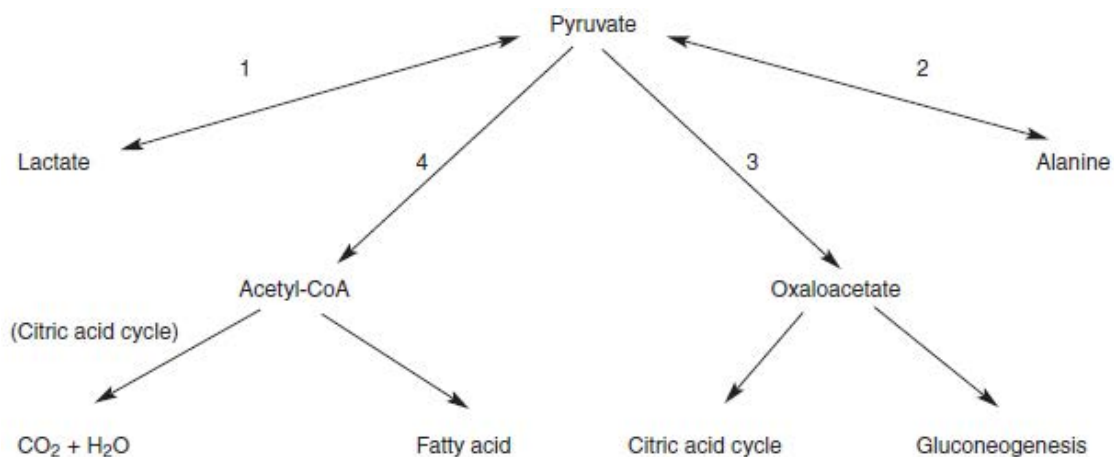
- Overall reaction of PDH:
 - Pyruvate + NAD + CoA $\rightarrow$ Acetyl-CoA + CO₂ + NADH
- Needs several cofactors:
 - Thiamin pyrophosphate
 - Needs vitamin B1 and phosphate groups
 - FAD (B2), NAD (B3), CoA (B5)
 - Lipoic acid
 - Arsenic inhibits lipoic acid, blocking respiration and causing vomiting, diffuse watery diarrhea (rice-water stool), and *garlic breath*. The treatment is **dimercaprol**.
- Inhibition of PDH: things that increase the ratios of ATP/ADP, NADH/NAD⁺, and acetyl-CoA/CoA

FA 2012: 104.3 • FA 2011: 99.1 • FA 2010: 99
ME 3e: 41

x1.5

BC07-9

Pyruvate Metabolism



FA 2012: 105.2 • FA 2011: 99.3 • FA 2010: 99
ME 3e: 41

x1.5

BC07-10

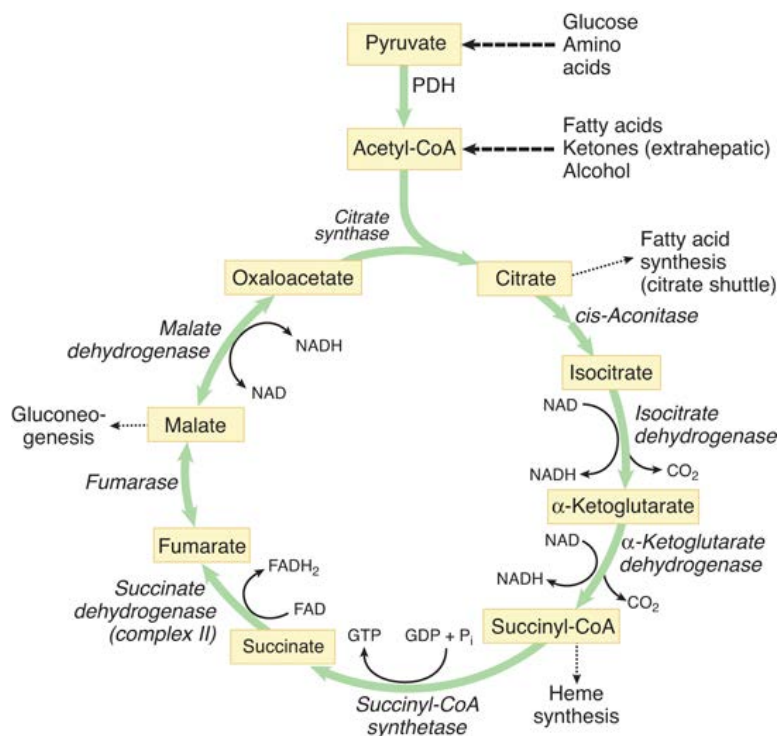
- PDH deficiency:

- Deficiency of PDH causes a backup of pyruvate, which will not be able to proceed into TCA
 - Pyruvate will therefore be converted via other pathways to lactate, alanine, and oxaloacetate
- May be congenital (enzyme deficiency) or acquired (vitamin B1 deficiency in alcoholics)
- Findings include lactic acidosis and neurologic defects
- Treatment
 - If acquired, give vitamin B1 (cofactor for pyruvate dehydrogenase)
 - If congenital, give food that bypasses glycolytic pathways (high fat diet, ketogenic AAs – lysine and leucine)

FA 2012: 105.1 • FA 2011: 99.2 • FA 2010: 99
ME 3e: 41

x1.5

BC07-11



TCA cycle

- Generates 3 NADH, 1 FADH₂, 1 GTP, and 2 CO₂
- Needs B1, B2, B3, B5, and lipoic acid

FA 2012: 105.3 • FA 2011: 100.1 • FA 2010: 100
ME 3e: 39

x1.5

BC07-12

- 1 NADH → generates 3 ATP
- 1 FADH₂ → 2 ATP
 - NADH is brought to mitochondria by the malate-aspartate or the glycerol-3-phosphate shuttle to enter ETC at Complex 1.
 - FADH₂ enters at Complex 2, at lower energy, so it generates less ATP
- ETC inhibitors: Rotenone, cyanide, antimycin A, carbon monoxide
- ATP synthase inhibitors: Oligomycin
- Uncouplers: 2,3-dinitrophenol, brown fat, aspirin

FA 2012: 106.1 • FA 2011: 100.2 • FA 2010: 100
ME 3e: 40

x1.5

BC07-13

- Question:
 - A 4-day-old boy is brought to the physician because of lethargy and weak crying. Laboratory studies show an inborn error in metabolism resulting in hemolytic anemia and ketosis. What does the O₂-dissociation curve look like for this infant?
- Answer:
 - This patient most likely can't make 1,3-BPG from glycolysis and therefore can't make 2,3-BPG, which would result in a rightward shift of the O₂-dissociation curve

FA 2012: 106.1 • FA 2011: 100.2 • FA 2010: 100
ME 3e:

x1.5

BC07-14

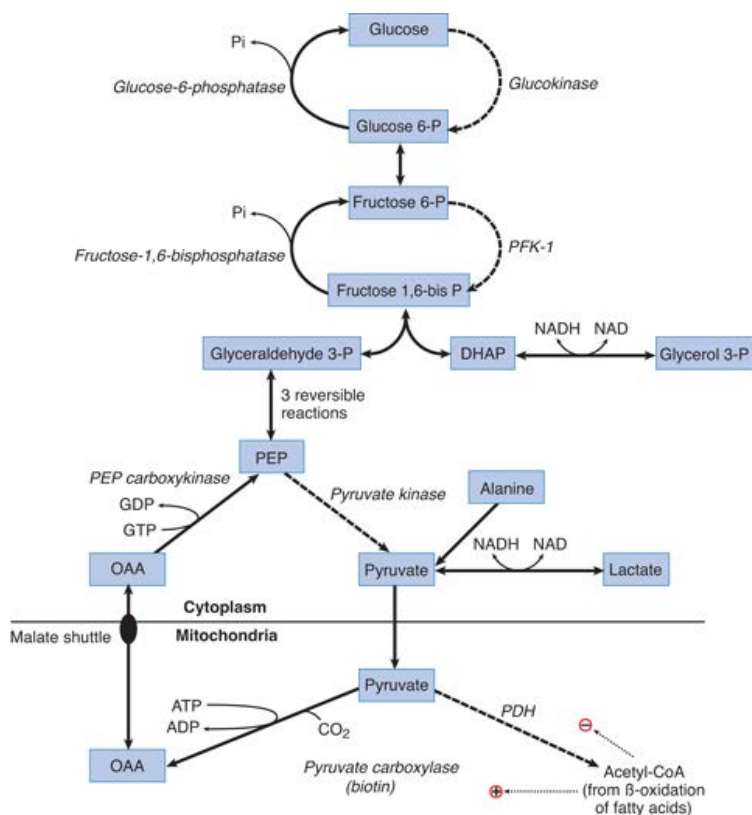


Metabolism: Gluconeogenesis, Other Sugars, and Amino Acids

Jonathan Faiwischewski, M4, UMDNJ.

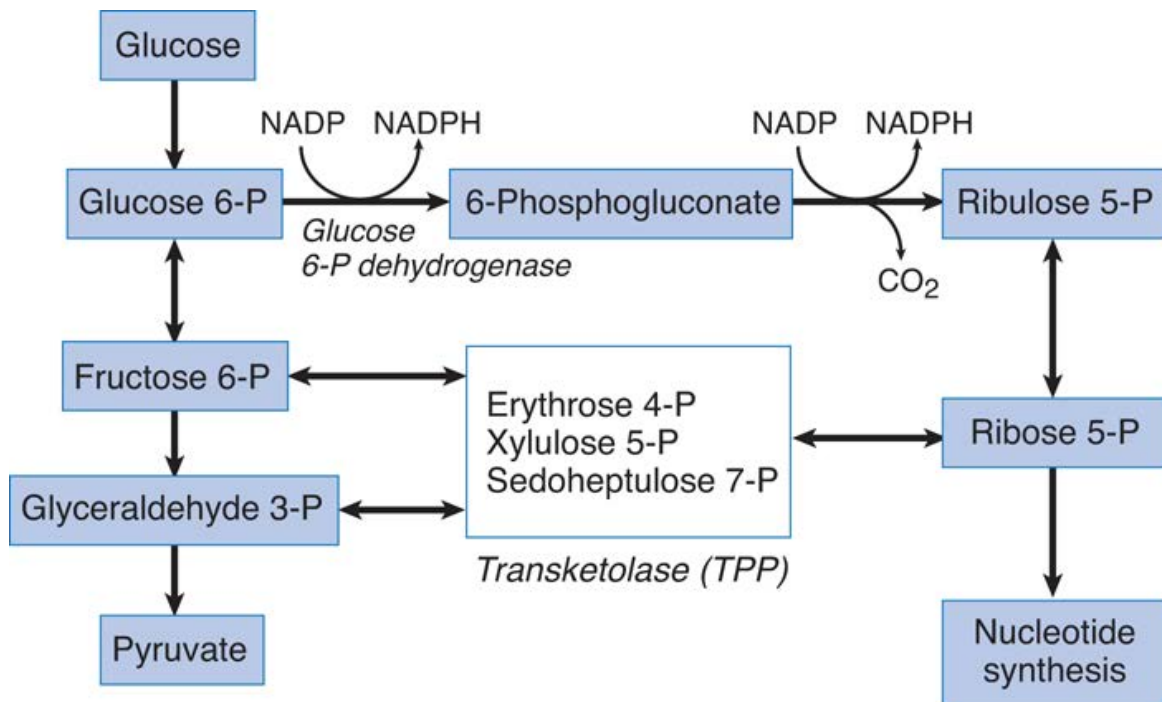
x1.5

BC08-1



x1.5

BC08-2

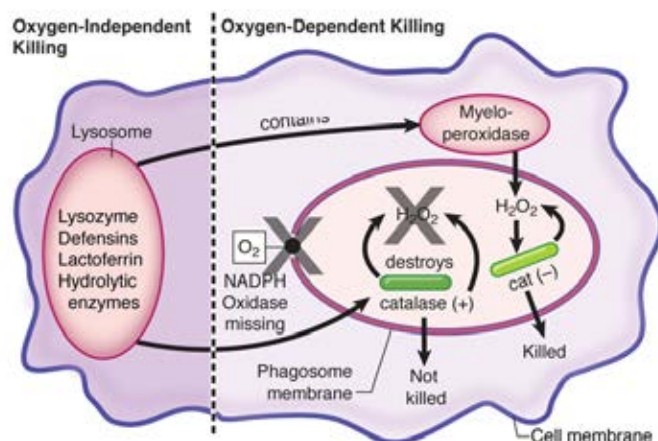


FA 2012: 106.1 • FA 2011: 101.2 • FA 2010: 101
ME 3e: 42

x1.5

BC08-3

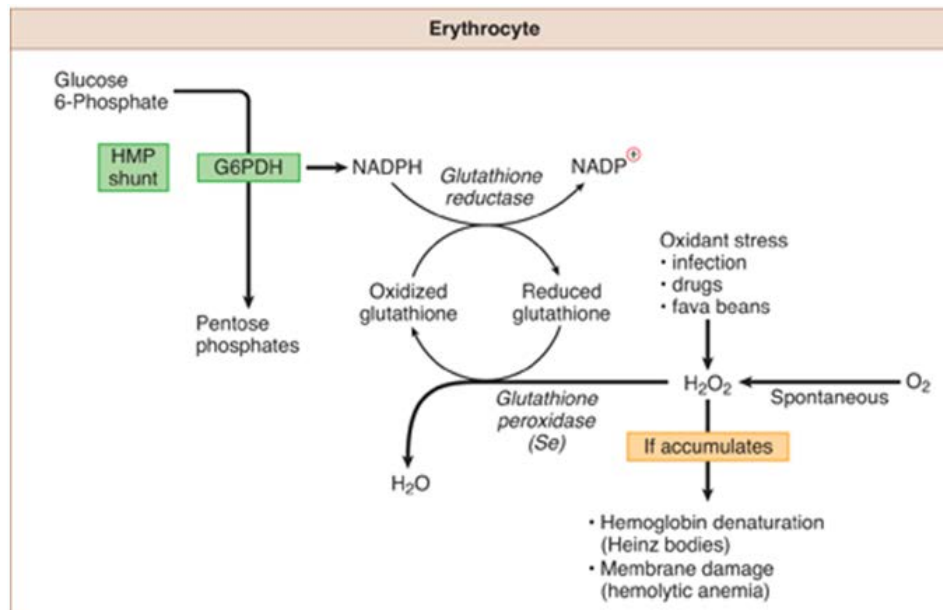
- Chronic Granulomatous Disease
 - Deficiency of NADPH oxidase
 - Chronic infections with catalase-positive bugs:
 - Pseudomonas*
 - Staphylococcus aureus*
 - Aspergillus*
 - Candida*
 - Enterobacteriaceae*



FA 2012: 107.2 • FA 2011: 102.1 • FA 2010: 102
ME 3e: 98

x1.5

BC08-4



FA 2012: 108.1 • FA 2011: 102.2 • FA 2010: 102
ME 3e: 42

x1.5

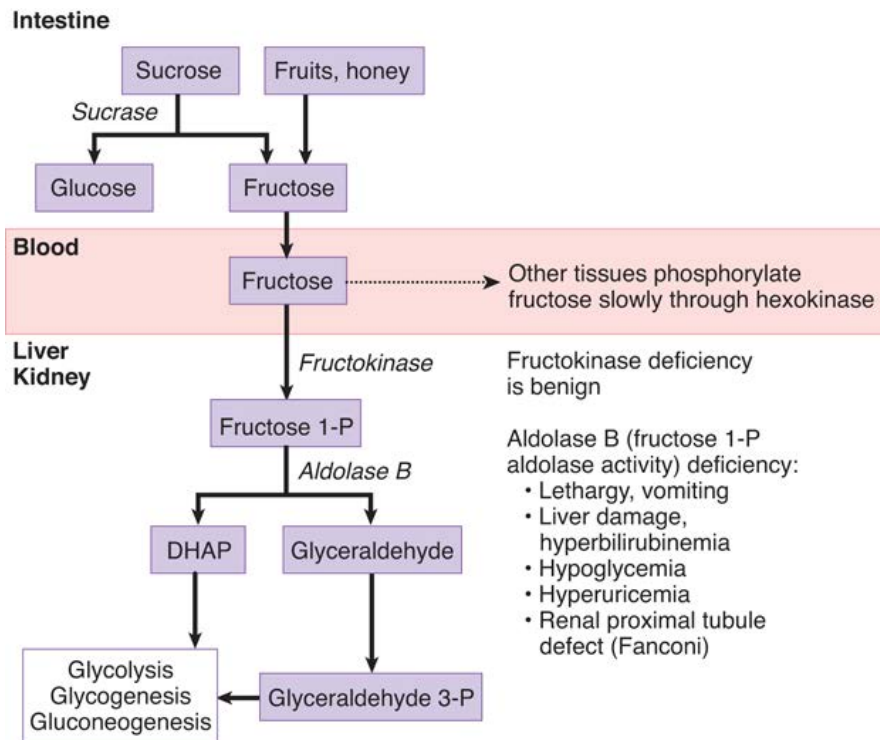
BC08-5

- G-6-PDH deficiency:
 - Can't reduce glutathione, which is an important antioxidant
 - Causes hemolysis during oxidative stress
 - Low hemoglobin/hematocrit
 - Heinz Bodies and Bite Cells on peripheral smear
 - Oxidative stress: fava beans, sulfonamides, quinolones, anti-TB drugs, infection.

FA 2012: 108.1 • FA 2011: 102.2 • FA 2010: 102
ME 3e: 42

x1.5

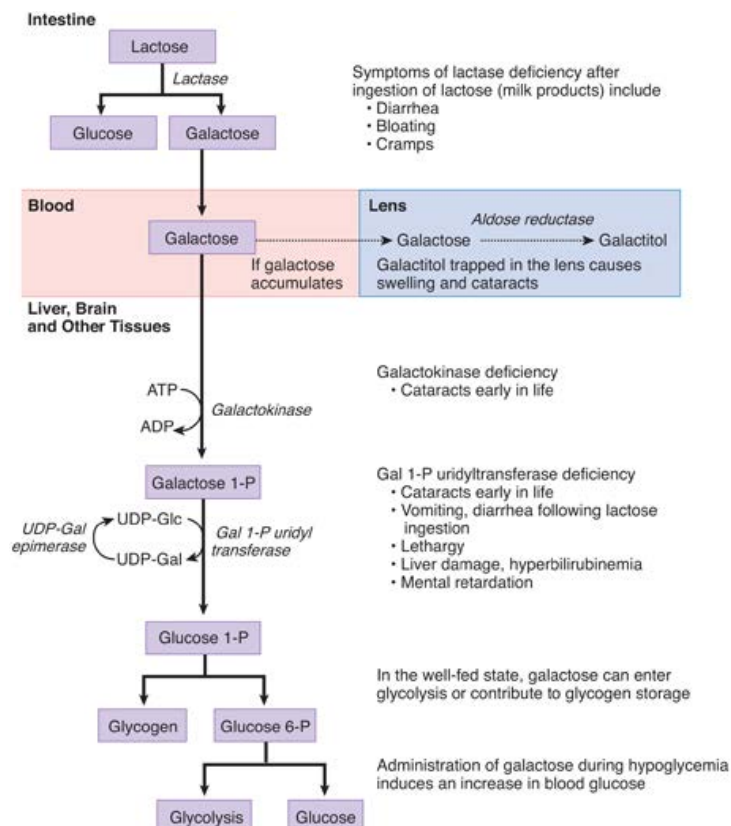
BC08-6



FA 2012: 108.2 • FA 2011: 103.1 • FA 2010: 103
ME 3e: 38

x1.5

BC08-7



FA 2012: 109.1 • FA 2011: 103.2 • FA 2010: 103
ME 3e: 38

x1.5

BC08-8

- Sorbitol
 - Phosphate groups are used to trap sugar in cells
 - Sugar groups can also be turned into sorbitol to trap them in cells
 - This is performed by **aldose reductase**
 - Sorbitol can be converted to fructose
 - Catalyzed by **sorbitol dehydrogenase**
 - Deficiency of this enzyme causes sorbitol buildup, increased osmotic pressure, and subsequent cataracts, retinopathy, and peripheral neuropathy
 - These effects are also seen in chronic hyperglycemia

FA 2012: 109.2 • FA 2011: 104.1 • FA 2010: 104
ME 3e: 38

x1.5

BC08-9

- Lactase deficiency
 - Lactase: breaks lactose down into galactose and glucose
 - Lactase deficiency
 - Age-related
 - Gastroenteritis causes sloughing of the mucosa and so lactase is lost
 - Symptoms: bloating, diarrhea (osmotic)

FA 2012: 109.3 • FA 2011: 104.2 • FA 2010: 104
ME 3e: 38

x1.5

BC08-10

- Amino Acids

- Nine essential amino acids

- May be glucogenic, ketogenic, or both

- Glucogenic: methionine, valine, arginine (essential in some cases), histidine
- Ketogenic: lysine, leucine
- Both: I Pee 3 Times (IPT³)
 - » Isoleucine, phenylalanine, threonine, tryptophan, tyrosine (essential in some cases)

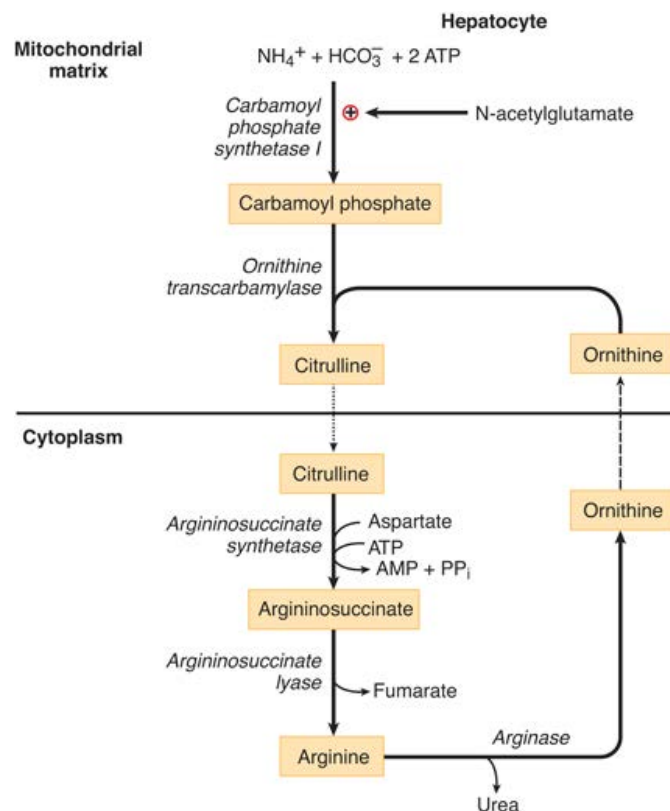
- Acidic amino acids: aspartate, glutamate

- Basic amino acids: arginine, lysine, histidine

FA 2012: 110.1 • FA 2011: 104.3 • FA 2010: 104
ME 3e: 45

x1.5

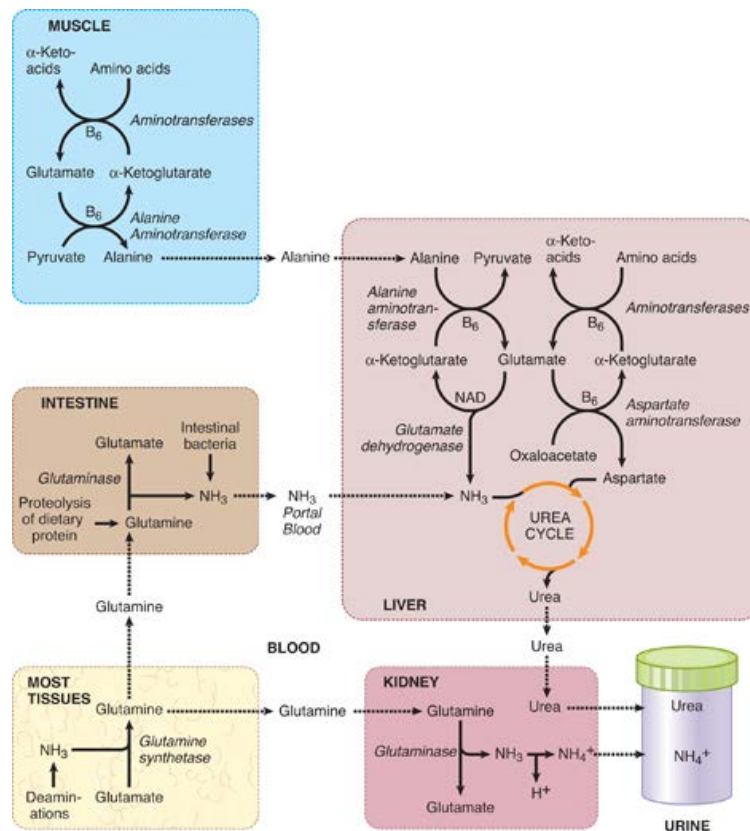
BC08-11



FA 2012: 110.2 • FA 2011: 105.1 • FA 2010: 105
ME 3e: 49

x1.5

BC08-12



FA 2012: 110.3 • FA 2011: 105.2 • FA 2010: 105
ME 3e: 48

x1.5

BC08-13

• Hyperammonemia

- May be hereditary or acquired
- Ammonia buildup causes depletion of α-ketoglutarate, which leads to inhibition of the TCA cycle
- Symptoms: neurologic findings, including blurred vision, slurred speech, lethargy, vomiting
- Treatment: limit protein intake to limit ammonia production
 - **Benzoate** and **phenylbutyrate** bind amino acids and help lower ammonia levels.
 - **Lactulose** binds ammonia in the gut and causes it to be excreted in the stool.

FA 2012: 111.1 • FA 2011: 105.3 • FA 2010: 105
ME 3e: 49

x1.5

BC08-14

- Ornithine transcarbamoylase deficiency
 - X-linked recessive condition
 - Most common urea cycle defect
 - Causes buildup of carbamyl phosphate, which leads to excess levels of orotic acid
 - Symptoms:
 - Orotic aciduria (crystals in diaper)
 - Low BUN (no urea)
 - Hyperammonemia

FA 2012: 111.2 • FA 2011: 105.4 • FA 2010: 105
ME 3e: 49

x1.5

BC08-15

- Some important amino acid metabolic products:
 - Phenylalanine → tyrosine, dopa, dopamine, and the catecholamines
 - Tryptophan → niacin and serotonin, which is converted to melanin
 - Histidine → histamine
 - Glycine → important for synthesis of heme
 - Arginine → creatine, urea, and nitric oxide
 - Glutamate → GABA and glutathione

FA 2012: 111.3 • FA 2011: 106.1 • FA 2010: 106
ME 3e: 48

x1.5

BC08-16

- **Question:**

A 16-year-old African-American girl is brought to the physician because of dysuria. The physician sends her home on a 3-day regimen of sulfamethoxazole-trimethoprim for the presumed diagnosis of simple cystitis. Two days later, the patient returns with vague complaints such as fatigue and weakness. On exam she is found to have a temperature of 36.9°C (98.4°F), pulse of 124/min, blood pressure of 108/74 mm Hg, respirations of 24/min. Which of the following is true?

- A. This is a rare allergic reaction to the medication
- B. This is an early presentation of septic shock
- C. This is a rare presentation of an X-linked recessive disease
- D. The initial diagnosis of simple cystitis was incorrect, begin treatment for pneumonia.

FA 2012: 111.3 • FA 2011: 106.1 • FA 2010: 106

x1.5

BC08-17

- **Answer:**

- This case outlines the key features of G-6-pyruvate dehydrogenase (G6PD) deficiency. This condition is most commonly found in boys, which makes this a very rare presentation. Note the presentation of fatigue in the setting of tachycardia and tachypnea.

FA 2012: 111.3 • FA 2011: 106.1 • FA 2010: 106

x1.5

BC08-18

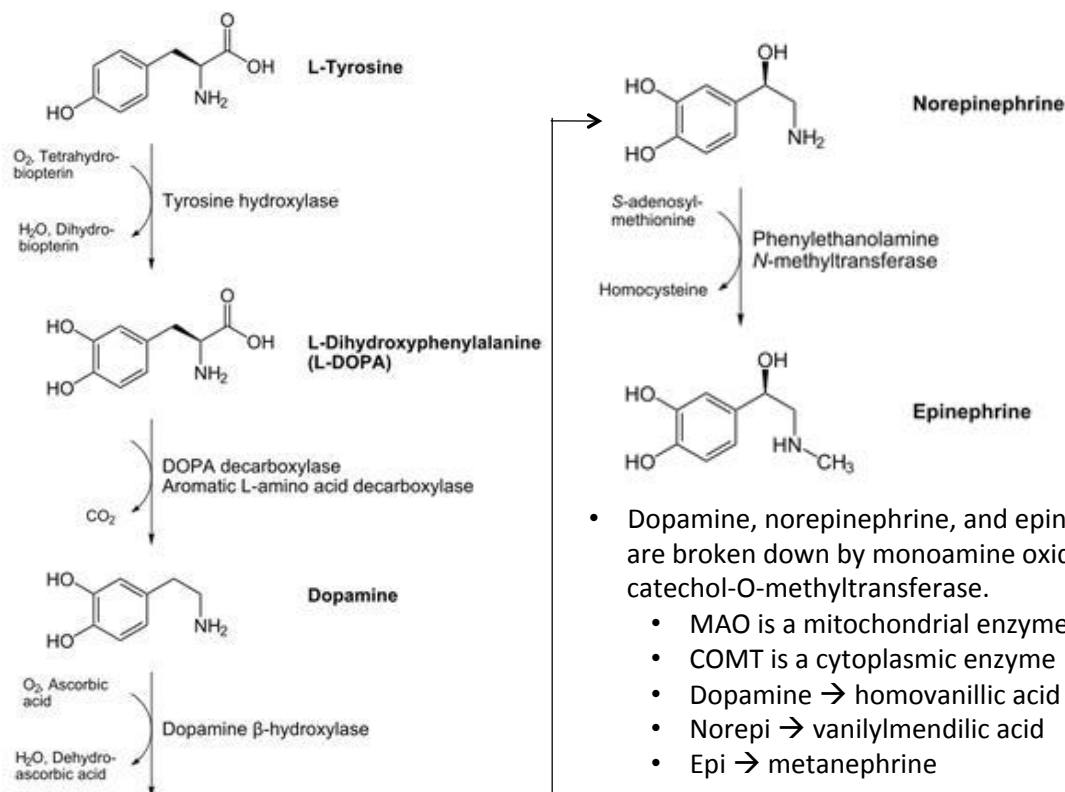


Metabolism: Amino Acid-related diseases & Glycogen metabolism

Jonathan Faiwyszewski, M4, UMDNJ.

x1.5

BC09-1



x1.5

BC09-2

- Phenylketonuria
 - Autosomal recessive condition
 - Caused by deficiency of phenylalanine hydroxylase
 - Phenylalanine can't be converted to tyrosine
 - Can also be caused by deficiency of tetrahydrobiopterin (BH₄), a cofactor for phenylalanine hydroxylase
 - Characterized by mental retardation, small stature, seizures, fair skin, eczema, musty “mousy” body odor
 - Treatment: decreased dietary phenylalanine, supplemental tyrosine
- Uncontrolled maternal PKU during pregnancy
 - Baby with microcephaly, mental retardation, congenital heart defects

FA 2012: 112.2 • FA 2011: 107.2 • FA 2010: 107
ME 3e: 48

x1.5

BC09-3

- Alkaptonuria (ochronosis)
 - Caused by deficiency of homogentisate oxidase
 - Homogentisic acid (alkapton) builds up, causing dark staining of connective tissue
 - Characteristics: stained tendons, dark sclera, and urine turns black after standing
 - May cause a debilitating arthritis

Phenylalanine → Tyrosine → → Homogentisic acid ~~→~~ Maleylacetoacetate

↑
Phenylalanine
hydroxylase

↑
Homogentisate
oxidase

FA 2012: 112.3 • FA 2011: 108.1 • FA 2010: 108
ME 3e: 48

x1.5

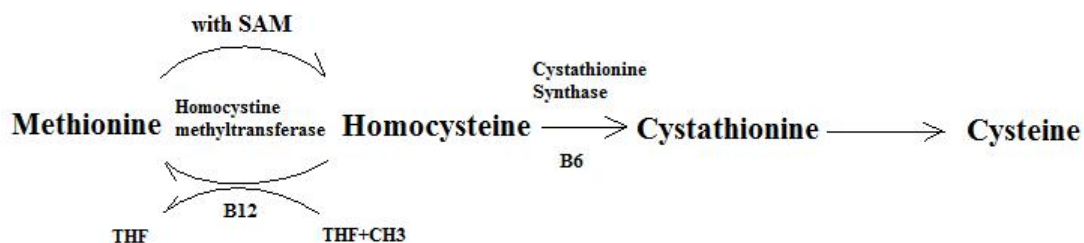
BC09-4

- Melanin production requires 2 things:
 1. Transport of tyrosine to the sites of melanin synthesis
 2. Machinery of melanin synthesis
- Albinism
 - A deficiency in either of the above will cause albinism due to lack of melanin production
 - Characterized by fair skin and increased risk for skin cancer

FA 2012: 112.4 • FA 2011: 108.2 • FA 2010: 108
ME 3e: 48

x1.5

BC09-5



- Homocystinuria
 - Caused by deficiency of cystathionine synthase
 - Cystathionine synthase has low affinity for B6
 - Deficiency of homocysteine methyltransferase
 - Findings:
 - Homocysteine in the urine
 - Mental retardation, osteoporosis, marfanoid appearance
 - Atherosclerotic disease (risk of CVA and MI)

FA 2012: 113.1 • FA 2011: 108.3 • FA 2010: 108
ME 3e: 48

x1.5

BC09-6

- Cystinuria
 - Autosomal recessive condition
 - Caused by hereditary defect of the renal tubular transporter
 - Transporter plays a role in reabsorption of cysteine, ornithine, lysine, and arginine in the PCT
 - Characterized by cystine kidney stones
 - Treatment: acetazolamide (carbonic anhydrase inhibitor) to alkalinize the urine, decrease the amount of precipitation

FA 2012: 113.2 • FA 2011: 108.4 • FA 2010: 108
ME 3e: 48

x1.5

BC09-7

- Maple syrup urine disease
 - Caused by deficiency of alpha-ketoacid dehydrogenase
 - Leads to inability to break down branched-chain amino acids (isoleucine, leucine, and valine)
 - Causes increased alpha-ketoacids in the blood, especially leucine
 - Findings:
 - Urine smells like maple syrup
 - Severe CNS defects
 - Mental retardation
 - Death

FA 2012: 113.3 • FA 2011: 108.5 • FA 2010: 108
ME 3e: 48

x1.5

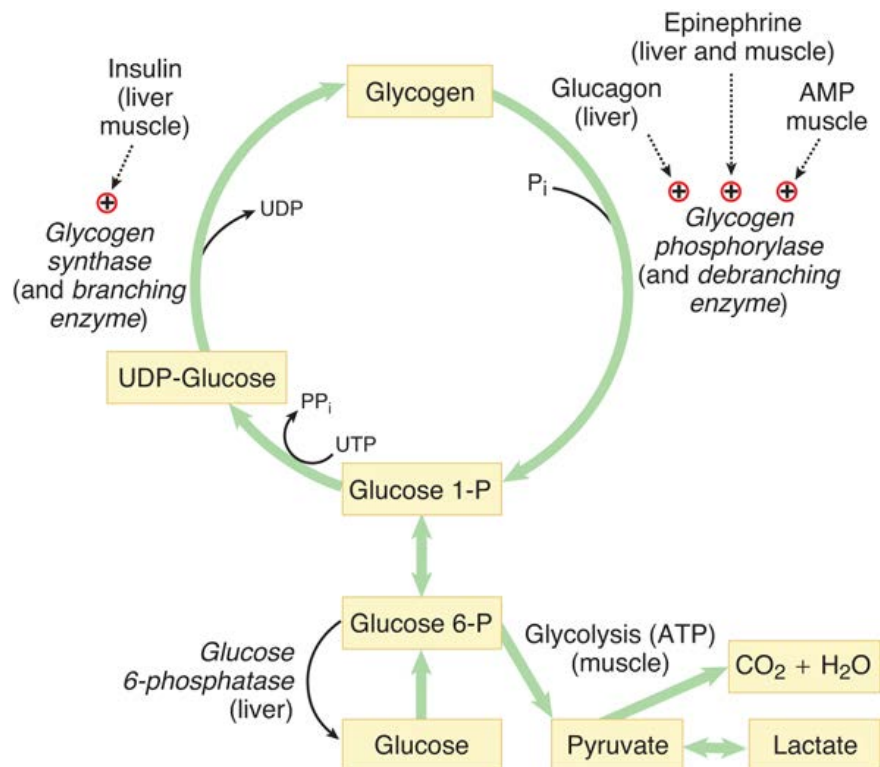
BC09-8

- Hartnup disease
 - Caused by deficiency of the transporter for tryptophan
 - Causes loss of tryptophan in the urine
 - Leads to vitamin B3 deficiency
 - Findings:
 - Tryptophan in urine
 - Pellagra (diarrhea, dementia, dermatitis, death)

FA 2012: 113.4 • FA 2011: 108.6 • FA 2010: 108
ME 3e: 48

x1.5

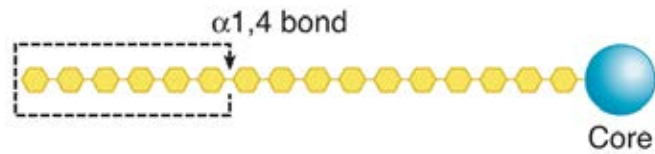
BC09-9



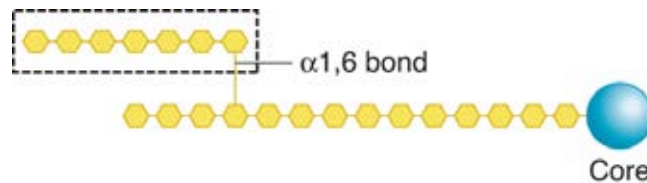
FA 2012: 115.1 • FA 2011: 110.1 • FA 2010: 110
ME 3e: 43

x1.5

BC09-10



1. Glycogen synthase makes a linear α 1,4-linked polyglucose chain (●●●●●●).
2. Branching enzyme hydrolyzes an α 1,4 bond.

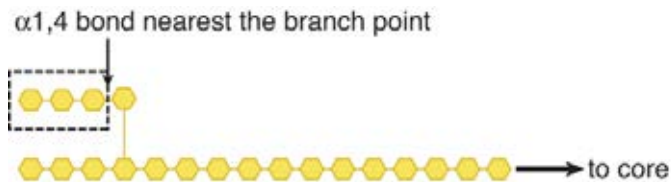


3. Transfers the oligoglucose unit and attaches it with an α 1,6 bond to create a branch.
4. Glycogen synthase extends both branches.

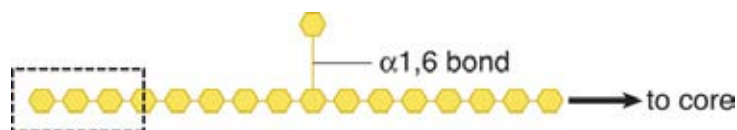
FA 2012: 114.2 • FA 2011: 109.2 • FA 2010: 109
ME 3e: 43

x1.5

BC09-11



1. Glycogen phosphorylase releases glucose 1-P from the periphery of the granule until it encounters the first branch points.
2. Debranching enzyme hydrolyzes the α 1,4 bond nearest the branch point, as shown.



3. Transfers the oligoglucose unit to the end of another chain, then
4. Hydrolyzes the α 1,6 bond releasing the single glucose from the former branch.

FA 2012: 114.2 • FA 2011: 109.2 • FA 2010: 109
ME 3e: 43

x1.5

BC09-12

Type	Deficient Enzyme	Cardinal Clinical Features	Glycogen Structure
I: von Gierke	Glucose-6-phosphatase	Severe hypoglycemia, lactic acidosis, hepatomegaly, hyperlipidemia, hyperuricemia, short stature doll-like facies, protruding abdomen emaciated extremities	Normal
II: Pompe	Lysosomal α 1,4-glucosidase	Cardiomegaly, muscle weakness, death by 2 years	Glycogen-like material in inclusion bodies
III: Cori	Glycogen debranching enzyme	Mild hypoglycemia, liver enlargement	Short outer branches Single glucose residue at outer branch
IV: Andersen (amylopectinosis)	Branching enzyme	Infantile hypotonia, cirrhosis, death by 2 years	Very few branches, especially toward periphery
V: McArdle	Muscle glycogen phosphorylase	Muscle cramps and weakness on exercise, myoglobinuria	Normal

FA 2012: 115.2 • FA 2011: 110.2 • FA 2010: 110
ME 3e: 43

x1.5

BC09-13

- Question:
 - A 6-year-old boy is brought to the physician for a routine physical examination. He attends school for special needs children, even though his two older brothers are developmentally normal for their ages. His only medical history is poor vision partially corrected by lenses. He is in the 99th percentile for height and the 60th percentile for weight. His back appears hunched forward, and his interaction with the physician is limited due to poor language capacity. Physical examination shows a carotid bruit but is otherwise normal. Which of the following is the most likely complication of this condition?
 - A. Early onset Alzheimer's disease
 - B. Stroke
 - C. Infertility
 - D. Development of self-mutilatory behavior

x1.5

BC09-14

- Answer:
 - This presentation of a tall, marfanoid-appearing child in a family without history, with special needs and poor language skills is suggestive of an inborn error of metabolism. The carotid bruit on exam is suspicious for atherosclerotic disease of the carotid artery. Combining these findings, the metabolic disease that presents with marfanoid habitus, atherosclerosis, and MR is homocysteinuria. Of note, the language deficit may be a congenital delay of development, and may also represent an old MCA infarct. The prognosis for those with homocysteinuria is poor: they will most likely die early from an MI or CVA in any vascular territory. The answer is B. Posterior circulation stroke



Metabolism: Fatty Acid Metabolism & Lipoproteins

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x1.5

BC10-1

- Lysosomal storage diseases
 - Lysosomal enzymes are important for cell functions, including:
 - Degradation of cellular molecules like proteins, engulfed virus particles and bacteria
 - Autolysis
 - Autophagy
 - 8 lysosomal storage diseases to know
 - 2 are X-linked recessive (Fabry's and Hunter's)
 - The others are autosomal recessive

x1.5

BC10-2

Sphingolipidoses	Findings	Enzyme deficiency	What accumulates	Other notes
Fabry's	Peripheral neuropathy, angiokeratomas, cardiovascular/renal disease	Alpha-galactosidase A	Ceramide trihexoside	X-linked recessive
Gaucher's	Hepatosplenomegaly, aseptic <u>necrosis of femur</u> , <u>Gaucher's cells</u> ("tissue paper" macrophages)	Beta-Glucocerebrosidase (Gaucher - Crumpled Bone)	Glucocerebroside	Ashkenazi Jews
Niemann-Pick	Hepatosplenomegaly, progressive neurodegeneration, <u>cherry red macula</u> , <u>foamy macrophages</u>	Sphingomyelinase	Sphingomyelin	Ashkenazi Jews. "No man picks his nose with his sfin-go" (Niemann-Pick sphingo)

FA 2012: 116.1 • FA 2011: 111.1 • FA 2010: 111
ME 3e: 54

x1.5

BC10-3

Sphingolipidoses	Findings	Enzyme deficiency	What accumulates	Other notes
Tay-Sachs	Progressive neurodegen., cherry red macula, lysosomes with "onion skin". NO H/S MEGALY	Hexosaminidase A	GM2 ganglioside	Ashkenazi Jews. Tay Sax (hexosaminidase)
Krabbe's	Peripheral neuropathy, <u>optic atrophy</u> , <u>globoid cells</u>	Galactocerebrosidase	Galactocerebroside	
Metachromatic leukodystrophy	Diffuse demyelination with <u>ataxia</u> , <u>dementia</u>	Arylsulfatase	Cerebroside <u>sulfate</u>	

FA 2012: 116.1 • FA 2011: 111.1 • FA 2010: 111
ME 3e: 54

x1.5

BC10-4

Muco-polysaccharidoses	Findings	Enzyme deficiency	What accumulates	Other notes
Hurler's	Gargoylism (dwarfism with facies), cataracts, airway obstruction	Alpha-L-iduronidase	Heparan, dermatan	
Hunter's	Milder hurler's, aggressive behavior, no cataracts	Iduronate sulfatase	Heparan, dermatan	Hunters See Clearly

FA 2012: 116.1 • FA 2011: 111.1 • FA 2010: 111
ME 3e: 54

x1.5

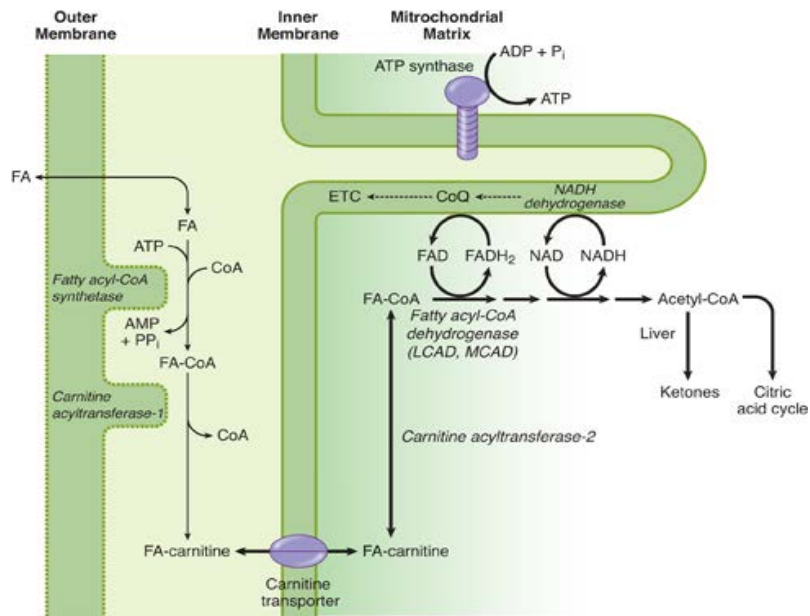
BC10-5

- Fatty Acid metabolism:
 - Fatty acids (FAs)
 - Important source of energy
 - Involved in other processes (like making myelin)
 - Important substrate for glucose, pyruvate
 - FAs oxidized to form ketones
 - Two kinds of oxidation:
 - Beta-oxidation
 - Straight-chain FAs
 - Takes place in mitochondria
 - Alpha-oxidation
 - Branched-chain FAs
 - Takes place in peroxisome

FA 2012: 117.2 • FA 2011: 112.1 • FA 2010: 112
ME 3e: 50

x1.5

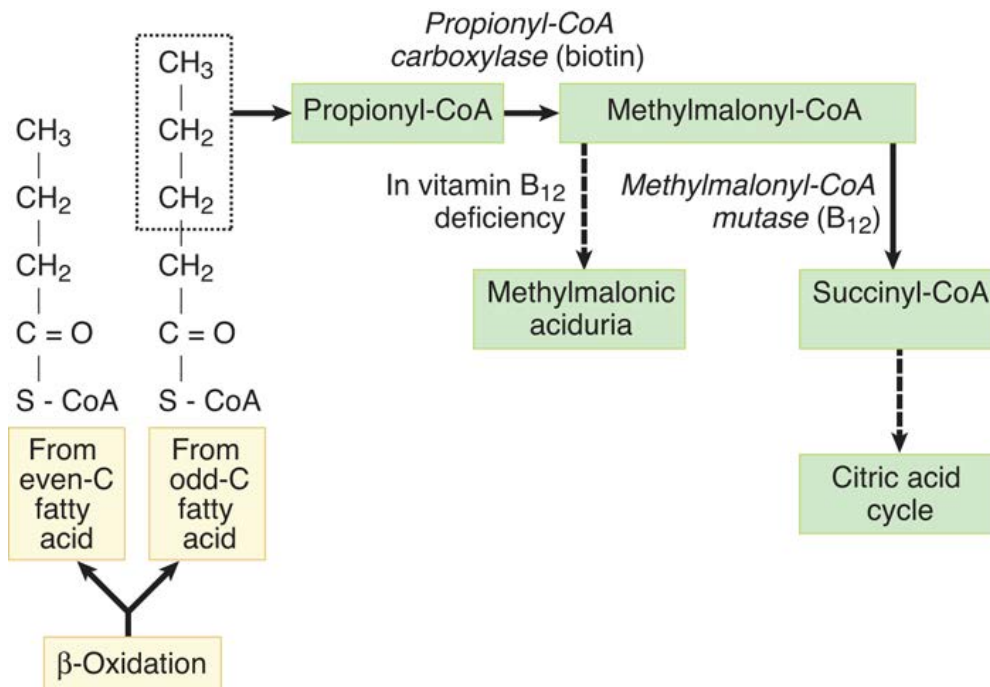
BC10-6



FA 2012: 117.2 • FA 2011: 112.1 • FA 2010: 112
ME 3e: 50

x1.5

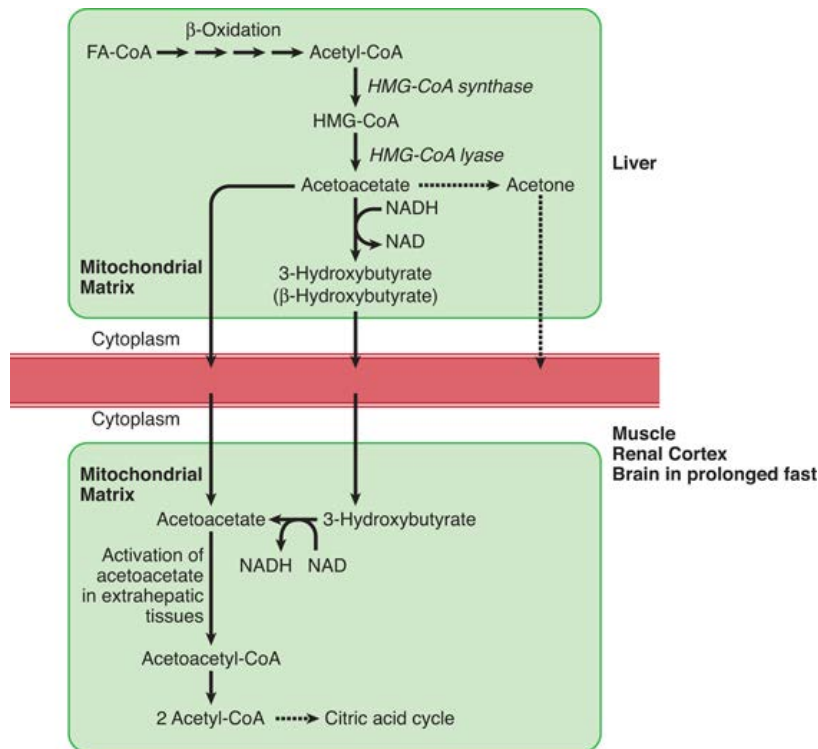
BC10-7



FA 2012: 117.2 • FA 2011: 112.1 • FA 2010: 112
ME 3e: 50

x1.5

BC10-8



FA 2012: 117.2 • FA 2011: 112.1 • FA 2010: 112
ME 3e: 50

x1.5

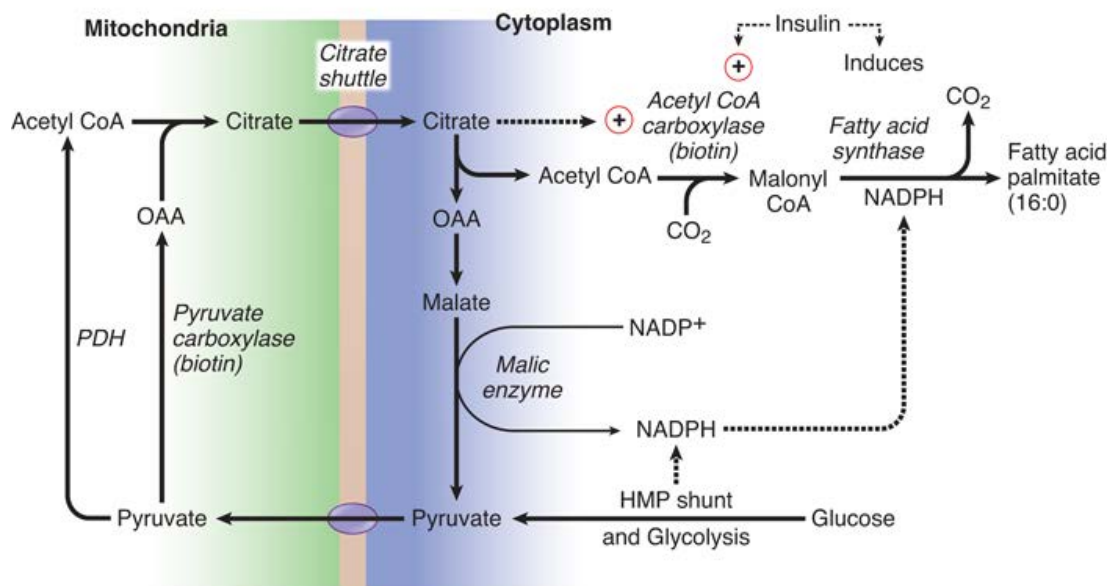
BC10-9

- Carnitine deficiency
 - Inability to transport long-chain FAs into the mitochondria
 - FAs accumulate in the cytoplasm of the cell
 - Characterized by weakness, hypotonia, and non-ketotic hypoglycemia
- Acyl-CoA dehydrogenase deficiency
 - Causes an increase in dicarboxylic acids
 - Non-ketotic hypoglycemia and poor fasting tolerance
 - May lead to SIDS

FA 2012: 117.2 • FA 2011: 112.1 • FA 2010: 112
ME 3e: 50

x1.5

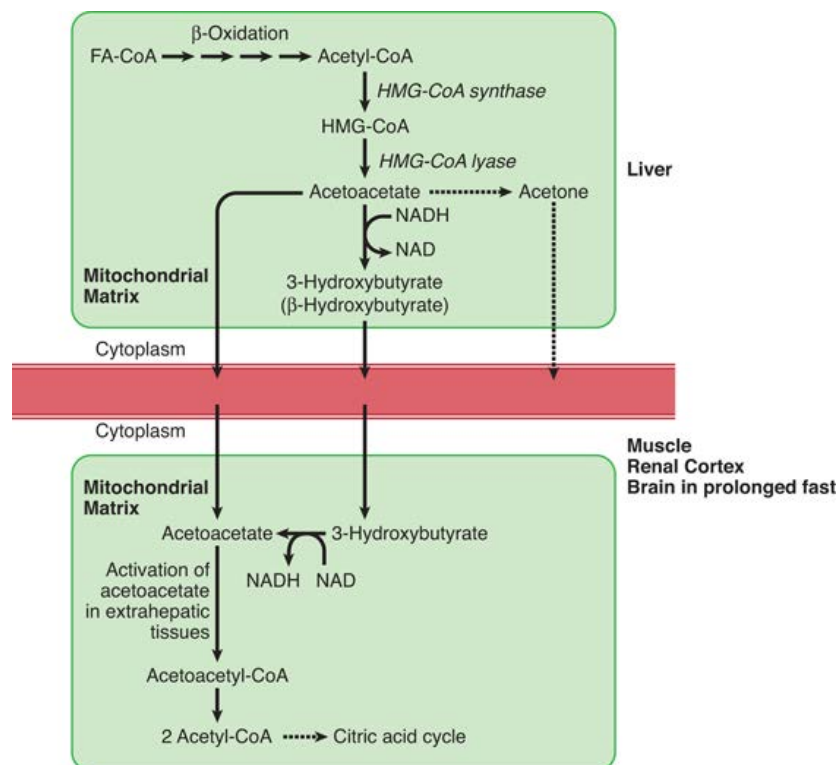
BC10-10



FA 2012: 117.2 • FA 2011: 112.1 • FA 2010: 112
ME 3e: 50

x1.5

BC10-11



FA 2012: 118.1 • FA 2011: 112.2 • FA 2010: 112
ME 3e: 52

x1.5

BC10-12

- Metabolic fuel sources

- Exercise:

- Initially: ATP-CK pathway
 - TCA and ETC can continue to produce new ATP
 - Later, glycogen and FAs are mobilized and gluconeogenesis begins

- Starvation:

- Initially: glycogenolysis, gluconeogenesis, FA oxidation
 - Later, protein from muscle is consumed
 - After a week, ketone bodies are pretty much the only source of fuel being used

FA 2012: 118.2 • FA 2011: 113.1 • FA 2010: 113
ME 3e: 52

x1.5

BC10-13

- Cholesterol metabolism

- Rate limiting step: HMG CoA reductase

- This enzyme converts HMG CoA to mevalonate
 - Statins target this step

- Most of the cholesterol in plasma is esterified by LCAT (lecithin-cholesterol acetyltransferase).

- One important product of cholesterol synthesis is Farnesyl-PP, which is important for CoQ in ETC, as well as N-glycosylation of proteins and membrane synthesis

FA 2012: 119.2 • FA 2011: 113.2 • FA 2010: 113
ME 3e: 52

x1.5

BC10-14

- Linoleic and linolenic acid
 - LinoLEANic acid is omega-3
 - Arachidonic acid is essential if linoleic acid is absent
 - Eicosanoids (prostaglandins, leukotrienes) are synthesized from the essential fatty acids
 - Trans fats decrease membrane fluidity (think of butter vs oil) and are associated with accelerated atherosclerosis
 - Omega nomenclature says which carbon in the FA has a double bond
 - Omega 3s are cardioprotective because they can be incorporated into platelets instead of arachidonic acid (which is an omega-6)

FA 2012: 120.1 • FA 2011: 114.1 • FA 2010: 114
ME 3e: 53

x1.5

BC10-15

- Pancreatic lipase
- Lipoprotein lipase
- Hepatic TG lipase
- Hormone-sensitive lipase
- VLDL, LDL, IDL, HDL float through the blood and function as carriers of fat and cholesterol
- LCAT (lecithin-cholesterol acetyltransferase) catalyzes the esterification of cholesterol
- CETP (cholesterol ester transfer protein) mediates the transfer of cholesterol to esters on other lipoprotein molecules

FA 2012: 120.1 • FA 2011: 114.1 • FA 2010: 114
ME 3e: 53

x1.5

BC10-16

- Apolipoproteins:
 - A: activates LCAT
 - B-100: Binds to LDL receptor to cause secretion of VLDL from the liver
 - C: is a cofactor for lipoprotein lipase (in the capillaries)
 - B-48: mediates the secretion of chylomicrons in the gut
 - E: mediates Extra cholesterol to be taken up (important in molecules with low protein:cholesterol ratios)

FA 2012: 120.2 • FA 2011: 114.2 • FA 2010: 115
ME 3e: 53

x1.5

BC10-17

Lipoprotein	Functions	Apoproteins	Functions
Chylomicrons	Transport dietary triglyceride and cholesterol from intestine to tissues	apoB-48 apoC-II apoE	Secreted by intestine Activates lipoprotein lipase Uptake of remnants by the liver
VLDL	Transports triglyceride from liver to tissues	apoB-100 apoC-II apoE	Secreted by liver Activates lipoprotein lipase Uptake of remnants (IDL) by liver
IDL (VLDL remnants)	Picks up cholesterol from HDL to become LDL Picked up by liver	apoE apoB-100	Uptake by liver
LDL	Delivers cholesterol into cells	apoB-100	Uptake by liver and other tissues via LDL receptor (apoB-100 receptor)
HDL	Picks up cholesterol accumulating in blood vessels Delivers cholesterol to liver and steroidogenic tissues via scavenger receptor (SR-B1) Shuttles apoC-II and apoE in blood	apoA-1	Activates lecithin cholesterol acyltransferase (LCAT) to produce cholesterol esters

FA 2012: 121.1 • FA 2011: 115.1 • FA 2010: 115
ME 3e: 53

x1.5

BC10-18

Type	Deficiency	Lipid Elevated in Blood	Lipoprotein Elevated in Blood	Comments
I	Familial lipoprotein lipase (rare) apoC-II (rare) Autosomal recessive	Triglyceride	Chylomicrons	Red-orange eruptive xanthomas Fatty liver Acute pancreatitis Abdominal pain after fatty meal
IIa	Familial hypercholesterolemia Autosomal dominant (Aa 1/500, AA 1/10 ⁶) LDL-receptor (LDL-R) deficiency	Cholesterol	LDL	High risk of atherosclerosis and coronary artery disease Homozygous condition, usually death <20 years Xanthomas of the Achilles tendon Tuberous xanthomas on elbows Xanthelasmas Corneal arcus

- Type 4, hypertriglyceridemia: overproduction of VLDL (especially dangerous in people who also have DM), Causes pancreatitis.

FA 2012: 121.2 • FA 2011: 115.2 • FA 2010: 115
ME 3e: 53

x1.5

BC10-19

- Abetalipoproteinemia (AR)
 - Deficiency of apoB (both kinds)
 - Characterized by:
 - failure to thrive
 - Steatorrhea (malabsorption)
 - Acanthocytosis
 - Ataxia (can't make myelin)
 - Night blindness (can't absorb vitamin A)
 - Biopsy of the intestine shows accumulation of cholesterol in the intestinal epithelium

FA 2012: 121.3 • FA 2011: 115.3 • FA 2010: 115
ME 3e: 53

x1.5

BC10-20

- **Question:**

- A 22-year-old man who is a bodybuilder is brought to the emergency department after his roommate found him slumped over the table in his apartment. He has no known history of any major medical illnesses. His roommate says the patient has been on the Atkins diet for the last few weeks, to “lose weight before a competition”. According to the roommate, the patient eats a protein shake with raw eggs after his workouts. His temperature is 36.8°C (98.2°F), pulse is 94/min, blood pressure is 112/76 mm Hg, respirations are 24/min, and oxygen saturation is 99%. Laboratory studies show a blood glucose of 32 mg/dL. He is obtunded and has a fruity odor on his breath. His heart and lung sounds are normal. He is treated with 50% dextrose and 10 minutes later begins to recover. Which of the following pathways was most likely responsible for this patient’s presentation?
 - A. Fatty acid synthesis
 - B. Ketogenesis
 - C. Pyruvate dehydrogenase
 - D. Glycogenolysis

x1.5

BC10-21

- **Answer:**

- This patient presents with hypoglycemia and ketosis following the Atkins diet for several weeks. In addition, he also has a history of consuming raw eggs, which contain the protein Avidin which binds biotin, making it impossible to carry out carboxylation reactions. Because he has not been consuming carbohydrates, he is extremely dependant on fatty acid metabolism. An important step of fatty acid synthesis is the carboxylation of acetyl CoA, which requires biotin as a cofactor. Thus, he was unable to maintain a proper amount of stored fat in order to maintain gluconeogenesis, and he presented with severe hypoglycemia and ketosis from the oxidation of whatever fat he had stored in his body. Thus, the answer is A. Fatty acid synthesis.

x1.5

BC10-22