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Prepared by Edward Goljan, M.D.

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GOLJAN HIGH YIELD NOTES FOR USMLE STEP 1®

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Abbreviations commonly used: AD = autosomal dominant, AR = autosomal recessive, COD = cause of death, Dx = diagnosis, MC = most common, MCC = most common cause, Rx = treatment, S/S = signs and symptoms, SXR = sex-linked recessive

High Yield Concepts in General Pathology

General Principles of Lab Medicine

- Sensitivity of a test:
  1. "positivity in disease"—
     A. TP = patient with the disease
     B. FN = patient with disease who has a negative test result
     C. formula for sensitivity—TP / (TP + FN)
  2. use of a test with 100% sensitivity—
     A. best used to screen for disease
     B. excludes disease when negative
     C. includes people with disease when positive
     D. catch words: excludes and includes
  3. interpretation of a test with 100% sensitivity when it returns normal in a patient—
     A. always has a negative predictive value of 100% (PV = TN / (TN + FN))
     B. it must be a TN test result (excludes disease) since there are no FNs; a TN is a true negative or a normal test result in a person without disease
     C. e.g., serum ANA has 100% sensitivity for SLE: a negative serum ANA excludes SLE.
  4. interpretation of a test with 100% sensitivity when it returns positive in a patient—
     A. may be a TP or FP:
        (1) FP = false positive or a positive test result in a normal person
        (2) note that FPs are not in the formula for sensitivity
     B. people with the disease are always included
     C. e.g., a positive serum ANA result includes all people with SLE; it does not confirm SLE since other diseases also have a positive ANA (e.g., rheumatoid arthritis, progressive systemic sclerosis)

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<tr>
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<td></td>
<td>(FP) 10</td>
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<tr>
<td>Negative test</td>
<td>(FN) 0</td>
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<td>(TN) 90</td>
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Calculate sensitivity of the test: TP / (TP + FN) = 100 / 100 + 0 = 100%
Calculate PV: TN / (TN + FN) = 90 / 90 + 0 = 100%

- Specificity of a test:
  1. "negativity in health"—
     A. TN = normal test result in a person without disease
     B. FP = patient without disease who has a positive test result
C. formula for specificity—TN / TN + FP
2. use of a test with 100% specificity—confirms disease: there are no FP test results, therefore, a positive test must be a TP
3. interpretation of a test with 100% specificity when it returns positive in a patient—
   A. confirms disease in that patient
   B. positive predictive value is always 100% (PV⁺ = TP / TP + FP)
   C. must be a TP (confirms disease) since there are no FPs
   D. e.g., anti-Sm for SLE has 100% specificity (no FPs): all patients with a positive anti-Sm have SLE
4. interpretation of a test with 100% specificity when it returns negative/normal in a patient—
   A. may be a TN or FN; note that the FN rate is not in the formula for specificity
   B. it does not exclude SLE
   C. e.g., anti-Sm is negative in a patient:
      (1) does not exclude SLE
      (2) use other tests to confirm SLE if your suspicions are high

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Calculate specificity of the test: TN / TN + FP = 100 / 100 + 0 = 100%
Calculate PV⁺: TP / TP + FP = 90 / 90 + 0 = 100%

Calculate the reference interval of the test when given the mean of the test and 1 SD (standard deviation):
1. remember to double the SD—2 SD covers 95% of the normal population
2. example—
   A. mean of the test = 100 mg/dL and 1 SD = 5 mg/dL (2 SD = 10 mg/dL)
   B. reference interval = 90–110 mg/dL (100 – 10 = 90 and 100 + 10 = 110)
3. for each test, 5% of normal people will have test results outside the reference interval—
   A. chance of a FP increases when more than one test is ordered on a patient
   B. example, 2 tests on a patient increases the chance of a FP test result on one of those tests to ~10%
4. SD is a marker of the precision (reproducibility) of the test— it is not a marker of how accurate the test result is

Accuracy: good
Precision: good

Effect of test sensitivity/specificity of a test on prevalence:
1. test with highest sensitivity (not specificity) increases prevalence of disease (number of people in a population that have disease)—
   A. it picks up more people with the disease since it is a good screening test
   B. tests with high specificity confirm disease and help differentiate a TP from a FP but they are poor screening tests
Effect of increasing the upper limit of normal of a test reference interval (e.g., raising a reference interval of 0-4 ng/mL to 0-10 ng/mL) on sensitivity, specificity, PV⁺, and PV⁻:

1. increases specificity and positive predictive value—
   A. higher values are more likely to represent TPs than FPs
   B. specificity always increases, which automatically increases PV⁺

2. decreases sensitivity and negative predictive value (PV⁻)—
   A. increasing specificity of a test always decreases its sensitivity and PV⁻
   B. FN rate increases, since more people with disease are encountered as the reference interval increases
   C. a normal test result is more likely to be a FN rather than a TN

Effect of decreasing the upper limit of normal of a test reference interval (e.g., lowering the fasting glucose level for diagnosing diabetes mellitus [DM] from >140 mg/dL to >126 mg/dL) on sensitivity, specificity, PV⁺, and PV⁻:

1. increases sensitivity and negative predictive value (PV⁻) –
   A. dropping the upper limit to a lower value means that more people with a negative test result are likely to be TNs (not have DM) rather than FNs
   B. sensitivity and PV⁻ always increase when the upper limit of a test is lowered

2. decreases specificity and positive predictive value (PV⁺)—
   A. fewer people are likely to have DM, a test result >126 mg/dL is more likely to be a FP than a TP test result
   B. summary schematic

Prevalence:

1. Prevalence (number of people with disease in the population studied) = Incidence (number of new cases over a period of time) x Duration of the disease—
   A. P = I x D
   B. as duration (D) decreases, prevalence (P) decreases
**DISEASE COUNTRY**

- Interval 0 - 10
- Specificity 100% (no FPs)
- Sensitivity decreases (more FNs)
- PV^+ 100%
- PV^- decreases (more FNs)

**NORMAL COUNTRY**

- Interval 0 - 4
- Sensitivity 100% (no FNs)
- Specificity decreases (more FPs)
- PV^- 100%
- PV^+ decreases (more FPs)
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C. as D increases, P increases
D. incidence (I) is a constant in this relationship

2. **prevalence calculation**— TP + FN (all people with disease)/ TP + FN + TN + FP (all people with and without disease)

3. **example**— if treatment for leukemia lengthens the survival period but does not lead to its cure, prevalence (P) of leukemia increases owing to the increase in duration (D): no effect on incidence (number of new cases of leukemia)

**Example of a calculation for sensitivity, specificity, PV+, PV-, prevalence:**

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<td>(TP) 60</td>
<td>(FP) 40</td>
</tr>
<tr>
<td>Negative test</td>
<td>(FN) 20</td>
<td>(TN) 80</td>
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Sensitivity of the test: TP / TP + FN = 60 / 80 = 75%
Specificity of the test: TN / TN + FP = 80 / 120 = 66%
PV+: TN / TN + FN = 80 / 100 = 80% (80% chance it is a TN and a 20% chance it is a FN)
PV+: TP / TP + FP = 60 / 100 = 60% (60% chance it is a TP and 40% chance it is a FP)
Prevalence: TP + FN / TP + FN + TN + FP = 80 / 200 = 40%

**Normal changes in pregnancy:**
1. **greater increase in plasma volume than RBC mass**—
   A. decreases hemoglobin (Hb) and hematocrit (Hct): dilutional effect
   B. increases glomerular filtration rate (GFR) and creatinine clearance (CCr): due to increased plasma volume
   C. decreases serum BUN/creatinine/uric acid: dilutional effect + increased clearance
2. **increased alkaline phosphatase**— placental origin
3. **respiratory alkalosis**— estrogen/progesterone effect on CNS respiratory center causing increased clearance of CO₂ per breath
4. **increased T₄ and cortisol**—
   A. increased synthesis of their binding proteins
   B. free hormone levels are normal
   C. no signs of hyperthyroidism/hypercortisolism
   D. e.g., normal serum TSH and ACTH, respectively

**Main laboratory difference in adult male and female:**
1. iron studies are all lower in women— e.g., serum iron and ferritin
2. lower Hb concentration in women

**Children:**
1. **increased serum alkaline phosphatase (ALP)—**
   A. 3–5 times higher than adults
   B. osteoblasts release enzyme when stimulated by vitamin D
   C. ALP increases bone mineralization
2. **increased serum phosphate**— required to drive calcium into bone,
3. **slight decrease in hemoglobin concentration when compared to adult levels**

**Newborn:** high hemoglobin (Hb) due to increase in HbF—
1. left shifts oxygen dissociation curve (ODC): causes tissue hypoxia→
2. stimulus for erythropoietin (EPO) release→
3. increases RBC production with subsequent increase in Hb concentration
HbF:
1. left shifts oxygen dissociation curve (ODC)
2. protects newborns with sickle cell disease—
   A. most of the RBCs at birth contain HbF: inhibits sickling
   B. less HbS:
      (1) concentration not high enough for sickling
      (2) HbS must be >60% in RBC for spontaneous sickling
      (3) dactylitis (bone infarctions of digits) begins in 6–9 mths
3. protects newborn from severe β-thalassemia—
   A. HbF contain 2α and 2γ chains
   B. adult HbA will be markedly decreased after a few months since β-chain synthesis is decreased: HbA = 2α and 2β
4. HbF synthesis is increased with hydroxyurea— used to reduce sickle cell crises,
5. HbF is resistant to alkali/acid denaturation— basis for Kleihauer Betke test in determining amount of fetal blood in maternal circulation after delivery

Analytes increased with hemolyzed blood sample secondary to venipuncture:
1. LDH—
   A. LDH₁ isoenzyme fraction is primarily increased and is greater than LDH₂ isoenzyme fraction (LDH₁/LDH₂ flip)
   B. false positive acute myocardial infarction
   C. LDH₁ isoenzyme is also in cardiac muscle
2. potassium—
   A. pseudohyperkalemia
   B. K⁺ is the major intracellular cation
   C. ECG will not show a peaked T wave

Lipid most affected by fasting:
1. triglyceride (TG) component coming from chylomicrons— chylomicrons contain diet-derived TG
2. fasting or lack of fasting does not affect cholesterol (CH) and high-density lipoprotein (HDL) concentration—
   A. normally, CH is <3% of the chylomicron fraction
   B. fasting is unnecessary for an accurate CH or HDL
3. fasting is necessary for an accurate calculated low-density lipoprotein (LDL)—
   A. LDL = CH - HDL - TG/5
   B. if TG is falsely increased by chylomicrons from the diet, it will falsely lower the calculated LDL

Drugs enhancing the cytochrome system in the liver smooth endoplasmic reticulum (SER):
1. drugs—
   A. alcohol
   B. barbiturates
2. effect on SER—
   A. SER hyperplasia
   B. increased synthesis of γ-glutamyltransferase (GGT): enzyme is normally located in SER
   C. decreases drug levels owing to increased metabolism of the drug

Drugs inhibiting cytochrome system in the liver:
1. drugs—
   A. H₂ blockers (cimetidine)
   B. proton blockers
2. **dangers of drug toxicity**

**Significance of erythrocyte sedimentation rate (ESR) in old age:** probably indicates a disease process—

1. not an age-related finding
2. not recommended as a general screen for disease in the elderly

**Laboratory test alterations in alcoholics:**

1. enhancement of the liver cytochrome P-450 system—
   A. increased synthesis of γ-glutamyltransferase (GGT)
   B. excellent enzyme marker for alcoholic liver disease
2. increased production of NADH in its metabolic breakdown causes biochemical reactions involving NADH to move in its direction resulting in the following—
   A. lactic acidosis: pyruvate → lactate
   B. fasting hypoglycemia: pyruvate is unavailable for gluconeogenesis
   C. hypertriglyceridemia: 1,3 bisphosphoglycerate → dihydroxyacetone phosphate → glycerol 3-phosphate → TG
3. **increase in ketoacid synthesis**—
   A. acetyl CoA, the end product of alcohol metabolism is used in the following reaction
   B. acetyl CoA + acetyl CoA →
   C. acetoacetyl CoA →
   D. HMG CoA → acetoacetic acid: increase in NADH converts it into β hydroxybutyric acid (β-OHB)
4. **increase in fatty acid synthesis**— due to the increase in acetyl CoA
5. **hyperuricemia**— lactic acid/ketoacids compete with uric acid for excretion in the kidneys
6. increased anion gap metabolic acidosis— lactate + β-OHB

**Laboratory test alterations in smokers:**

1. **respiratory acidosis**— air gets in but cannot get out, so CO₂ is retained
2. hypoxemia (low PaO₂)— see Cell Injury notes
3. increased carbon monoxide (CO) levels— CO is present in cigarette smoke
4. secondary polycythemia— low PaO₂ stimulates erythropoietin release
5. absolute neutrophilic leukocytosis— metabolites in smoke mobilize the neutrophil marginating pool in the circulation by decreasing leukocyte adhesion to endothelial cells

**Plasma/serum turbidity:**

1. due to an increase in triglyceride (TG)— turbidity does not occur with an increase in cholesterol (CH) in plasma
2. TG is carried by lipoproteins—
   A. chylomicrons: 85%
   B. very low-density lipoprotein (VLDL): 55%
3. TG is falsely increased after eating— due to diet-derived chylomicrons
4. chylomicrons form a supranate in plasma— contain very little protein: less dense than VLDL
5. VLDL forms an infranate (no supranate)— contains more protein than chylomicrons and does not float on the surface of plasma
6. increased turbidity interferes with measurement of enzymes and serum Na⁺— falsely low enzyme values and sodium (pseudohyponatremia)
Relation of serum albumin concentration with serum calcium concentration:
1. albumin binds 40% of total calcium in blood—
   A. 13% of calcium is bound to other substrates
   B. 47% calcium is free, ionized calcium: metabolically active calcium
2. low serum albumin decreases calcium bound to albumin—
   A. hypocalcemia
   B. no tetany is present, since the ionized levels are normal

**USMLE scenarios:**
1. calculation of sensitivity, specificity, PV+ and PV−
2. two tests are ordered on a patient, what is chance for a FP result—answer is ≈10%
3. increase/decrease upper limit of a test
4. effect of sensitivity on prevalence
5. using triple therapy for HIV positive people and effect on prevalence—
   A. it has extended the time interval (Duration) before an AIDS-defining condition occurs
   B. prevalence of HIV positive people has increased
6. effect of pregnancy on serum cortisol—answer is that it is increased due to an increase in the binding protein and not the free hormone level

**Questions used in Board Review:**

Assuming the use of 2 standard deviations to establish the reference interval of a test, in a test with a reference interval of 10–30 mg/dL, 1 standard deviation would equal...

A. 2.5
B. 5.0
C. 7.5
D. 10.0
E. 20.0

B. mean of the test is 20 mg/dL, 2 SD = 10 mg/dL, therefore 1 SD = 5 mg/dL

If the prostate specific antigen (PSA) test for prostate cancer is lowered from a reference interval of 0–10 ng/mL to 0–4 ng/mL, this will...

A. increase the number of false negatives
B. decrease the number of false positives
C. increase the test’s specificity
D. increase the PV+
E. increase the PV−
Study the following schematic involving a control group and disease X.

Reference interval
Which of the following correctly describes test results in the space occupied by each of the lettered groups?

A. Group A: true negatives + false negatives
B. Group B: true negatives + false positives
C. Group C: true positives + false positives
D. Group D: true positives + false negatives

C: group A = all TNs, group B = TNs + FNs, group C = FPs + TPs, group D = all TPs

A pregnant woman in her first trimester complains of heat intolerance and palpitations. Physical exam reveals an enlarged, non-tender thyroid gland. Her serum T₄ is elevated and the TSH is normal. Which of the following applies to this case?

A. Thyroid binding globulin is increased
B. Free T₄ hormone levels are increased
C. Estrogen increased the synthesis of thyroid hormone
D. Progesterone increased the synthesis of thyroid binding globulin

A
Cell Injury

Causes of tissue hypoxia (inadequate oxygenation of tissue):
1. ischemia—
   A. definition—decreased arterial blood flow to tissue
   B. example
      (1) atherosclerosis in coronary artery: MCC
      (2) decreased cardiac output
2. hypoxemia—
   A. definition—low arterial partial pressure of O₂ (PaO₂)
      (1) respiratory acidosis: whenever alveolar PCO₂ increases alveolar PO₂ must decrease and PaO₂ must decrease
      (2) ventilation problems: e.g., atelectasis
      (3) perfusion problems: e.g., pulmonary embolus
      (4) diffusion problems: e.g., interstitial fibrosis in the lungs
   B. anemia
   C. CO poisoning
   D. methemoglobinemia
   E. left shifted oxygen dissociation curve (ODC)
3. problems with oxidative pathway in mitochondria—
   A. carbon monoxide (CO) inhibits cytochrome oxidase
   B. cyanide inhibits cytochrome oxidase
4. uncoupled oxidative phosphorylation in mitochondria—
   A. mitochondrial poisons (alcohol, salicylates) render inner mitochondrial membrane permeable to protons
   B. decreases ATP synthesis
5. arteriovenous shunting—
   A. AV fistula from trauma:
      (1) direct communication of arterial system with venous system
      (2) microcirculation is bypassed
   B. spider angiomas: due to hyperestrinism
   C. mosaic bone in Paget's disease of bone

Ultimate effect of tissue hypoxia: decrease in ATP production by oxidative phosphorylation in the mitochondria
1. O₂ is normally the electron acceptor at the end of the oxidative pathway
2. all proximally located biochemical reactions must cease if O₂ is not present
3. no protons come off the oxidative pathway → no ATP production

Effects of a decrease in ATP in the cell:
1. cell must utilize anaerobic glycolysis to generate ATP—
   A. phosphofructokinase (PFK), the rate limiting reaction in glycolysis, is activated by
      (1) low citrate
      (2) increase in adenosine monophosphate (AMP)
   B. net gain of 2 ATP
   C. no gain in NADH:
      (1) NADH is converted into NAD⁺ when pyruvate is converted into lactate
      (2) NAD⁺ generated by this reaction is used to produce 2 more ATP
   D. decrease in intracellular pH from lactate production:
      (1) denatures cellular enzymes and other proteins (called coagulation necrosis)
      (2) produces an increased anion gap metabolic acidosis
2. **impaired Na⁺/K⁺ ATPase pump**
   A. water enters the cell producing cellular swelling
   B. reversible change if O₂ is restored
3. **ribosomes fall off rough endoplasmic reticulum**– decreased protein synthesis

**O₂ content formula:**

1. **O₂ content**
   A. **definition:** total amount of O₂ carried in blood
   B. **formula:** 1.34 (Hb) x SaO₂ + PaO₂, where Hb = hemoglobin, SaO₂ = O₂ saturation, and PaO₂ is the amount of O₂ dissolved in plasma

2. **PaO₂**
   A. **definition:** amount of O₂ dissolved in plasma and not O₂ attached to Hb in RBCs, which is called the oxygen saturation (SaO₂)
   B. **PaO₂ is dependent on:**
      (1) percent O₂ in inspired air (21%)
      (2) atmospheric pressure: decreases with high elevation even though O₂ percent is still 21%
      (3) matched ventilation/perfusion in the lungs
      (4) diffusion of O₂ through the alveolar-capillary interface
   C. **decreased alveolar PO₂ always leads to hypoxemia:**
      (1) must have adequate O₂ in the alveoli in order to diffuse into the pulmonary capillaries
      (2) low alveolar O₂ always leads to low arterial PO₂
   D. **hypoxemia always leads to less O₂ carried by the Hb in RBCs in the blood:**
      (1) decreases SaO₂, which is the average percentage of heme groups in Hb occupied by O₂
      (2) see discussion below
   E. **PO₂ at the tissue level**
      (1) driving force for diffusion of O₂ from the capillaries into the tissue
      (2) capillary PO₂ must be higher than PO₂ in tissue for diffusion to occur

3. **SaO₂**
   A. **definition:** percentage of O₂ attached to the 4 heme groups in Hb within the RBCs: normal range is 94–96%
   B. **SaO₂ is dependent on:**
      (1) PaO₂
      (2) valence of heme iron: must be ferrous (+2) to bind O₂
      (3) if oxidized to ferric (+3), it cannot bind O₂ and is called methemoglobin
   C. **measurement of SaO₂:**
      (1) measured non-invasively with a pulse oximeter
      (2) calculated from measured PaO₂
      (3) directly measured in arterial blood
   D. **decreased SaO₂ correlates with cyanosis** of skin/mucous membranes: SaO₂ <80% produces visible cyanosis

**Respiratory acidosis:**

1. **increase PaCO₂**
2. **low O₂ content**
   A. decreased PaO₂
   B. decreased SaO₂
Anemia:
1. decreased O₂ content—
   A. decreased Hb concentration
   B. normal PaO₂/SaO₂: normal O₂ exchange in the lungs so these parameters remain normal
2. decreased Hb concentration—
   A. most important component for carrying O₂
   B. determines the amount of O₂ delivered to tissue
3. iron deficiency is MCC of anemia

Carbon monoxide (CO) poisoning:
1. decreased O₂ content—
   A. normal PaO₂
   B. decreased SaO₂: CO has a higher affinity for heme on Hb than O₂
2. additional causes of tissue hypoxia—
   A. left shifts the O₂ dissociation curve (ODC)
   B. inhibits cytochrome oxidase
3. causes CO poisoning—
   A. car exhaust
   B. space heaters (USMLE)
   C. smoke inhalation in fires
   D. wood stoves
4. Rx (treatment)— 100% O₂
5. S/S—
   A. headache first symptom
   B. cherry red color of carboxyhemoglobin masks cyanosis
6. long term effect— necrosis of globus pallidus leading to Parkinson-like findings

Methemoglobinemia:
1. methemoglobin (metHb) is heme with iron +3— heme cannot bind O₂
2. O₂ content decreased—
   A. normal PaO₂
   B. decreased SaO₂: decreased even though PaO₂ is normal
3. cause— heme oxidized by nitro/sulfa compounds
4. S/S—
   A. cyanotic
   B. blood is chocolate colored from increased deoxyhemoglobin
5. Rx—
   A. IV methylene blue is gold standard for Rx: activates a methemoglobin reductase system that is not normally operative
   B. ascorbic acid: reducing agent that is used as ancillary therapy

Factors altering the oxygen dissociation curve (ODC):
1. left shifted ODC—
   A. increased affinity for O₂: does not release O₂ into blood
   B. examples:
      (1) ↓2,3 bisphosphoglycerate (BPG)
      (2) CO
      (3) metHb
      (4) HbF
      (5) hypothermia
      (6) alkalosis
RESPIRATORY ACIDOSIS

\[ O_2 \text{ content} = 1.34 \times [Hb] \times S\text{a}O_2 \times P\text{a}O_2 \]

\[ S\text{a}O_2 = 50\% \]

\[ P\text{a}O_2 = 50 \text{ mm Hg (blood)} \]

\[ P\text{a}O_2 = 60 \text{ mm Hg (lungs)} \]

\[ P\text{a}CO_2 = 40 \text{ mm Hg} \]

\[ P\text{a}CO_2 = 45 \text{ mm Hg} \]

\[ P\text{a}CO_2 = 47 \text{ mm Hg} \]

NORMAL
2. **Right shifted ODC**-
   A. decreased affinity for O$_2$; readily releases O$_2$ into blood
   B. examples:
      1. ↑2,3 BPG
      2. fever
      3. acidosis

**Cytochrome oxidase inhibitors:**
1. CO
2. cyanide
3. **Clinical effects of inhibition**—
   A. blocks oxidative pathway in the mitochondria even though O$_2$ may be present as an electron acceptor
   B. protons from the electron transfer system are no longer entering the intermembranous space
   C. protons are not entering the proton pores in the inner mitochondrial membrane; no ATP is produced

**Causes of tissue hypoxia with a normal O$_2$ content:**
1. **Ischemia**—MCC
2. cyanide poisoning
3. **Uncoupling of oxidative phosphorylation**—
   A. uncoupling is where the inner mitochondrial membrane is rendered permeable to protons; protons are drained off without forming ATP
   B. examples of drugs that uncouple include:
      1. alcohol
      2. salicylates (important in Reye syndrome)
      3. dinitrophenol
4. **Possible outcome of uncoupling**—hyperthermia
   A. loss of protons into the mitochondria without forming ATP increases the rate of chemical reactions
   B. reactions increase production of NADH and NADPH to provide additional protons to the electron transport chain

**First histologic sign of tissue hypoxia: cellular swelling**—
1. due to reduction in ATP and impaired Na$^+$/K$^+$ **ATPase** pump
2. sodium and water enter the cell

**Causes of irreversible cell injury due to tissue hypoxia:**
1. disruption of the cell membrane—
   A. **Lipid peroxidation** by free radicals; reversed by vitamin E
   B. activation of phospholipase by calcium
   C. complement activation with damage to cell membrane
2. damage to mitochondria

**Role of calcium in irreversible cell injury:**
1. enters the cytosol
2. activates enzymes in following locations—
   A. cell membrane phospholipase: enhances lipid peroxidation
   B. activates enzymes in the nucleus: produces nuclear pyknosis
3. enters mitochondria—produces electron dense deposits and destroys mitochondria
4. **Contributes to coagulation necrosis**—intracellular buildup of lactic acid also leads to coagulation necrosis
Free radicals:
1. **definition**– unpaired electrons in outer orbit
2. **examples**–
   A. **superoxide**; \( \text{O}_2^- \) generated FR inactivated by superoxide dismutase (SOD)
   B. \( \text{OH} \)
   C. **peroxide**
      1. inactivated by catalase and glutathione (GSH)
      2. GSH is synthesized in the hexose monophosphate shunt
   D. **drugs/chemicals**:
      1. acetaminophen (inactivated by GSH)
      2. \( \text{CCl}_3 \) converted into \( \text{CCl}_4 \)
      3. oxidized low density lipoprotein (LDL, greater atherogenicity than native LDL)
3. iron increases the synthesis of \( \text{OH}^- \) FRs via the Fenton reaction—FRs are the mechanism of damage in iron overload diseases: e.g., **hemochromatosis**

Examples of FR injury:
1. normal aging process–
   A. wear and tear theory
   B. lipofuscin accumulates in cells damaged by FRs:
      1. indigestible lipid from lipid peroxidation
      2. gives tissue a brown appearance
2. \( \text{O}_2^- \)-dependent myeloperoxidase (MPO) system–
   A. most lethal bactericidal system present in neutrophils/monocytes: see Inflammation notes
   B. NADPH oxidase in cell membrane converts molecular \( \text{O}_2 \) into superoxide FR
3. \( \text{O}_2 \) toxicity–
   A. superoxide FR damage
   B. e.g., *retrolental fibroplasia*: leads to blindness in newborns
4. ionizing radiation–
   A. generates hydroxyl (OH) FRs in tissue from radiolysis of water in cells
   B. damages DNA with potential for cancer: e.g., squamous cell carcinoma of the skin
5. *acetaminophen toxicity*– mainly *analgesic* & *antipyretic*, \( \text{N}^\text{-acetyl} \) cysteine converts into FRs that act on sulfhydryl groups in hepatocyte cell membranes: **MCC of fulminating hepatic necrosis due to drugs**
   B. \( \text{N}^- \)–acyethylcysteine therapy (Mucomyst)
      1. replenishes GSH
      2. GSH neutralizes the drug FRs
6. **CCl\(_4\) poisoning**–
   A. dry cleaning industry
   B. \( \text{CCl}_4 \) converted by cytochrome system into \( \text{CCl}_3 \) FR→ liver cell necrosis

**Apoptosis**:
1. **definition**– individual cell necrosis
2. **microscopic appearance**–
   A. deeply eosinophilic staining cytoplasm
   B. pyknotic nucleus
   C. no inflammatory infiltrate
   D. cells "drop out"
3. **normal functions of apoptosis**–
   A. involution of structures: cell/organ atrophy in old age/thymus/gravid uterus
B. **apoptosis gene**: programmed cell death
C. **embryogenesis**:
   1. loss of Müllerian structures in male fetus and Wolffian structures in female fetus
   2. creates lumens for bowel

4. **pathologic roles of apoptosis**—
   A. **Councilman (acidophilic) bodies** in viral hepatitis
   B. **psammoma bodies**: apoptosis of neoplastic cells with subsequent dystrophic calcification
   C. **cancer**
      1. inactivation of apoptosis gene in B cells leads to B cell follicular lymphoma
      2. see Neoplasia notes

**Types of cell necrosis:**

1. **coagulation necrosis**—
   A. widespread coagulation necrosis is called infarction
   B. **pale types of infarction** → the tissue has a light consistency because blood vessels are damaged, the tissue can’t diffuse readily
   1. heart
   2. kidneys → via embolus from left side of heart
   3. liver (least likely to infarct due to dual portal vein/hepatic artery blood supply)
   4. spleen
   C. **hemorrhagic types of infarction**—tissue has a loose consistency so RBCs can diffuse through the tissue
      1. small bowel
      2. lungs
      3. testicles
   D. **dry gangrene**
      1. predominantly coagulation necrosis without evidence of infection
      2. example: diabetic foot

2. **CNS infarcts**—liquefactive not coagulative necrosis

3. **liquefactive necrosis**—
   A. neutrophil destruction of tissue
      1. abscesses/cellulitis
      2. wet gangrene (infection superimposed on dry gangrene)
   B. brain infarct/infection

4. **caseous necrosis**—
   A. cheese-like material noted on gross exam of tissue: represents lipid material in granulomas from macrophage destruction of typical/atypical TB and systemic fungi (molds, Cryptococcus, blastomyces)
   B. other types of granulomas are non-caseating:
      1. Crohn’s disease
      2. sarcoidosis

5. **enzymatic fat necrosis**—
   A. key finding in acute pancreatitis
   B. release of amylase and lipase from damaged pancreas (elevated blood enzymes)

6. **fibrinoid necrosis**—
   A. necrosis of immunologic injury with protein material appearing like fibrin
   B. examples:
      1. small vessel vasculitis (Henoch-Schönlein)
      2. rheumatic heart disease vegetations on mitral valve
      3. immunocomplex types of glomerulonephritis (systemic lupus erythematosus)

7. **gummatus necrosis**—
   A. tertiary syphilis
   B. rubbery masses that are very destructive in tissue
Fatty liver:
1. alcohol MCC
   A. increased NADH in the metabolism of alcohol causes a build-up of dihydroxyacetone phosphate (DHAP), an intermediate in glycolysis: DHAP produces glycerol 3-phosphate, the carbohydrate backbone of TG
   B. increased acetyl CoA in alcohol metabolism is used to increase fatty acid (FA) synthesis
   C. alcohol decreases β-oxidation of FAs in mitochondria
2. kwashiorkor—fatty liver due to decreased synthesis of apolipoproteins necessary to coat very low density lipoprotein (VLDL)
3. CO poisoning
4. shock
5. drugs—
   A. tetracycline
   B. amiodarone
6. Reye's syndrome

Increased melanin pigment:
1. nevus—benign melanocytic neoplasm
2. malignant melanoma—malignancy of melanocytes
3. increased ACTH—
   A. ACTH has melanocyte stimulating hormone activity
   B. causes of increased ACTH:
      (1) functioning pituitary adenoma
      (2) ectopic synthesis in small cell carcinoma of lung and medullary carcinoma of thyroid
      (3) Addison's disease with hypocortisolism
      (4) adrenogenital syndrome with enzyme deficiencies leading to hypocortisolism
4. African-Americans—
   A. African-Americans have the same number of melanocytes as whites
   B. melanosomes are larger and more numerous than in whites
   C. dendritic processes in melanocytes are more abundant than in whites: more transfer of melanin to keratinocytes

Absence of melanin pigment:
1. albinism—
   A. AR disease
   B. absence of tyrosinase
   C. melanocytes present in the epidermis: devoid of melanosomes
2. vitiligo—
   A. autoimmune destruction of melanocytes
   B. patchy areas of skin depigmentation
3. phenylketonuria (PKU)—
   A. AR disease
   B. deficient phenylalanine hydroxylase:
      (1) normally converts phenylalanine into tyrosine
      (2) phenylalanine increases and tyrosine decreases
      (3) tyrosine is the key amino acid substrate for melanin synthesis
      (4) PKU children have blond hair

Alcaptonuria
→ def. of homogentisate oxidase
 - dark urine
 - arthritis
Melanin look-alikes:
1. anthracotic pigment—
   A. coal dust
   B. inhaled as an environmental pollutant
      (1) phagocytized by alveolar macrophages
      (2) called dust cells
   C. "black lung" disease: disabling lung disease
2. alcaptonuria— see Genetics
3. melanos imedi—
   A. black bowel syndrome
   B. deposition of black anthracene pigment in macrophages within the lamina propria of
      large bowel: sign of laxative abuse
4. hematin—
   A. black pigment derived from acid effect on hemoglobin (Hb)
   B. black color of melena

Increased iron:
1. iron overload—
   A. hemochromatosis: AR disease
   B. hemosiderosis: acquired excess
2. anemia of chronic disease (ACD)— increased iron in macrophages that is unavailable for Hb
   synthesis
3. stasis dermatitis—
   A. deep vein thrombosis in the calf with hemorrhage of vessels around ankles
   B. hemosiderin deposits in subcutaneous tissue give tissue a rusty colored appearance
4. sideroblastic anemia—
   A. defect in heme synthesis in mitochondria
   B. iron accumulation producing ringed sideroblasts
5. Prussian blue— stain for iron

Decreased iron: iron deficiency anemia— GI loss of blood is MCC

Glycogen excess states: glycogenoses— see Genetics

Glycogen depletion: fasting/starvation state (USMLE)—
1. glycogenolysis
2. electron microscopy (EM) on USMLE showed hepatocyte with black granules (glycogen)
   in fed state and another EM with a lack of the black granules in fasting state

Excess glycosaminoglycans:
1. myxomatous degeneration— pathogenesis of mitral valve prolapse
2. mucopolysaccharidoses— lysosomal storage diseases (e.g., Hurler's disease)
3. pretibial myxedema— non-pitting edema noted in Hashimoto's thyroiditis and Graves disease

Hemoglobin-derived pigments:
1. bilirubin—
   A. unconjugated type
      (1) lipid soluble
      (2) e.g., extravascular hemolytic anemia
   B. conjugated type
      (1) water soluble
      (2) obstructive jaundice
2. **hemosiderin**—
   A. storage product of iron
   B. consists of packets of ferritin
   C. small circulating fraction of ferritin represents macrophage iron stores; serum ferritin is the best screening test for iron disorders

3. **hematin**

   Decreased hemosiderin: first sign of iron deficiency anemia

**Dystrophic calcification:**

1. **definition**—
   A. calcium deposition in damaged tissue
   B. normal serum calcium/phosphate

2. **examples**—
   A. atherosclerotic plaques
   B. enzymatic fat necrosis: visible on plain films
   C. damaged cardiac valves: *congenital bicuspid aortic valve* → *Acute of Infectious Endocarditis*
   D. psammoma bodies
      1. serous cystadenocarcinoma of ovary
      2. papillary adenocarcinoma of thyroid
      3. meningioma
      4. mesothelioma
   E. periventricular calcification in congenital cytomegalovirus infections

**Metastatic calcification:**

1. **definition**—
   A. increased serum calcium and/or phosphate
   B. deposition of calcium in normal tissue

2. **examples**—
   A. *nephrocalcinosis* in primary hyperparathyroidism: calcification of tubular basement membranes
   B. calcification of basal ganglia in primary hypoparathyroidism: high phosphorous levels in hypoparathyroidism drives calcium into the brain tissue

**Genetic example of a microtubule dysfunction:** Chediak-Higashi syndrome

1. **AR disease**
2. **defect in microtubule polymerization** → *Calchicine a drug used to treat gout, prevents microtubule polymerization*
3. **defective phagocytosis:** increased susceptibility to infections
4. **giant red inclusions in peripheral blood leukocytes:** represent giant lysosomes filled with enzymes that have never been released

**Genetic example of a membrane defect:** congenital spherocytosis

1. **AD disease**
2. **defect in spectrin in the cell membrane**
   A. results in RBCs with too little membrane
   B. spherocytes develop in peripheral blood
3. **extravascular hemolysis of spherocytes by splenic macrophages**

**Examples of intermediate filament defects:**

1. **Mallory bodies**—
   A. ubiquinated (marked for destruction by ubiquitin) *keratin* intermediate filaments
   B. microscopic feature of *alcoholic hepatitis*
2. **Lewy body**— ubiquinated neurofilaments from degenerated substantia nigra neurons in *Parkinson's disease*.
3. **neurofibrillary tangles**— ubiquinated neurofilaments in the brain in old age/Alzheimer's disease

**Labile cells:**
1. **contain stem cells**— >1.5% of cells are in the cell cycle at any one time
2. **examples**—
   A. bone marrow stem cells
   B. skin: stratum basalis
   C. intestine: base of the glands
3. **clinical significance**— most affected by radiation and S phase chemotherapy drugs due to the high rate of mitotic activity of labile cells

**Stable cells:**
1. **cells usually in Go (resting) phase**—
   A. must be **stimulated to enter the G1 phase**
      (1) hormones (estrogen)
      (2) growth factors (epidermal derived growth factor)
      (3) loss of parenchymal tissue (removal of liver tissue)
   B. <1.5% of the cells are in the cell cycle at any one time
2. **examples**—
   A. most parenchymal cells in organs:
      (1) liver
      (2) endothelial cells
   B. smooth muscle: not striated or cardiac cells
   C. astrocytes/other neuroglial cells
3. **clinical significance**— capacity to undergo hypertrophy and/or hyperplasia

**Permanent cells:**
1. **cells cannot enter the cell cycle**— permanently differentiated
2. **examples**—
   A. skeletal/cardiac muscle: can only hypertrophy
   B. neurons

**Cell cycle:**
1. **inactive cdk (cyclin-dependent kinase) is activated by cyclin D (see diagram)**—
   A. cyclin D is synthesized in the G1 phase of the cell cycle: key phase of the cycle
   B. G1 phase is the most variable phase
2. **Rb suppressor gene on chromosome 13 produces the unphosphorylated Rb protein**—
   A. Rb protein prevents the cell from moving from the G1 phase into the S phase: S phase functions include chromosome replication and organelle replication
   B. phosphorylation of the Rb protein by the active cyclin D/cdk complex: allows the cell to pass into the S phase and finish the cycle which includes the Gm phase (mitotic spindle synthesized) and the M phase (mitosis)
   C. inactivation of the Rb suppressor gene:
      (1) loss of the inhibitory effect of the Rb protein on the cell
      (2) cells constantly enter the S phase once they are phosphorylated
3. **p53 suppressor gene functions in cell cycle**—
   A. located on chromosome 17
   B. produces a protein product that **inhibits the active cyclin D/cdk complex**
      (1) prevents phosphorylation of the Rb protein
      (2) keeps cell in the G1 phase
      (3) allows cell to repair any defects in DNA ("guardian of the cell")
p53 suppressor gene inhibits (allows DNA repair in cell or cell undergoes apoptosis)

G1 phase

The only part of the cell cycle that can alter its time length

**G1 phase**

Rb suppressor gene → Rb → Rb phosphorylated → cyclin D degraded

inactive cdk +

cyclin D

cyclin D synthesized

hormone, growth factors

inactive cdk

inactive cdk

* cdk = cyclin-dependent kinase
* Rb (hypophosphorylated form) inhibits cell from going from G1 to S phase
* Rb phosphorylated form allows cell to go from G1 to S phase

Inactive cdk is activated by cyclin D, which is synthesized in the G1 phase of the cell cycle. The Rb suppressor gene on chromosome 13 produces the Rb protein, which inhibits a cell from moving from the G1 phase into the S phase of the cell cycle. When the Rb protein is phosphorylated by the active cyclin D/cdk complex, the cell passes into the S phase and finishes the cycle. The p53 suppressor gene located on chromosome 17 produces a product that inhibits the active cyclin D/cdk complex, hence preventing the phosphorylation of the Rb protein and keeping the cell in the G1 phase. Inactivation of the Rb suppressor gene results in the loss of the inhibitory effect of the Rb protein in keeping the cell from entering the S phase. Furthermore, inactivation of the p53 suppressor gene allows the active cyclin D/cdk complex to continually phosphorylate the Rb protein, which allows the cell to complete cell division. Inactivation of either the Rb or p53 suppressor gene leads to unrestricted cell growth and the potential for cancer.
(4) cells incapable of repair undergo apoptosis
C. inactivation of the p53 suppressor gene:-
(1) active cyclin D/cdk complex continually phosphorylates Rb proteins
(2) cells continually mitose
4. important concept-
A. inactivation of either the Rb or p53 suppressor gene
   (1) unrestricted cell growth
   (2) potential for cancer
B. see Neoplasia notes for additional discussion

Examples of growth alterations: 

1. atrophy–
   A. decrease in cell/tissue mass
   B. organ less weight
   C. capsular surface wrinkled
   D. less mitochondria than normal cell
   E. increased lipofuscin in cells
2. agenesis–
   A. anlage (primordial tissue) is absent
   B. e.g., renal agenesis
3. aplasia– anlage present but never develops
4. hypoplasia–
   A. anlage develops incompletely
   B. tissue present is histologically normal
5. hypertrophy– increased cell size
   (not due to hormone excess)
6. hyperplasia–
   A. increase in number of cells
   B. common in hormone excess states
   C. can progress to dysplasia and cancer if left unregulated
7. metaplasia– replacement of one adult cell type by another adult cell type
8. dysplasia–
   A. atypical hyperplasia with potential for evolving into cancer
   B. premalignant growth alteration

Examples of atrophy:
1. muscle in a cast– disuse of muscle leads to atrophy
2. thyroid gland in someone taking excess thyroid hormone– decrease in TSH from increase in T4 causes atrophy of thyroid
3. renal artery atherosclerosis–
   A. potential for secondary hypertension
   B. stimulation of renin-angiotensin-aldosterone system
4. compression atrophy of renal cortex by hydronephrosis
5. muscle atrophy in lower motor neuron disease
6. marasmus–
   A. tissue atrophy due to total calorie deprivation
   B. broomstick extremities
7. carotid artery atherosclerosis–
   A. cerebral atrophy
   B. site for atherosclerotic stroke
8. atrophy of pancreatic ducts and islet cells in cystic fibrosis (USMLE)–
   A. thick ductal secretions obstruct the lumen leading to glandular atrophy and fibrosis
B. fibrosis destroys islet cells

Clinical examples of predominantly hypertrophy:
1. left ventricular hypertrophy—
   A. causes due to increased afterload:
      (1) essential hypertension
      (2) aortic stenosis
   B. causes due to volume overload
   C. valvular insufficiencies: e.g., mitral or aortic valve insufficiency
2. skeletal muscle in weight training
3. removal of kidney and hypertrophy of remaining kidney (USMLE)

Clinical examples of predominantly hyperplasia:
1. hormone excess—
   A. unopposed estrogen: endometrial hyperplasia/cancer
   B. increased ACTH (e.g., pituitary adenoma): adrenal cortical hyperplasia
   C. increased dihydrotestosterone + estrogen: prostate hyperplasia
   D. prolactin-induced lactation:
      (1) normal finding in postpartum state
      (2) prolactinoma is benign neoplasm producing excess prolactin
   E. gynecomastia: excess estrogen develops male breast tissue
   F. acromegaly: excess growth hormone/insulin-like growth factor due to a pituitary adenoma secreting growth hormone
   G. RBC hyperplasia: erythropoietin stimulation by hypoxia
   H. secondary hyperparathyroidism: parathyroid gland hyperplasia due to hypocalcemia
2. gum hyperplasia—phenytoin therapy
3. persistent injury to tissue—e.g., regenerative nodules in cirrhosis due to chronic injury
4. psoriasis—hyperplasia of squamous epithelium
5. increased goblet cells in bronchial epithelium in smokers—example of metaplasia if goblet cells are found in terminal bronchioles

Clinical examples of equal hyperplasia/hypertrophy:
1. uterine smooth muscle hyperplasia/hypertrophy—pregnancy
2. iodine deficiency—goiter

Clinical examples of squamous metaplasia:
1. transformation zone of cervix in human papilloma virus (HPV) infections—
   A. mucous secreting columnar cells normally undergo squamous metaplasia to replace exocervical epithelium
   B. may progress to squamous dysplasia/cancer if HPV is present
2. bladder transitional epithelium in schistosomiasis—
   A. Schistosoma hematobium eggs in submucosal venous plexus cause mucosal squamous metaplasia
   B. may progress to dysplasia/cancer
3. true vocal cords/bronchial epithelium in smokers—
   A. epithelium is normally ciliated columnar epithelium
   B. carcinogens in cigarette smoke/alcohol irritate mucosa: may progress to dysplasia/cancer
4. cornea in vitamin A deficiency—
   A. cornea is normally cuboidal epithelium
   B. in vitamin A deficiency, it undergoes squamous metaplasia: vitamin A normally prevents squamous metaplasia
Clinical examples of glandular metaplasia:
1. mucous secreting cells/goblet cells in the distal esophagus in acid injury (gastroesophageal reflux disease)—
   A. normally squamous epithelium in distal esophagus
   B. acid injury due to gastric reflux causes glandular metaplasia: called Barrett’s esophagus
   C. adenocarcinoma of esophagus due to Barrett’s esophagus has replaced squamous cell carcinoma as the MC cancer of the esophagus
2. goblet cells/Paneth cells in pylorus/antrum in chronic atrophic gastritis due to *Helicobacter pylori*—
   A. goblet/Paneth cells are normally present in the small intestine
   B. cytokines released by *H. pylori* damage stomach mucosa and produce intestinal metaplasia: precursor of stomach adenocarcinoma

USMLE scenarios:
1. cyanosis not relieved by oxygen in a patient coming home from a camping trip in the Rocky Mountains—
   A. methemoglobinemia
   B. water in the mountains has nitrites that oxidize iron to ferric condition
2. antioxidant that prevents lipid peroxidation of cell membranes—vitamin E
3. USMLE pictures of coagulation necrosis—
   A. acute myocardial infarction
   B. hemorrhagic infarct of small bowel incarcerated in inguinal hernia sac in a weight lifter
4. glycogen depletion—electron micrograph: present in fed state and absent in fasting state
5. what happens to the other kidney if one is damaged or removed—undergoes compensatory hypertrophy
6. dysplasia—precursor to cancer
7. fatty change in the liver—alcohol MCC
8. first sign of tissue hypoxia in tissue—swelling due to inactivation of the Na+/K+ ATPase pump
9. picture of adrenal cortex and asks what part is atrophied in a patient on corticosteroids—
   A. fasciculata and reticularis are atrophied due to suppression of ACTH by the corticosteroids
   B. glomerulosa is normal:
      (1) where aldosterone is located
      (2) glomerulosa is stimulated by ATII not ACTH
10. growth alterations—see previous examples
11. enzyme markers of cell death—
    A. transaminases: hepatitis
    B. creatine kinase: muscle
    C. CK:MB: cardiac muscle
    D. amylase/lipase: acute pancreatitis
    E. lactate dehydrogenase:
       (1) malignant lymphoma
       (2) disseminated cancer
       (3) intravascular hemolysis
       (4) 1/2 flip in myocardial infarction
12. CNS infarct—liquefactive not coagulative necrosis
13. apoptosis—see previous discussion
14. free radicals—see previous discussion
15. antioxidants—see previous discussion
Questions used during Board Review:

Hyperplasia is primarily operative in which of the following growth alterations?
A. Appearance of the affected kidney in renovascular hypertension
B. Thickened bladder wall in a patient with urethral obstruction
C. Barrett's esophagus in a patient with gastroesophageal reflux
D. Enlarged left atrium in a patient with severe mitral stenosis
E. Galactorrhea in a woman with a prolactinoma

Which of the following disorders is an example of coagulation necrosis?
A. Lobar pneumonia in an alcoholic
B. Hepatic abscess in a patient with amebiasis
C. Pseudomembranous colitis in a patient on ampicillin
D. Diminished brain mass in a patient with Alzheimer's disease
E. Embolus to the superior mesenteric vein leading to bowel infarction

In which of the following diseases would you expect a low arterial PO2 and a low oxygen saturation (SaO2)?
A. Carbon monoxide poisoning
B. Iron deficiency anemia
C. Decreased cardiac output
D. Respiratory acidosis
E. Cyanide poisoning

Which of the following disorders is an example of metaplasia?
A. Increased goblet cells in the mainstem bronchus of a smoker
B. Squamous epithelium in the mainstem bronchus of a smoker
C. Proliferative endometrial glands in a woman on unopposed estrogen
D. Hyperkeratosis of the skin in a patient with psoriasis
E. Multinucleated giant cells in a granuloma
Inflammation/Repair

Latin terms for acute inflammation:

1. calor—
   A. heat
   B. histamine-dependent vasodilatation

2. rubor—
   A. redness
   B. histamine-dependent vasodilatation

3. tumor—
   A. tissue swelling
   B. histamine-dependent increase in vessel permeability in venules

4. dolor—
   A. pain
   B. due to prostaglandin E₂ and bradykinin

5. functio laesa—
   A. loss of function
   B. sum total of the effects of acute inflammation

Sequence of vascular events in acute inflammation:

1. vasodilatation—
   A. histamine-dependent
   B. increases blood flow/hydrostatic pressure

2. increased vessel permeability—
   A. histamine-dependent
   B. histamine receptors on endothelial cells in venules stimulated to contract leaving a bare basement membrane
   C. transudate initially moves into the interstitium
   D. lymphatics take up excess fluid

Sequence of cellular events in acute inflammation:

1. neutrophil margination—
   A. neutrophils pushed to periphery of the vessel
   B. due to adhesion molecule synthesis in neutrophils/endothelial cells

2. neutrophil adhesion to endothelial cells (pavementing)—
   A. adhesion molecules are CD₁₈/CD₁₈ complexes of glycoprotein and β1 and β2 integrins
   B. endothelial cell-derived adhesion molecules:
      (1) leukocyte adhesion molecules (ELAM)
      (2) intercellular adhesion molecules (ICAM)
      (3) chemical mediators involved for synthesis of endothelial-derived adhesion molecules are interleukin (IL)-1 and tumor necrosis factor
   C. neutrophil adhesion molecule synthesis: C₅a and LTB₄ mediated

3. emigration of neutrophils—
   A. neutrophils emit collagenase and destroy type IV collagen in bare basement membrane
   B. protein/cell rich fluid accumulates in interstitium (called exudate)

4. directed chemotaxis—
   A. receptor-mediated
   B. chemical mediators:
      (1) C₅a
      (2) LTB₄
      (3) bacterial products
5. phagocytosis—
   A. receptor-mediated opsonization of bacteria by IgG and C3b enhances neutrophil/
      monocyte/macrophage phagocytosis, all of which have Fc receptors for IgG and C3b:
      (1) primary opsonizing agents IgG/C3b
      (2) nonspecific opsonizing agents: C-reactive protein, fibrinogen, fibronectin
   B. bacteria internalized by leukocytes into vacuoles (phagosomes), which become filled
      with lysosomal enzymes (phagolysosomes)

6. bacteriocidal mechanisms in leukocytes—
   A. neutrophils and monocytes have three systems:
      (1) O₂-dependent myeloperoxidase (MPO) system (most potent system)
      (2) O₂-dependent free radicals
      (3) lysosomal enzymes
   B. macrophages only have the latter two systems

respiratory burst mechanism in neutrophils/monocytes—
1. part of the O₂-dependent myeloperoxidase (MPO) bacteriocidal system
2. NADPH oxidase—
   A. enzyme located in the membrane of neutrophils and monocytes
   B. uses NADPH derived from the hexose monophosphate shunt as a cofactor
   C. converts molecular oxygen into superoxide free radicals: energy given off in this reaction
      is called the respiratory burst
3. superoxide FRs—
   A. located in the phagolysosomes
   B. converted by superoxide dismutase into peroxide
4. myeloperoxidase (MPO)— combines peroxide with chloride anions to form bleach, which
   destroys bacteria
5. NBT (nitroblue tetrazolium test) dye test—
   A. evaluates the integrity of the respiratory burst
   B. neutrophils convert a colorless dye into a colored dye if the respiratory burst system is
      intact

Chronic granulomatous disease of childhood:
1. SXR disease— microbicidal defect
2. absent NADPH oxidase—
   A. absent respiratory burst: negative NBT dye test
   B. no peroxide is produced in phagolysosome
   C. MPO and chloride anions are present in phagolysosomes
3. patients cannot kill catalase positive S. aureus—
   A. S. aureus releases peroxide, which is all the leukocyte needs to synthesize bleach
   B. catalase is released by the bacteria, which neutralizes the peroxide
4. leukocytes can kill catalase negative streptococci— peroxide released by streptococci is used
   by MPO to make bleach and kill the bacteria

Summary of chemical mediators in acute inflammation:
1. histamine—
   A. overall most important mediator
   B. released/synthesized by basophils/mast cells
   C. vasodilator/increases vessel permeability
   D. important in anaphylactic shock
   E. produces the "wheat and flare reaction"
2. **serotonin**—
   A. released/synthesized by basophils/mast cells/platelets
   B. synthesized from tryptophan
   C. functions:
      (1) vasodilator (can also be a vasoconstrictor)/increases vessel permeability
      (2) neurotransmitter
      (3) synthesized from tryptophan
   D. important in carcinoid syndrome:
      (1) flushing
      (2) increases collagen synthesis
      (3) diarrhea
      (4) metabolized in the liver into 5-hydroxyindoleacetic acid

3. **C3a/C5a**—
   A. anaphylatoxins
   B. directly stimulate histamine release from basophils/mast cells
   C. important in tissue swelling and shock

4. **C3b**—
   A. opsonizing agent
   B. neutrophils/monocytes/macrophages have receptors for C3b

5. **C5a**—
   A. adhesion molecule synthesis on neutrophils
   B. chemotactic agent
   C. anaphylatoxin

6. **bradykinin**—
   A. vasodilator/increases vessel permeability
   B. bronchoconstrictor
   C. pain (dolor) of acute inflammation
   D. cough and angioedema with ACE inhibitors

7. **prostaglandins in general**—
   A. derived from arachidonic acid (called eicosanoids):
      (1) released from phospholipids in cell membranes by activation of phospholipase A2
      (2) synthesized from linoleic acid
   B. most prostaglandins are vasodilators/increase vessel permeability

8. **PGH₂ products**—
   A. thromboxane A₂ (TXA₂):
      (1) PGH₂ is converted by platelet-derived thromboxane synthase into TXA₂
      (2) product of arachidonic acid metabolism
      (3) platelet aggregator
      (4) vasoconstrictor/bronchoconstrictor (USMLE)
      (5) TXB₂ is end-product of its metabolism: no biologic function
   B. prostacyclin (PGI₂):
      (1) PGH₂ is converted by endothelial cell-derived prostacyclin synthase into PGI₂
      (2) prostacyclin synthase is not inhibited to any significant degree by aspirin and NSAIDs
      (3) inhibits platelet aggregation
      (4) vasodilator
   C. PGE₂:
      (1) makes skin hypersensitive to pain
      (2) vasodilator in kidneys (blocked by NSAIDs but not acetaminophen)
      (3) increases renal blood flow (counteracted by angiotensin II)
4. decreases renal reabsorption of sodium
5. increases gastric mucosal blood flow (important in generation of the mucosal barrier)
6. activates osteoclasts (important in producing hypercalcemia in malignancy)
7. important in fever production (IL-1 stimulates its synthesis in the anterior hypothalamus)
8. inhibits platelet aggregation/IL-1 and IL-2 leukocyte aggregation

D. PGF₂α:
   1. constricts uterine muscles (cause of primary dysmenorrhea)
   2. vasoconstricts/bronchoconstricts

E. PGD₂:
   vasodilator/increased vessel permeability

9. LTB₄:
   A. derived from arachidonic acid
   B. adhesion molecule synthesis on neutrophils
   C. chemotactic agent

10. LTC₄:
    A. derived from arachidonic acid
    B. bronchoconstrictor/vasoconstrictors
    C. important in asthma

11. nitric oxide:
    A. endothelial cell-derived
    B. vasodilator/increase vessel permeability
    C. important in shock

12. endothelin:
    A. potent vasoconstrictor in endothelial cells
    B. important in shock

13. interleukin (IL)-1:
    A. fever: stimulates prostaglandin E₂ synthesis in anterior hypothalamus
    B. B cell stimulation to synthesize immunoglobulins
    C. activates osteoclasts:
        1. called osteoclast activating factor
        2. inhibited by estrogen in women and testosterone in men
        3. release from osteoblasts is stimulated by parathormone
        4. present in plasma cells (cause of lytic bone lesions in multiple myeloma)
    D. increases adhesion molecule synthesis by endothelial cells
    E. increases liver synthesis of acute phase reactants:
        1. coagulation factors (fibrinogen, V, VIII)
        2. C-reactive protein

14. Hageman factor XII:
    A. activates intrinsic coagulation system
    B. activates plasminogen in fibrinolytic system
    C. activates kinin system: produces bradykinin
    D. important in the pathogenesis of disseminated intravascular coagulation

Essential fatty acids (FAs):
1. linoleic acid (see below) – C₁₈:₂ω₆
2. α-linolenic (see below) – C₁₈:₃ω₃
3. both are required in the diet – cannot be synthesized in the body
4. functions:
   A. synthesis of biologically active FAs
B. synthesis of eicosanoids—e.g., arachidonic acid (polyunsaturated C20 FA) is the precursor of eicosanoids, which include:
   1. prostaglandins
   2. leukotrienes
   3. thromboxanes

**Importance of linoleic acid:**
1. precursor of ω-6 FAs—
   A. linoleic acid produces arachidonic acid (C20)
   B. arachidonic acid is the precursor for ω-6 FAs (eicosanoids)
2. eicosanoids derived from ω-6—
   A. PGE1 and E2
   B. thromboxane A1 and A2
3. sources—
   A. corn oil
   B. safflower oil
   C. cottonseed oil
   D. soybean oil
4. not cardioprotective

**Importance of linolenic acid:**
1. precursor of ω-3 FAs—
   A. PGE3
   B. PGI2
   C. TXA3
2. sources—
   A. fish oils:
      (1) eicosapentaenoic acid (C20:5ω3, precursor of ω-3 FAs)
      (2) docosahexaenoic acid (C22:6ω3)
   B. soybean oil
   C. canola oil: best oil
   D. walnuts
   E. wheat germ
3. cardioprotective—
   A. greatest effect on lowering triglycerides (not cholesterol)
   B. inhibit platelet aggregation: e.g., via the action of PGI2
   C. produce anti-inflammatory prostaglandins
   D. protect myocardium: less damage to myocardial tissue in infarctions

**Enzymes involved in arachidonic acid metabolism:**
1. cyclooxygenase—
   A. inhibited by aspirin and other NSAIDs
   B. prostaglandins and thromboxanes produced
2. lipoxygenase—leukotrienes produced

**γ-Interferon:**
1. produced by CD4 T helper cells and NK cells
2. functions—
   A. activates macrophages to kill microbial pathogens
   B. antiviral activity
   C. induces class I and II antigens
   D. increases production of IL-2 and IL-12 by CD4-T helper cells
Interleukin (IL)-2:
1. produced by CD4 T helper cells
2. functions—
   A. primarily a T cell growth factor
   B. promotes B cell/NK cell proliferation

IL-3:
1. produced by T cells and thymic epithelial cells
2. function—
   A. stimulates pluripotent stem cell marrow
   B. increases hematopoiesis

IL-4:
1. produced by activated T cells
2. functions—
   A. mainly promotes growth of B cells
   B. switch of IgM synthesis in B cells to IgE synthesis in type I hypersensitivity reactions

IL-5:
1. produced by T cells and mast cells
2. functions—
   A. promotes growth of eosinophils
   B. promotes IgE synthesis

IL-6:
1. produced by T cells, macrophages, endothelial cells, fibroblasts, epithelial cells
2. functions— primarily stimulates synthesis of acute phase reactants in the liver in acute inflammation

IL-12:
1. produced by macrophages
2. functions—
   A. promotes growth of CD4 T cells
   B. promotes differentiation of CD4 T helper cells into Th1 and Th2 classes
      (1) important in granuloma formation
      (2) important in production of memory T cells
   C. promotes production of γ-interferon
   D. enhances NK activity

Granulocyte colony stimulating factor (G-CSF):
1. produced by fibroblasts
2. function— stimulates neutrophil development in the bone marrow

Granulocyte/macrophage colony stimulating factor (GM-CSF):
1. produced by macrophages and T cells
2. function— stimulates neutrophil and monocyte development in the bone marrow

Factors increasing and decreasing adhesion molecule synthesis:
1. increase synthesis—
   A. C5a
   B. LTB4
   C. endotoxins: causes severe peripheral blood neutropenia
   D. IL-1
   E. tumor necrosis factor (TNF)
2. decrease synthesis—
   A. catecholamines: released by stress
   B. corticosteroids
   C. lithium

Congenital adhesion molecule (β2-integrins) defect (USMLE):
1. failure of the umbilical cord to separate in newborns
2. no adhesion of neutrophils to the endothelial cells
3. no inflammatory cells in the umbilical stump

Corticosteroid effects in acute inflammation:
1. block phospholipase A2—decreased synthesis of prostaglandins and leukotrienes
2. decreases leukocyte adhesion synthesis—
   A. marginating pool (normally 50% of the peripheral blood leukocyte pool) is now circulating
   B. absolute neutrophilic leukocytosis
3. decreases peripheral blood lymphocytes—
   A. lymphopenia
   B. decreases synthesis of antibodies
4. decreases peripheral blood eosinophils—eosinopenia
5. stabilizes the basophil/mast cell membrane—
   A. prevents release reaction of preformed mediators
   B. important in Rx of asthma

Neutrophils:
1. key cell in—
   A. acute inflammation
   B. immunocomplex reactions:
      (1) activation of complement by immunocomplexes increases C5a
      (2) C5a is chemotactic to neutrophils
      (3) neutrophils damage the tissue wherever immunocomplexes are deposited
2. contains receptors for IgG/C3b
3. bone marrow mitotic pool (can divide)—
   A. myeloblasts
   B. progranulocytes
   C. myelocytes
4. bone marrow post-mitotic pool (can no longer divide)—
   A. metamyelocytes
   B. band neutrophils
   C. segmented neutrophil
5. peripheral blood pools—
   A. marginating pool:
      (1) adherent to endothelium
      (2) ~50% of peripheral blood pool
      (3) >50% in African-Americans (reason for neutropenia in African-Americans)
      (4) become part of circulating pool when adhesion molecule synthesis is decreased
   B. circulating pool:
      (1) measured in CBC
      (2) ~50% in non-African-American populations
      (3) decreases if adhesion molecule synthesis is increased
Monocytes/macrophages:
1. key cell in chronic inflammation
2. receptors for IgG/C3b: important in extravascular removal of RBCs, leukocytes, platelets
3. monocytes become macrophages—
   A. fixed macrophages:
      (1) Kupffer cells
      (2) macrophages in splenic red pulp
      (3) macrophages outside sinusoids in the bone marrow
   B. wandering:
      (1) alveolar
      (2) microglial cells in CNS
4. functions—
   A. process antigen
   B. scavenger cells
   C. enhance host immunologic response: secrete cytokines like IL-1, IL-12, TNF
   D. secrete growth factors
   E. secrete nitric oxide in endotoxic shock

Lymphocytes: primary inflammatory cell in—
1. viral infections
2. type IV reactions
3. pertussis infections

Plasma cells:
1. derive from activated B lymphocytes
2. functions—
   A. antibody production
   B. IgM produced on first antigen exposure in acute inflammation:
      (1) IgM is more potent than IgG in activation of the classical complement pathway, hence ensuring complement components for acute inflammatory process
      (2) IgG is synthesized after 10–14 d (isotype switching)
      (3) IgG is the main immunoglobulin of chronic inflammation
3. morphology—
   A. well-developed rough endoplasmic reticulum: easily identified on electron microscopy
   B. bright blue cytoplasmic staining with Wright-Giemsa
   C. cartwheel appearing nuclear chromatin pattern,
   D. peripheral nucleus

Natural killer cells:
1. key cell in—
   A. antibody-dependent type II reactions
   B. graft versus host reactions
   C. killing of tumor cells/virally infected cells
2. large granular lymphocytes— noted in the peripheral blood, particularly in cancer patients

Platelets:
1. derived from megakaryocytes
   A. bud off of the cytoplasm
   B. ~5000 platelets per megakaryocyte
2. functions—
   A. platelet aggregation:
      (1) TXA₂ (synthesized)
(2) ADP (released from platelet granules)
B. growth factors for wound healing
C. contain von Willebrand factor (VWF) for platelet adhesion: adhesion molecule of the platelet

Endothelial cells: synthetic functions
1. prostacyclin (PGI₂)
2. von Willebrand factor (VWF): platelet adhesion
3. nitric oxide: vasodilator
4. endothelin: vasoconstrictor
5. tissue thromboplastin: activates factor VII in the extrinsic system

Mast cells/basophils:
1. function—main effector cell for type I hypersensitivity reactions
2. activated by—
   A. histamine
   B. specific allergens interacting with IgE antibodies on their surface
   C. C3a/C5a (anaphylatoxins)
   D. temperature changes
   E. pressure
3. preformed mediators—
   A. histamine
   B. serotonin
   C. heparin
   D. chemotactic factors: eosinophil chemotactic factor
4. late phase reaction—synthesis of the following chemicals:
   A. prostaglandins
   B. leukotrienes \( \left(LTC_4, LTB_4\right) \)
5. early and late phase release reaction is prevented by—
   A. Chromelin sodium
   B. corticosteroids

Eosinophils:
1. functions—
   A. neutralize histamine/leukotrienes
   B. destruction of helminths:
      (1) type II (not type I) hypersensitivity reaction
      (2) eosinophils have Fc receptors for IgE
      (3) receptors interact with IgE coating the surface of invasive helminths
      (4) antibody dependent cytotoxicity reaction causes the release of major basic protein→kills helminth
2. granules contain crystalline material—become Charcot-Leyden crystals in sputum, particularly in asthmatics
3. chemical mediators—
   A. major basic protein: kills invasive helminths
   B. histaminase
   C. arylsulfatase: neutralize leukotrienes
4. eosinophilia—
   A. type I hypersensitivity reactions:
      (1) allergic rhinitis
      (2) bronchial asthma
      (3) drug allergies

Causes of Eosinophilia: NAACP

Neoplastic
Asthma
Allergic Processes
Collagen Vase Diseases
Parasites (invasive helminths)
(4) response to invasive helminthic infections (not the mechanism of killing helminths, excludes pinworms, which are not invasive)

B. miscellaneous:
   (1) Hodgkin's disease
   (2) polyarteritis nodosa
   (3) Churg-Strauss
   (4) lung hypereosinophilia syndromes
   (5) hypocortisolism

5. eosinopenia—
   A. corticosteroids
   B. Cushing's syndrome

**Important cluster designation (CD) types for USMLE:**

1. CD1—
   A. histiocytes (Langerhans cells)
   B. dendritic cells
   C. used in a histiocytosis X question on USMLE

2. CD3—
   A. T cell antigen recognition site
   B. OKT3 monoclonal antibody is an immunosuppressive agent that blocks this site

3. CD4—
   A. helper T cell marker
   B. gp 120 antigens in HIV-1 and 2 bind to this molecule

4. CD8— marker for cytotoxic and suppressor T cells

5. CD15 and CD30— markers for Reed-Sternberg cell in Hodgkin's disease

6. CD21— receptor for EBV on B cells

7. CD45—
   A. leukocyte marker
   B. leukocyte common antigen
   C. very useful in surgical pathology in separating leukocyte from epithelial malignancies

8. CD56— NK cell marker

**Role of fever in inflammation:**

1. right shifts oxygen dissociation curve (ODC) — more O2 available for O2-dependent MPO system

2. provides a hostile environment for bacterial/viral reproduction

**Types of acute inflammation:**

1. suppurative—
   A. e.g., abscess
   B. *Staphylococcus aureus* contains *coagulase*: cleaves fibrinogen into fibrin and traps bacteria/neutrophils

2. cellulitis—
   A. commonly (not exclusively) due to streptococcus
   B. bacteria contain hyaluronidase, which allows bacteria to spread through subcutaneous tissue
   C. examples include: erysipelas and impetigo

3. pseudomembranous—
   A. toxin-induced damage of tissue
   B. not invasive infection
   C. examples:
      (1) diphtheria

*Footnotes:

- Osteomyelitis → occurs in metaphysis of bone (the most vascularized part of bone).
- Septic arthritis is a purport.
- Staphylococcus aureus, usually occurs in the setting of *pneumonia* and *Sickle Cell Anemia*.
- Blood culture will not be positive.
- Suppurative = pus.
- Diphtheria toxin inhibits β-oxidation of fatty acids, thus doesn't get ATP.
(2) *Clostridium difficile* in pseudomembranous colitis

4. **fibrinous**-
   A. protein-rich fluid that has a "bread and butter" appearance on serosal membranes
   B. e.g., pericarditis

5. **serous**-
   A. protein-poor fluid
   B. e.g., blister fluid in second degree burn

6. **phlegmoneous (catarrhal)**-
   A. excess mucous secretions
   B. e.g., common cold

Types of wound healing:
1. **primary intention**—wound edges are apposed
2. **secondary intention**—
   A. wound is left open
   B. myofibroblasts are important in closing wound
   C. takes longer to heal

Sequence in primary intention healing of wound:
1. **first day**—
   A. clot develops in wound
   B. neutrophils infiltrate

2. **second day**—
   A. squamous cells from basal cell layers of apposing skin margins seal off the wound after 48 hs
   B. macrophages emigrate into wound

3. **third day**—
   A. beginning of granulation tissue formation:
      (1) angiogenesis due to basic fibroblast growth factor
      (2) fibroblasts lay down type III collagen
   B. fibronectin is key chemical mediator:
      (1) derived from macrophages/fibroblasts/endothelial cells
      (2) chemotactic to fibroblasts/macrophages
      (3) opsonizing agent
      (4) adhesion agent

4. **4th–6th days**—granulation tissue formation peaks
5. **7–10 days**—tensile strength 10% of normal
6. **weeks–months**—
   A. collagenization:
      (1) type III collagen replaced by type I to increase tensile strength
      (2) collagenases important in remodeling (zinc is a cofactor)
   B. maximum tensile strength of ~80% after 3 mths

Sequence of collagen synthesis:
1. **initial synthesis in fibroblasts**—
   A. formation of polypeptide pro-α1 and pro-α2 chains
   B. hydroxylation of proline and lysine by vitamin C: site for cross-linking outside the fibroblast
   C. glycosylation of lysine residues with glucose and galactose
   D. assembly of 3 pro-α chains-inter and intra chain disulfide bonds at C terminal extensions
   E. formation of triple helix

Patient presents to physician with a foul-smelling, purulent wound, indicating a *clostridial infection*. Poor wound healing, and a rash on the face, indicates a zinc deficiency.
F. procollagen molecules translocated to Golgi apparatus for packaging and secretion

2. **extracellular synthesis of collagen**
   A. procollagen molecule secreted into extracellular space
   B. procollagen peptidases cleave N-terminal and C-terminal propeptides to release triple helix
   C. collagen molecules form fibrils
   D. cross-linking of collagen fibrils to increase tensile strength: lysyl oxidase (copper is a cofactor) is a cross-linking enzyme

**Important collagen types:**

1. **type I**—
   A. highest tensile strength
   B. tissues:
      1. bone (90%)
      2. skin (80%)
      3. tendons

2. **type II**— cartilage

3. **type III**—
   A. initial type in wound repair
   B. skin (10%)
   C. blood vessels

4. **type IV**— basement membrane

5. **type IX**— cartilage

6. **type X**— epiphyseal plate (picture of bone in USMLE)

**Key factors interfering with wound healing:**

1. **infection**—
   A. most important
   B. *Staphylococcus aureus* MC pathogen

2. **tissue hypoxia**

3. **malnutrition**

4. **zinc deficiency**— cofactor in collagenase involved in wound remodeling

5. **vitamin C deficiency**—
   A. no hydroxylation of proline and lysine
   B. hydroxylation sites are where cross-bridges attach to form strong collagen bundles
   C. structurally weak collagen in scurvy

6. **genetic disorders**—
   A. Marfan's: defect in fibrillin
   B. Ehlers-Danlos: defects in collagen

**Keloid:**

1. **hypertrophic scar tissue**—
   A. resembles a tumor
   B. contains type III collagen

2. **predisposition to squamous cancer**— particularly if due to third degree burns

**Characteristics of chronic inflammation:**

1. **pathogenesis**—
   A. previous acute inflammation
   B. de novo:
      1. granulomatous inflammation
      2. autoimmune disease
2. cell types—
   A. monocytes/macrophages
   B. lymphocytes
   C. plasma cells
   D. fibroblasts
   E. endothelial cells

3. IgG is the predominant immunoglobulin—polyclonal peak in γ-globulin region in a protein electrophoresis

4. complications of chronic inflammation—
   A. production of serum associated amyloid (SAA) protein by liver: secondary/reactive amyloidosis
   B. excess fibrous tissue deposition: e.g., fibrosis in liver with formation of regenerative nodules (cirrhosis)

Recognition of a granuloma (USMLE picture):
1. histology—
   A. well-circumscribed
   B. red
   C. contain multinucleated giant cells
2. usually a type IV hypersensitivity reaction—
   A. cell-mediated immunity
   B. CD4 T helper cell and macrophage are main cells

Formation of TB granuloma:
1. phagocytosis of TB by alveolar macrophages
2. systemic lymphohematogenous spread of macrophages with bacteria—
   A. macrophages begin processing TB antigen
   B. no systemic infection
3. macrophage interacts with CD4 T helper cell via class II antigen sites—
   A. macrophage release of IL-12
   B. CD4 T cell differentiates into Th1 class cells:
      1. retain memory of encounter
      2. important in PPD reaction and reactivation TB
4. macrophages secrete IL-1—
   A. augments T cell proliferation by causing IL-2 release from CD4 T helper cells
   B. produces fever
5. CD4 T helper cells secrete cytokines—
   A. γ-interferon:
      1. activates macrophages to kill TB
      2. PPD becomes positive
      3. lipid from killed bacteria is responsible for caseous necrosis
      4. activated macrophages are called epithelioid cell
   B. macrophage inhibitory factor: keeps macrophages together to form discreet granulomas
6. macrophages fuse into multinucleated giant cells—best marker for granulomas
7. PPD reaction—
   A. injection of purified protein derivative (PPD) into skin
   B. Langerhans cells (histiocytes of the skin) phagocytose and process the PPD antigen: present antigen to previously sensitized Th1 CD4 cells
   C. reactivated Th1 CD4 cells locally release cytokines into tissue leading to redness and induration

- Immune suppressed: 5mm
- High risk group: 10mm
- Average person: 15mm
Fistula versus sinus:
1. fistula—
   A. communication between two hollow structures
   B. MC fistula is colovesical fistula (colon with bladder) due to diverticulitis
2. sinus—
   A. tract leading to skin surface
   B. common with skin abscesses due to S. aureus and Actinomyces infections

Liver reaction to injury:
1. stable tissue in G0 phase enters cell cycle—
   A. regeneration of hepatocytes
   B. persistent injury causes regenerative nodules to form
2. scar tissue formation— in alcoholics, an acetaldehyde-protein complex stimulates Ito cells
   (normally stores retinoic acid) to synthesize collagen

Cardiac muscle reaction to injury: permanent tissue, hence it is replaced by non-contractile scar tissue

Kidney reaction to injury:
1. stable tissue enters cell cycle—
   A. renal cortex responds better to injury than medulla: receives 90% of the blood versus
      only 10% in the medulla
   B. renal tubular cells regenerate only if the basement membrane is intact:
      (1) reason why nephrotoxic damage is more likely to recover than ischemic damage
      (2) in ischemic damage there is disruption of the basement membrane
2. thick ascending limb—
   A. *most susceptible part of nephron for hypoxia *
   B. where the Na⁺/K⁺/2Cl⁻ co-transport pump is located (USMLE)

Lung reaction to injury: type II pneumocyte is key repair cell—
1. replaces damaged type I pneumocytes
2. synthesizes surfactant—
   A. lowers surface tension to keep airways open on expiration
   B. surfactant is present in lamellar bodies (look like whorled-bodies on electron microscopy)
3. other names for surfactant—
   A. lecithin
   B. phosphatidyl choline
   C. phosphatidyl glycerol

Central nervous system reaction to injury:
1. astrocyte is analogous to the fibroblast
2. CNS response to injury is called gliosis—
   A. gliosis is primarily a proliferation of astrocytes
   B. protoplasmic processes offer some structural support
   C. microglial cells (macrophages) are scavenger cells in the repair process

Peripheral nerve reaction to injury (USMLE): undergoes wallerian degeneration—
1. distal degeneration of axon and myelin sheath and proximal degeneration up to the
   nearest internode
2. macrophages/Schwann cells phagocytose axonal/myelin debris
3. muscle undergoes atrophy in ~15 d
4. nerve cell body undergoes central chromatolysis—
A. swells
B. Nissl substance disappears centrally
C. nucleus peripheralized
5. Schwann cells proliferate and enlarge in distal stump
6. axonal sprouts develop in proximal stump and extend distally using Schwann cells for guidance
7. regenerated axon grows 2–3 mm/d
8. axon becomes remyelinated
9. muscle eventually reinnervated

Bone healing:
1. hematoma organization (procallus) at fracture site
2. conversion of procallus into fibrocartilaginous callus
3. fibrocartilaginous callus replaced by mature bone—bone remolds along lines of stress
4. factors interfering with bone healing—
   A. not properly aligned
   B. infection
   C. not immobilized properly
   D. inadequate blood supply

Femoral neck fracture:
1. bleeds into the capsule
2. may compromise medial femoral circumflex artery (USMLE)—may lead to avascular necrosis
3. posterior dislocations are most dangerous

Erythrocyte sedimentation rate (ESR):
1. measure of rate of settling of RBCs in a vertical tube in mm/h
2. RBC and plasma factors are responsible for ESR—
   A. aggregation of RBCs increases settling:
      (1) agglutination (clumping) of RBCs is due to increased IgM (e.g., cold agglutinins) or cold reacting globulins called cryoglobulins
      (2) rouleaux (stack of coins) is due to increase in fibrinogen and/or γ-globulins
   B. abnormally shaped RBCs (e.g., sickle cells) do not settle
   C. too many RBCs (e.g., polycythemia) interferes with settling
   D. anemia enhances settling
3. ESR increased—
   A. acute/chronic inflammation
   B. monoclonal gammopathies: e.g., multiple myeloma
   C. best initial screen for temporal arteritis:
      (1) if normal, temporal arteritis unlikely
      (2) if increased, start corticosteroids
   D. anemia
4. low ESR—
   A. sickle cell anemia
   B. polycythemia

Lab findings in acute bacterial infections:
1. absolute neutrophilic leukocytosis
2. left shift—
   A. >10% band neutrophils or
   B. presence of any neutrophil less mature than a band
3. **toxic granulation**— prominence of azurophilic granules containing myeloperoxidase (MPO)
4. **Dohle bodies**— dull gray inclusions representing dilated endoplasmic reticulum

**Prealbumin (transthyretin):**
1. **function**— binds thyroxine/retinoic acid (vitamin A, called retinol-binding protein)
2. **clinical**—
   A. transthyretin is an indicator of protein status: short half-life of 1–2 d
   B. converted into amyloid in familial, senile, and cardiac amyloidosis
   C. retinol-binding protein:
      (1) most sensitive indicator of visceral protein mass
      (2) 12 h half-life bound to transthyretin and only 3.5 h half-life if free

**Albumin:**
1. **functions**—
   A. binding protein for:
      (1) calcium/magnesium
      (2) drugs
      (3) unconjugated bilirubin
      (4) free fatty acids
   B. 80% of oncotic pressure
2. **clinical**—
   A. hypoalbuminemia due to:
      (1) chronic liver disease (MCC)
      (2) malnutrition
      (3) nephrotic syndrome
      (4) GI loss (malabsorption)
   B. when albumins binding capacity is exceeded:
      (1) drugs displaced leading to drug toxicity
      (2) unconjugated bilirubin displaced in newborns resulting in kernicterus
   C. marker of protein status: long half-life of 20 days limits its usefulness
   D. marker of severe liver injury

**Alpha_1 antitrypsin (AAT):**
1. **function**— antiprotease:
   A. serine protease inhibitor
   B. inhibits elastases released by neutrophils
2. **clinical**—
   A. acquired deficiency in cigarette smokers: smoke denatures AAT
   B. genetic deficiency:
      (1) AR disease
      (2) newborn cirrhosis (problem with secretion of AAT by hepatocytes)
      (3) panacinar lower lobe emphysema (decreased synthesis of AAT)
   C. marker for hepatocellular carcinoma

**Haptoglobin:**
1. **synthesized in liver**
2. **binds free hemoglobin (Hb)**— so called "suicide" protein
3. **low in intravascular hemolysis**— macrophages remove/destroy haptoglobin-Hb complex

**Transferrin:**
1. **function**—
   A. synthesized in liver
B. binds iron and delivers it to developing normoblasts in the bone marrow for Hb synthesis/storage

2. **clinical**
   A. corresponds with total iron binding capacity (TIBC):
      (1) low/absent iron stores in bone marrow (e.g., iron deficiency) result in increased liver synthesis of transferrin (increased TIBC)
      (2) increased iron stores (e.g., anemia chronic disease, iron overload states) result in decreased transferrin synthesis (decreased TIBC),
   B. excellent marker of protein status: short half-life of 10 d

<table>
<thead>
<tr>
<th>Increased iron stores</th>
<th>Decreased iron stores</th>
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<tr>
<td>High TIBC</td>
<td>Low TIBC</td>
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**Immunoglobulin G:**

1. **functions**
   A. 80% of total γ-globulins
   B. opsonin
   C. warm-reacting antibodies
   D. transplacental transfer of antibodies protects fetus: any IgG antibodies in newborn are maternal in origin: e.g., HIV antibodies
   E. activates the classical complement pathway

2. **clinical**
   A. causes of hypergammaglobulinemia:
      (1) chronic inflammation (called polyclonal gammopathy on a serum protein electrophoresis)
      (2) monoclonal gammopathies (e.g., multiple myeloma, called monoclonal gammopathy on a serum protein electrophoresis)
   B. causes of a hypogammaglobulinemia:
      (1) B cell deficiency disorders (e.g., Bruton’s agammaglobulinemia)
      (2) nephrotic syndrome (lost in the urine)
      (3) chronic lymphocytic leukemia (neoplastic B cells cannot differentiate into plasma cells)

**Immunoglobulin A:**

1. **function**—important in mucosal defenses due to its secretory IgA component
2. **clinical**—MC genetic immune deficiency:
   A. sinopulmonary infections
   B. malabsorption
   C. allergies
   D. GI parasitic infections (e.g., giardiasis)

**Immunoglobulin M:**

1. **function**
   A. largest immunoglobulin (Ig):
      (1) pentamer with 10 antigen recognition sites
      (2) μ heavy chain is antigen recognition site on B cells
   B. most potent activator of classical complement pathway
2. **Clinical**—
   A. synthesized shortly after birth: increased IgM at birth indicates a congenital infection
   B. first antibody produced in acute infections
   C. monoclonal increase in Waldenstrom's macroglobulinemia
   D. increased in primary biliary cirrhosis
   E. cold-reacting antibodies/globulins:
      (1) cold autoimmune hemolytic anemias (intravascular hemolysis, RBC agglutination)
      (2) cold agglutinins (Mycoplasma pneumoniae infections)
      (3) cryoglobulins (produce Raynaud's phenomenon): do not contain IgM

**Immunoglobulin D**: heavy chain also antigen receptor on B cells

**Immunoglobulin E**: reaginic antibody in type I reactions

**C reactive protein**:
   1. functions—
      A. activates complement
      B. opsonin
   2. clinical— excellent marker for bacterial (increased) versus viral infections (normal)

**Questions used during the board review:**

**A** 4-year-old child with recurrent *Staphylococcus aureus* infections and an absent respiratory burst
   MOST LIKELY has a/an...
   A. defect in spectrin in the cell membrane
   B. defect in microtubule polymerization
   C. deficiency of IgG gamma globulins
   D. deficiency of NADPH oxidase
   E. deficiency of myeloperoxidase

**B**
Which of the following is MOST responsible for the anti-inflammatory activity of corticosteroids?
   A. Increased leukocyte adhesion to endothelial cells
   B. Inhibition of phospholipase A2
   C. Destruction of eosinophils
   D. Inhibition of cyclooxygenase
   E. Inhibition of lipoxygenase

**Items 3–5**
   A. Cellulitis
   B. Suppurative inflammation
   C. Fibrinous inflammation
   D. Pseudomembranous inflammation
   E. Granulomatous inflammation

**A** 52-year-old man with chronic renal failure has chest pain and a scratchy 3 component sound heard over the anterior chest
   answer: C

**A** febrile 8-year-old child, who has not received any immunizations, has a grayish-white exudate in the oropharynx and prominent cervical lymphadenopathy
   answer: D
A febrile 3 year old child has a diffuse, raised, hot red area of inflammation extending around the right periorbital tissue leading to swelling and closure of the eye.

Answer: A

A newborn child has failure of separation of the umbilical cord. Histologic sections of the surgically removed cord reveal an absence of neutrophil margination and emigration into the interstitial tissue. The clinical and histologic findings in this case are MOST CLOSELY associated with a defect in...

A. activation of the complement system
B. microtubule polymerization
C. the respiratory burst mechanism
D. an adhesion molecule in neutrophils
E. the production of myeloperoxidase

D

Items 7–9

A. Neutrophils
B. Macrophages
C. Eosinophils
D. Mast cells
E. Plasma cells

They represent the epithelioid cells and multinucleated giant cells in a granuloma.

Answer: B

C3a and C5a activate them.

Answer: D

The granules of these cells contain refractile material that form Charcot-Leyden crystals in the sputum of asthmatics.

Answer: C
Immunopathology

Risk factors for immune disorders:
1. prematurity
2. autoimmune diseases—e.g., systemic lupus erythematosus
3. lymphoproliferative disorders—e.g., malignant lymphoma
4. infections—e.g., AIDS
5. immunosuppressive drugs—e.g., corticosteroids

B cells:
1. peripheral blood—10–20% of total lymphocyte count
2. markers—
   A. intracytoplasmic \( \mu \) heavy chains: pre-B cell
   B. surface \( \mu \) and \( \delta \) heavy chains:
      (1) mature B cell
      (2) antigen recognition site
   C. surface receptors:
      (1) IgG Fc receptor
      (2) CD21 for EBV
3. functions—
   A. immunoglobulin (Ig) synthesis:
      (1) no Igs present at birth
      (2) newborn IgG antibodies are transplacentally-derived from mother (persist 3–5 mths)
      (3) high IgA/IgG in colostrum
      (4) IgM synthesis begins at birth (presence of IgM indicates congenital infection)
   B. IgG synthesis begins in 2–3 mths: defense against extracellular encapsulated bacteria (e.g., *Streptococcus pneumoniae*)
4. testing—
   A. B cell count: flow cytometry
   B. immunoglobulin concentration: order of decreasing concentration IgG, IgA, IgM, IgD, and IgE
   C. detect isohemagglutinins:
      (1) anti A-IgM in blood group B person
      (2) none present in newborns and AB blood groups
   D. lymph node biopsy:
      (1) germinal follicles present
      (2) presence of plasma cells
   E. mitogen stimulation:
      (1) functional test
      (2) e.g., pokeweed is the mitogen

T cells:
1. peripheral blood—
   A. 60–70% of total lymphocyte count
   B. lymphopenia in AIDS due to loss of CD4 T helper cells
2. markers—
   A. monoclonal antibody marker studies are used to identify T cells and subsets: see inflammation for cluster designation (CD) types
   B. ratio of CD4/CD8 2/1: <1 in AIDS
C. immature T cells have nuclear enzyme terminal deoxynucleotidyl transferase (TdT) on their surface.

3. functions--
   A. type IV hypersensitivity
   B. cytokines regulate B cells
   C. defense against intracellular pathogens (e.g., TB)

4. testing--
   A. mitogen assays: functioning T cells are specifically activated by phytohemagglutinin and concanavalin A
   B. skin tests:
      (1) evaluate cellular immunity
      (2) Candida is the main antigen used
      (3) absence of an immune response (no redness and induration) indicates anergy or a lack of cellular immunity (e.g., AIDS patient, DiGeorge syndrome)
   C. lymph node biopsy:
      (1) T cells present in paracortical areas
      (2) absent in T cell deficiency states

Bruton's agammaglobulinemia:
1. pure B cell immunodeficiency-- SXR disease
2. pathogenesis-- failure of pre-B cells to differentiate into mature B cells
3. clinical-- infants develop sinopulmonary (SP) disease:
   A. Streptococcus pneumoniae
   B. Hemophilus influenzae
   C. Staphylococcus aureus
4. Rx-- IV γ-globulin

Common variable immune deficiency (CVID):
1. no inheritance pattern
2. pathogenesis-- intrinsic defect in B cell maturation into antibody-producing plasma cells
3. clinical--
   A. presents between 15–35 ys of age
   B. recurrent sinopulmonary infections: decreased Ig production
   C. giardiasis
   D. malabsorption:
      (1) celiac sprue
      (2) lactase deficiency
   E. autoimmune disease: pernicious anemia
4. lab-- all lgs decreased
5. Rx-- IV γ-globulin

Selective IgA deficiency:
1. MC hereditary immunodeficiency
2. pathogenesis--
   A. intrinsic defect in B cell differentiation into committed B cells synthesizing IgA
   B. possible T cell defect that prevents B cells from synthesizing IgA
3. clinical--
   A. recurrent sinopulmonary infections: lack of secretory IgA
   B. giardiasis
   C. autoimmune disease
   D. allergies
E. develop anti-IgA antibodies with exposure to blood products: danger of anaphylactic reaction when exposed to blood products with IgA
4. lab- serum and secretory IgA levels decreased

Sex-linked lymphoproliferative syndrome:
1. SXR-
   A. B cell deficiency
   B. EBV-related disease
2. clinical-
   A. hypogammaglobulinemia
   B. malignant lymphoproliferative disorders

DiGeorge syndrome (thymic hypoplasia):
1. pure T cell deficiency- no inheritance pattern
2. pathogenesis (USMLE)- failure of the 3rd (inferior parathyroids/thymus)/4th (superior parathyroids) pharyngeal pouches to develop
3. clinical-
   A. abnormal facies
   B. hypoparathyroidism: hypocalcemia and tetany
   C. absent thymic shadow
   D. truncus arteriosus: cyanotic congenital heart disease
   E. chronic candidiasis
   F. Pneumocystis carinii pneumonia (PCP)
   G. graft vs host reaction (GVH): must irradiate blood to destroy donor immunocompetent lymphocytes
4. Rx-
   A. thymic grafts
   B. bone marrow transplants

Severe combined immunodeficiency (SCID):
1. B/T cell immunodeficiency-
   A. AR or SXR disease.
   B. ~50% AR pattern have adenosine deaminase deficiency: accumulation of adenine, which is toxic to B/T lymphocytes
2. clinical-
   A. P. carinii pneumonia
   B. diarrhea
   C. disseminated CMV
   D. graft vs host reactions: must irradiate blood
3. Rx-
   A. bone marrow transplant
   B. gene therapy: first disease successfully cured with gene therapy

Wiskott-Aldrich syndrome:
1. B/T immunodeficiency- SXR disease
2. clinical-
   A. thrombocytopenia (bleeding) → the only immunodeficiency w/ platelet abnormalities
   B. eczema
   C. recurrent sinopulmonary infections
   D. increased risk for malignant lymphomas
3. lab-
   A. low IgM
B. increased IgG, IgA, IgE
C. defects in cell mediated immunity develop late
4. Rx— bone marrow transplantation

Ataxia telangiectasia:
1. B/T immunodeficiency—
   A. AR disease
   B. develops in 2–5 year olds
2. clinical—
   A. cerebellar ataxia
   B. telangiectasias in eyes/skin
   C. sinopulmonary infections
   D. chromosome instability syndrome:
      (1) increased susceptibility for chromosomal mutations
      (2) DNA enzyme repair defects (increased risk for lymphomas/leukemias)
   E. thymic hypoplasia
3. lab—
   A. low IgA/IgE
   B. increased serum α-fetoprotein

AIDS epidemiology:
1. MC acquired immunodeficiency syndrome—
   A. MC COD in black men and women (black/white) between 25–44
   B. average life span from the beginning of infection to AIDS defining lesion is 10 years
2. virus characteristics—
   A. HIV-1 RNA retrovirus MC in United States
   B. HIV-2 MC in third world countries
   C. gp 120 viral envelope protein of virus attaches to CD4 molecule of T helper cells and other cells:
      (1) monocytes/macrophages/dendritic cells/microglial cells (CNS macrophage)
      (2) astrocytes
   D. p24 core protein surrounds viral genomic RNA:
      (1) only increased during initial infection and when the patient develops AIDS
      (2) 2 separate peaks (USMLE, beginning and end)
   E. CD4 T helper cell is lysed by the virus: usually direct HIV cytotoxicity
   F. reverse transcriptase converts genomic RNA into proviral double stranded DNA: integrated into host cell’s DNA with virally encoded integrase enzyme
   G. after transcription, HIV messenger RNA is translated into various proteins:
      (1) env encodes gp120/gp41
      (2) pol encodes reverse transcriptase/integrase
      (3) gag encodes p24 core antigen
   H. viral core consists of genomic RNA surrounded by an inner membrane composed of p24 antigen: assembled near the host cell’s plasma membrane
   I. budding of the progeny virion through the host cell membrane is where the viral core acquires the external envelope to become a mature HIV virion
   J. body fluids containing the virus:
      (1) blood (most infective body fluid)
      (2) saliva (chemical in saliva inactivates virus, virus is not transmitted by kissing)
      (3) semen
      (4) amniotic fluid
      (5) breast milk (breast feeding contraindicated in HIV+ women)
(6) spinal fluid
(7) urine
(8) tears
(9) bronchoalveolar lavage material

3. **mode of transmission in the United States in descending order**—
   A. receptive anal intercourse between men
   B. vaginal intercourse male to female: infected semen has more surface area to infect
   C. female to male: less surface area in male urethra to infect

4. **mode of transmission in women**—
   A. heterosexual transmission in minority females who are IV drug abusers
   B. sharing contaminated needles and/or vaginal intercourse with males who are HIV positive

5. **mechanism of transmission by anal intercourse**— direct inoculation into the blood from mucosal trauma or an open wound:
   A. syphilitic chancre
   B. proctitis

6. **blood transfusion transmission risk**— 1:676,000 per unit

7. **mode of transmission in health care workers**—
   A. accidental needle stick from an HIV+ patient
   B. 0.3% (1/300) risk

8. **mode of transmission to children**—
   A. vertical transmission (mother to fetus) from an infected mother (90%)
   B. most cases are transplacental, followed by breast feeding

9. **Rx of pregnant women who are HIV positive**—
   A. AZT
   B. reduces the rate of newborn's developing AIDS from ~25–30% to 7.6%

10. **positive enzyme immunoabsorbent assay (EIA) test for HIV in a newborn**—
    A. due to transplacental transmission of the IgG antibody from the infected mother
    B. document HIV infection in newborn by detection of HIV RNA by PCR (best test) and p24 antigen capture assay

11. **reservoir cells for viral replication**— monocyte lineage cells most often located in lymph nodes

**AIDS testing:**

1. **enzyme immunoabsorbent assay (EIA)**—
   A. initial screening test
   B. detects anti-gp120 antibody
   C. sensitivity 99.5–99.8%
   D. poor specificity due to low prevalence of HIV positivity in the general population
   E. usually positive in 4–8 wks

2. **western blot**—
   A. confirmatory test for indeterminate or positive EIA
   B. positive western blot: presence of p24 and gp41 antibodies and either gp120 or gp160 antibodies
   C. combined positive predictive value of a positive EIA/western blot is 99.5%

3. **tests for monitoring immune status**—
   A. CD4 T helper cell count
   B. HIV RNA by PCR: best overall test to monitor viral burden

**AIDS immunologic abnormalities:**

1. **lymphopenia**— low CD4 count
2. hypergammaglobulinemia— polyclonal stimulation of B cells by EBV and CMV
3. anergy to skin testing
4. decreased mitogen blastogenesis of T cells
5. decreased production of cytokines
6. dysfunctional NK cells
7. increased p24 antigens
8. CD4/CD8 ratio < 1
9. PPD skin test— >5 mm induration is positive test

AIDS clinical:
1. **acute HIV syndrome**— mononucleosis-like syndrome 3–6 wks after contracting the virus
2. asymptomatic, clinically latent phase—
   A. viral replication in dendritic cells in lymph nodes
   B. average span of 4–10 yrs
3. early symptomatic phase—
   A. non-AIDS defining infections:
      (1) oral thrush
      (2) oral hairy leukoplakia (EBV glossitis)
      (3) recurrent *H. simplex*/ *H. genitalis*
      (4) condyloma acuminata (HPV)
      (5) shingles (*H. zoster*)
      (6) molluscum contagiosum (poxvirus)
   B. generalized lymphadenopathy
   C. thrombocytopenia:
      (1) MC hematologic abnormality in AIDS
      (2) immunocomplex destruction (type III hypersensitivity) or antibodies directed against platelet antigens (type II hypersensitivity)
4. AIDS— HIV positive plus:
   A. CD4 T helper cell count: <200 cells/µL
   B. specific malignancies: e.g., Kaposi’s sarcoma
   C. specific infections: e.g., *P. carinii* pneumonia

AIDS-defining malignancies:
1. **Kaposi’s sarcoma**—
   A. MC malignancy
   B. associated with Herpesvirus 8
2. **Burkitt’s lymphoma**— EBV
3. **invasive cervical cancer**— HPV
4. **anal squamous cancer**— HPV
5. **primary CNS malignant lymphoma**—
   A. HIV + EBV
   B. rapidly increasing due to AIDS

AIDS-defining opportunistic bacterial infections:
1. **MAI**—
   A. fever
   B. night sweats
   C. weight loss
   D. infectious cause of a Whipple’s-like syndrome
2. *M. kansasii*
3. *M. tuberculosis*
4. recurrent pneumonia— usually *Streptococcus pneumoniae*
5. *Salmonella* septicemia

**AIDS-defining opportunistic fungal infections:**
1. *P. carinii* pneumonia—MC AIDS-defining infection
2. candidiasis—
   A. MC overall fungal infection
   B. airways/esophagus
3. coccidioidomycosis
4. cryptococcosis—MC fungal CNS infection
5. histoplasmosis

**AIDS-defining opportunistic viral infections:**
1. CMV—
   A. retinitis:
      1. MCC of blindness in AIDS
      2. Rx with ganciclovir
      3. use foscarin if ganciclovir does not work
   B. esophagitis
   C. diarrhea
   D. cholecystitis (USMLE)
2. *H. simplex*—
   A. chronic ulcers
   B. esophagitis
   C. bronchitis/pneumonia
3. HIV-related encephalopathy—AIDS-dementia
4. HIV-related wasting syndrome—
   A. weight loss
   B. fever
   C. chronic diarrhea
   D. fatigue
5. progressive multifocal leukoencephalopathy—
   A. papovavirus
   B. demyelinating disease

**AIDS-defining opportunistic parasitic viral infections:**
1. CNS toxoplasmosis—MCC of a focal space occupying lesion in AIDS
2. cryptosporidiosis—
   A. MC pathogen in diarrhea
   B. partially acid-fast oocyst
3. isosporiasis—AIDS diarrhea

**AIDS miscellaneous infections:**
1. viral hepatitis—HBV most common type
2. bacillary angiomatosis—
   A. due to *Bartonella henselae*
   B. simulates Kaposi's sarcoma
3. infections/malignancy encountered with CD4 T helper count 200–500 cells/µL—
   A. hairy leukoplakia/oral candidiasis
   B. TB
   C. recurrent bacterial pneumonia: *Streptococcus pneumoniae*
4. infections encountered with CD4 T helper count 100–200 cells/µL—
   A. PCP
5. **infections encountered with CD4 T helper count <100 cells/μL—**
   A. disseminated MAI: usually <75 cells/μL
   B. *Candida* esophagitis
   C. CMV retinitis/esophagitis
   D. *Toxoplasma* encephalitis
   E. *Cryptosporidiosis*: diarrhea
   F. cryptococcal meningitis

**AIDS organ pathology:**

1. **lung—**
   A. MC organ involved
   B. PCP
   C. TB
   D. *Streptococcus pneumoniae* pneumonia

2. **hematologic system—**
   A. thrombocytopenia: MC hematologic manifestation
   B. cytopenias
   C. anemia of chronic disease
   D. autoimmune hemolytic anemia
   E. non-Hodgkin’s malignant lymphoma:
      (1) B cell immunoblastic
      (2) poor prognosis

3. **renal disease—**
   A. focal segmental glomerulosclerosis: nephrotic syndrome
   B. drugs with nephrotoxicity:
      (1) amphotericin (Rx of systemic fungal infections)
      (2) pentamidine (Rx of PCP)
      (3) foscarine (Rx of disseminated CMV)

4. **CNS—**
   A. AIDS-dementia complex:
      (1) MC CNS lesion
      (2) multinucleated giant cells are fused microglial cells
   B. vacuolar myelopathy:
      (1) posterior column and lateral corticospinal tract disease
      (2) similar to B12 deficiency but not due to B12 deficiency
   C. ascending type of paralysis: similar to Guillain-Barré syndrome
   D. toxoplasmosis: focal epileptic seizures
   E. CMV retinitis: MCC of blindness

5. **GI/liver—**
   A. esophagitis:
      (1) *Candida* MC
      (2) HSV
      (3) CMV
   B. biliary tract disease:
      (1) CMV (USMLE)
      (2) cryptosporidium (partially acid-fast oocyst)
   C. colitis:
      (1) CMV
      (2) cryptosporidium
6. skin–
   A. Kaposi's sarcoma: MC cancer in AIDS
   B. bacillary angiomatosis
   C. disseminated molluscum contagiosum
   D. disseminated seborrheic dermatitis: *Malassezia furfur*

AIDS drug treatment:
1. initial drug regimen used in Rx of HIV– 2 nucleoside analogs (e.g., AZT, lamivudine) + 1 protease inhibitor (e.g., indinavir)
2. tests to monitor Rx of HIV–
   A. HIV RNA by polymerase chain reaction (PCR):
      (1) monitors viral burden during
      (2) best test
   B. CD4 T helper count:
      (1) immune status
      (2) prophylaxis marker
3. mechanism of action (MOA) of nucleoside drugs– block reverse transcriptase
4. MOA of protease inhibitors– suppress HIV replication by blocking protein processing later in the HIV cycle
5. MOA of nonnucleoside reverse transcriptase inhibitors– non-competitively inhibit reverse transcriptase: e.g., nevirapine
6. side-effects of AZT–
   A. headache
   B. insomnia
   C. GI intolerance
   D. bone marrow suppression:
      (1) macrocytic anemia unrelated to B12 deficiency
      (2) neutropenia
      (3) anemia
   E. proximal muscle disease
   F. dark blue nails
7. side-effects of didanosine–
   A. pancreatitis
   B. hepatitis
   C. peripheral neuropathy
8. side-effects of lamivudine (3TC)–
   A. rash
   B. peripheral neuropathy
   C. bone marrow toxicity
9. side effects of indinavir– protease inhibitor associated with renal stones
10. side-effect of non-nucleoside reverse transcriptase inhibitors– rash
11. CD4 helper T cell count for prophylaxis against PCP–
    A. <200 cells/µL
    B. Rx with TMP/SMX
12. CD4 helper T cell count for prophylaxis against toxoplasmosis–
    A. <100 cells/µL
    B. Rx with TMP/SMX
13. CD4 helper T cell count for prophylaxis against MAI–
    A. <50–100 cells/µL
B. Rx with azithromycin

Recommendations to prevent AIDS:
1. abstinence
2. latex condoms with non-opxynol-9 viral spermicide

Immunizations in HIV positive patients:
1. SALK—
   A. killed vaccine
   B. live vaccine not recommended
2. HBV
3. influenza
4. Hemophilus influenza b (Hib)
5. Pneumococcal vaccine
6. measles/mumps/rubella—
   A. only live viral vaccine permitted in HIV positive patients
   B. natural infection is worse than the potential infection from the vaccination

COD in AIDS:
1. bacterial infection—
   A. MC COD
   B. S. pneumoniae
   C. disseminated MAI
   D. disseminated CMV
2. wasting disease

Functions of the complement system:
1. augment vessel/cellular events in acute inflammation—
2. lyse cells
3. participate in cytotoxic immunity—
   A. type II antibody (IgG/IgM) complement-mediated
   B. type III immunocomplex reactions
4. complement pathways— classical and alternative pathways
   A. both converge on C3
   B. activates the membrane-attack complex (MAC)
   C. MAC is cytolytic
5. function of decay accelerating factor (DAF)—
   A. located on cell membranes
   B. enhances degradation of C3 and C5 convertase: protects cell against MAC destruction
   C. deficient in paroxysmal nocturnal hemoglobinuria
6. function of C1 esterase inhibitor—
   A. negative control on the activation of C1 in the classical pathway
   B. deficient in hereditary angioneurotic edema

Testing of complement system:
1. classical pathway— low C4 or C2 if activated
2. alternative pathway— low factor B if activated
3. integrity of both pathways— low C3, if either system is activated
4. activation increases the concentration of split fragments— e.g., C3a, C5a, C3b
5. functional assessment of the complement system— total hemolytic complement assay (CH50)

Complement disorders:
1. acquired (MC) or hereditary
2. **low serum complement level**—
   A. MC used up in antibody-complement reactions
   B. e.g., immunocomplex diseases like SLE

3. **paroxysmal nocturnal hemoglobinuria (PNH)**—
   A. acquired stem cell disorder associated with a membrane-defect involving the loss of decay accelerating factor (DAF)
   B. intravascular destruction by MAC of:
      (1) RBC (anemia, hemoglobinuria)
      (2) WBCs (neutropenia, infections)
      (3) platelets (thrombocytopenia, bleeding)

4. **C1 esterase inhibitor deficiency (hereditary angioedema)**—
   A. AD disorder
   B. excessive release of C2-derived kinins:
      (1) increase vessel permeability
      (2) recurrent swelling of the face and oropharynx (MC COD)
   C. lab:
      (1) low C4 (most sensitive screen)
      (2) low C2
      (3) normal C3
      (4) low enzyme assay
   D. Rx: androgens

5. **C2 deficiency**—
   A. MC hereditary complement deficiency
   B. increased incidence of autoimmune disease: particularly SLE

6. **C5–C9 deficiency**—associated with disseminated gonococcal

**Major Histocompatibility Complex (MHC):**
1. **collectively known as HLA (human leukocyte antigen) system**—located on chromosome 6
2. **gene products**—
   A. class I and II antigens: membrane-associated glycoproteins
   B. located on all nucleated cells
   C. markers of identity
   D. HLA-A, -B, -C gene loci code for class I antigens:
      (1) recognized by CD8 cytotoxic T cells
      (2) mature RBCs lack class I antigens
   E. HLA-D/DR/DP/DQ/DO gene loci code for class II antigens:
      (1) recognized by CD4 helper T cells
      (2) located on antigen-presenting cells (macrophages, Langerhans cells in the skin, B cells, activated T cells)
   F. individuals inherit 1 HLA haplotype from each parent in codominant fashion: both haplotypes are expressed

**Laboratory assessment in transplantation:**
1. **uses for HLA testing**—
   A. transplantation work-ups
   B. paternity suits
   C. identifying patients at risk for certain disorders: e.g., HLA B-27 and ankylosing spondylitis

2. **transplantation success requirements**—
   A. ABO blood group compatibility: most important test
   B. absence of preformed anti-HLA cytotoxic antibodies in the recipient’s serum
C. close matches for HLA-A, B and D loci between recipient and donor

3. lymphocyte crossmatch— screens for recipient anti-HLA antibodies against donor lymphocytes

4. lymphocyte microcytotoxicity test— identifies HLA-A and B derived class I antigen profiles on recipient and donor lymphocytes using known test sera

5. mixed lymphocyte reaction—
   A. used for class II antigen (D loci) matching
   B. functional lymphocytes from the recipient and previously irradiated (killed) donor lymphocytes are mixed together with tritiated thymidine to detect the degree of compatibility between their D loci: increased radioactivity indicates incompatibility
   C. recipient’s lymphocytes are irradiated (killed) and functional donor lymphocytes are reacted against the host’s HLA-D loci to check for a graft versus host reaction (GVH)

Transplant rejection:

1. transplant donors—
   A. siblings are best source: chance of a sibling having another sibling with a 0, 1, or 2 haplotype match is 25%, 50%, and 25%, respectively
   B. parents are automatically a 1 haplotype match

2. graft types—
   A. autograft:
      (1) transfer of tissue from self to self
      (2) best survival
   B. syngeneic graft (isograft): graft between identical twins
   C. allograft: graft between unrelated individuals
   D. xenograft:
      (1) transplant of tissue from one species to another
      (2) e.g., pig heart transplant

3. hyperacute rejection—
   A. usually occur within minutes of vascular attachment of the allograft: e.g., kidney/heart
   B. causes:
      (1) ABO incompatibility (e.g., O person receives an A heart)
      (2) preformed cytotoxic antibodies directed against donor antigens
   C. pathology:
      (1) small vessel injury with thrombosis
      (2) type II hypersensitivity

4. acute rejections—
   A. MC rejection: usually occur within the first 3 mths of the transplantation
   B. pathophysiology:
      (1) cell mediated reaction most important
         a. interaction between donor macrophages and host cytotoxic/helper T cells
         b. extensive interstitial infiltrate in the graft, edema, and cytokine damage to the tissue
      (2) antibody-mediated (type II necrotizing vasculitis with vessel damage and thrombosis: intimal thickening with obliteration of the vessel lumen for older grafts
   C. reversible with immunosuppressive drugs
   D. cyclosporin A:
      (1) blocks CD4 helper cell release of IL-2
      (2) side effects of cyclosporine include
         a. dose-related nephrotoxicity
         b. interstitial fibrosis
c. hypertrichosis
d. hemolytic uremic syndrome
e. hepatotoxicity
f. hyperkalemia
g. hypertension
h. lymphoproliferative malignancy

E. prednisone:
   (1) blocks IL-1 and cytokine production from T cells
   (2) lymphotoxic

F. OKT3: monoclonal antibody directed against the CD3 antigen receptor

G. azathioprine: inhibits proliferation of activated T cells

5. chronic rejections—
   A. irreversible; generally occur over a period of months to years
   B. pathogenesis: not well characterized
   C. pathology: extensive fibrosis and chronic ischemia owing to vessel damage with intimal thickening and luminal obliteration

Graft versus host (GVH) reaction:

1. transplant types—
   A. bone marrow
   B. liver transplants
   C. blood transfusions in patients with T cell immunodeficiencies

2. pathogenesis—
   A. donor lymphocytes produce IL-2, which activate NK cells
   B. activated NK cells are called lymphokine-activated NK cells or LAKs
   C. LAKs are the primary effector cells in acute GVH reactions

3. pathology—
   A. extensive epithelial cell necrosis in the biliary tract with jaundice
   B. maculopapular skin rash
   C. diarrhea

Types of transplants:

1. corneal transplants—
   A. best overall allograft survival rate
   B. can transmit Creutzfeldt Jakob disease

2. renal transplants—
   A. cadaver: 1 year graft survival rate is 80%
   B. living-donor: 1 year graft survival rate is 90%
   C. increase graft survival if patient receives multiple blood transfusions prior to surgery: ? induces tolerance to the allograft
   D. COD in renal transplant patients:
      (1) opportunistic infections (CMV, Aspergillus)
      (2) acute myocardial infarction

3. bone marrow transplants—
   A. indications:
      (1) aplastic anemia
      (2) leukemia
      (3) certain immunodeficiencies (see above)
   B. donor bone marrow contains pluripotent stem cells: repopulate recipients lymphoid, erythroid, myeloid, megakaryocytic series
   C. recipient assumes the donor's ABO group

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4. **heart transplants**—
   A. adults:
      (1) chronic ischemic heart disease
      (2) congestive cardiomyopathy
   B. children: endocardial fibroelastosis
   C. survival: ~80% 1 y survival

5. **liver transplants**—
   A. adults:
      (1) cirrhosis
      (2) severe hemophilia (liver synthesizes factor VIII)
   B. children: biliary atresia
   C. survival: 90% 1 y survival

Complications of immunosuppressive therapy:

1. **malignancy**—
   A. squamous cell carcinomas of the skin: MC overall malignancy associated with immunosuppression
   B. cervical cancer
   C. malignant lymphomas: immunoblastic
   D. basal cell carcinoma

2. **infection**

3. **aplastic anemia**

**HLA haplotypes and disease:**

1. **risks**—
   A. familial predisposition to disease
   B. weak penetrance:
      (1) disease is not invariable
      (2) usually requires exposure to an environmental factor (e.g., virus)
   C. predisposition to autoimmune disease

2. **important HLA relationships**—
   A. HLA-A3:
      (1) hemochromatosis
      (2) risk 7%
   B. HLA-B8/DR3:
      (1) celiac disease
      (2) risk 13%
   C. HLA-B27:
      (1) ankylosing spondylitis
      (2) risk 80% (highest risk)
      (4) high penetrance
   D. HLA-DR2:
      (1) multiple sclerosis
      (2) risk 3%
   E. HLA-DR3/DR4:
      (1) type 1 insulin-dependent diabetes mellitus
      (2) risk 3%
   F. HLA-DR4:
      (1) rheumatoid arthritis
Type I hypersensitivity reactions:

1. **atopy**—familial predisposition (multifactorial inheritance) to develop an allergic reaction
2. **pathogenesis**—
   A. **IgE antibody-mediated**
   B. **mast cell/basophil activation**
      1. pollens
      2. anaphylatoxins
      3. drugs (e.g., penicillin)
   C. release of preformed chemical mediators: e.g., histamine (see inflammation)
   D. sequence of mast cell/basophil sensitization to allergens:
      1. antigen processing by macrophages/dendritic cells
      2. interact with CD4 T<sub>H</sub>2 cells, which release IL 4, 5, 6
      3. ILs stimulate B cell proliferation/differentiation
      4. IL-4 causes B cells to switch synthesis from IgM to IgE
      5. IgE antibodies attach to mast cell/basophil cell membrane
      6. allergens (e.g., pollens) cross-link two subjacent IgE antibodies on mast cells/basophils causing the release reaction (see inflammation)
      7. late phase reaction (enhances acute inflammatory reaction) involves synthesis of prostaglandins/leukotrienes from arachidonic acid
3. **clinical examples**—
   A. skin:
      1. eczema (face, flexor/extensor surfaces)
      2. hives
   B. eyes: seasonal conjunctivitis
   C. nose:
      1. seasonal rhinitis
      2. membranes boggy and pale blue
   D. respiratory tract:
      1. asthma
      2. anaphylactic reactions
   E. GI tract:
      1. cramping
      2. diarrhea
   F. hypersensitivity to bee/wasp/hornet stings:
      1. anaphylactic reactions to bee stings are MC COD due to venomous animal bites in United States
      2. skin (diffuse urticarial swelling)
      3. respiratory tract (wheezing, laryngeal swelling/obstruction)
      4. cardiovascular (hypotension, arrhythmias)
      5. **Rx of anaphylactic reactions**—sc. administration of aqueous epinephrine 1:1000 dilution (USMLE)
4. **lab tests**—
   A. total IgE concentration: paper-based radioimmunosorbent test (PRIST) procedure
   B. prick skin testing of allergens:
      1. most sensitive test
      2. **wheal and flare types of reactions involving histamine** (USMLE)
   C. measurement of specific IgE antibodies: radioallergosorbent test (RAST)
   D. nasal smears: look for eosinophils
   E. eosinophilia
5. **USMLE scenarios**
   A. patient is stung by a bee and begins to have respiratory difficulty, flushing, and abdominal cramping; Rx with aqueous epinephrine 1:1000 sc (0.01 mL/kg sc or IM)
   B. man went under a house to work on pipes and came out screaming; multiple wheals over the body that later developed into vesicles, and pustules: fire ant bites

- **Type II cytotoxic hypersensitivity reactions:**
  1. **antibody (IgG/IgM) complement-mediated cell lysis**
     A. antibody attachment to a target cell with subsequent MAC cell destruction of the cell
     B. e.g., ABO mismatch
     C. e.g., hyperacute transplant reaction
  2. **antibodies attach to target tissue**
     A. activate complement system
     B. chemotactic agents (e.g., C5a) attract neutrophils
     C. neutrophils damage tissue
     D. e.g., Goodpasture's syndrome: anti-glomerular/pulmonary capillary basement membrane antibodies
  3. **hematopoietic cells (RBCs, leukocytes, platelets) coated by IgG and/or C3b are phagocytosed and destroyed by macrophages**
     A. warm autoimmune hemolytic anemias and cytopenias
     B. Rh/ABO hemolytic disease of newborn
  4. **antibody-dependent cell-mediated cytotoxicity (ADCC)**
     A. cells/helminths coated by specific IgG/IgE antibodies, respectively (without complement) are destroyed by cells (e.g., NK cells/eosinophils, respectively) with low affinity IgG/IgE Fc receptors
     B. e.g., NK destruction of tumor cells
     C. e.g., eosinophil destruction of helminths coated by IgE antibodies
  5. **IgG autoantibodies (without complement) against receptors**
     A. myasthenia gravis: anti-acetylcholine receptor antibodies
     B. Grave's disease: IgG thyroid-simulating Ig directed against TSH receptor

- **Lab testing**
  A. direct Coombs' test: detects IgG and/or C3 on RBCs
  B. indirect Coombs' test:
     1. detects specific antibodies in the serum
     2. e.g., anti-D in Rh HDN
  C. immunofluorescent studies that localize deposits of antibody and/or complement in tissue: e.g., antibodies in Goodpasture's
  D. major crossmatch: patient serum against donor RBCs
  E. lymphocyte crossmatch: check for recipient anti-HLA antibodies directed against donor HLA antigens
  F. lymphocyte microcytotoxicity test: used for HLA profiling of donor/recipient

- **Type III immunocomplex (IC) hypersensitivity reactions:**
  1. **pathogenesis of systemic reactions**
     A. circulating ICs (antigen + IgG/IgM) deposit in target tissue (e.g., glomerulus, small vessel)
     B. activate complement system
     C. chemotactic agents recruit neutrophils/macrophages that damage the tissue
  2. **pathogenesis of localized IC reactions (Arthus reactions)**
     A. first antigen exposure results in antibody production
B. second exposure to antigen deposited in tissue leads antigen-antibody ICs→
   (1) complement system activation→
   (2) neutrophil/macrophage damage of tissue
3. **clinical examples of systemic reactions**–
   A. serum sickness: Rx of rattlesnake envenomations with use of horse serum antitoxins
   B. SLE glomerulonephritis (GN): anti-DNA + DNA ICs
   C. post-streptococcal GN: anti-bacterial antigen antibodies + bacterial antigen ICs
   D. Henoch-Schönlein purpura: anti IgA antibodies against IgA
   E. polyarteritis nodosa:
      (1) HBsAg + anti-HBs ICs
      (2) "serum sickness-like" prodrome in HBV infections
      (3) vasculitis
      (4) glomerulonephritis
      (5) urticaria
   F. rheumatoid arthritis: IgM antibodies against IgG (rheumatoid factor)
4. **clinical example of an Arthus reaction**– Farmer's lung:
   A. antigen is thermophilic actinomycetes
   B. interstitial pneumonitis
5. **lab testing**–
   A. immunocomplex (IC) assays: Raji (uses Burkitt's lymphoma cells, detects ICs activating alternative pathway)
   B. complement assays:
      (1) low levels from IC utilization
      (2) classical pathway activation:
         a. low C4/C2 + low C3
         b. normal factor B
      (3) alternative pathway activation:
         a. low factor B + C3
         b. normal C4/C2
   C. immunofluorescent testing of tissue: band test on skin in SLE to detect anti-DNA + DNA antibodies deposited in basement membrane

**Type IV T cell-mediated hypersensitivity reactions:**
1. **definition**– antibody-independent cellular immune reactions involving CD4 helper T cells (DRH reactions) and CD8 cytotoxic T cells
2. **types of DRH reactions**–
   A. allergic contact dermatitis:
      (1) poison ivy
      (2) nickel
      (3) soaps
   B. skin tests:
      (1) tuberculin sensitivity
      (2) patch test in contact dermatitis: suspected irritant placed on a patch and applied to the skin
   C. granulomas:
      (1) histoplasmosis
      (2) TB
      (3) sarcoidosis
3. **pathogenesis of allergic contact dermatitis**–
   A. exposure to low molecular weight antigen (must penetrate skin)→
   B. antigen phagocytosed/processed by Langerhans cells→
C. processed antigen transported to regional lymph nodes and presented to T lymphocytes →
D. T lymphocytes become sensitized to the antigen (memory T cells) →
E. antigen reexposure causes local release of cytokines from the previously sensitized T lymphocytes causing an inflammatory reaction (vesicles, erythema)
F. USMLE question on child with a vesicular rash after running through bushes; poison ivy

4. **Pathogenesis of a positive PPD**— see inflammation note discussion

5. **Pathogenesis of cytotoxic T cell reactions**—
   A. cytotoxic T cells normally interact with class I antigens on nucleated cells →
   B. alteration of class I antigens on target cells activates cytotoxic T cells to release perforins that destroy the cell
   C. examples:
      (1) neoplastic/virally infected cell
      (2) foreign antigens in a transplant cell
      (3) destruction of hepatitis B infected hepatocytes
Fluids and Hemodynamics/Acid Base

**Types of edema (excess fluid in interstitial space of extracellular fluid compartment):**

1. **transudate**—
   A. protein poor (<3 g/dL)
   B. cell-poor
   C. alterations in Starling's forces are present:
      (1) increased hydrostatic pressure
      (2) decreased oncotic pressure (hypoalbuminemia)
   C. clinical presentations:
      (1) dependent pitting edema: correlates with an increase in total body Na⁺
      (2) body cavity effusions (e.g., ascites)

2. **exudate**—
   A. increased vessel permeability in acute inflammation
   B. protein >3 g/dL
   C. cell-rich: neutrophils
   D. clinical presentations:
      (1) swelling of tissue but no pitting edema
      (2) pus in cavities: e.g., peritonitis

3. **lymphedema**—
   A. due to obstruction of lymphatics with egress of lymphatic fluid:
      (1) protein
      (2) lymphocytes
      (3) chylomicrons with triglyceride (produces supranate)
   B. initially pitting edema but eventually non-pitting edema
   C. clinical examples:
      (1) post-radical mastectomy (MCC in United States)
      (2) filariasis
      (3) peau d' orange of inflammatory carcinoma: plugging of dermal lymphatics by tumor
      (4) scrotal/vulvar lymphedema in lymphogranuloma venereum → Chlamydia trachomatis

**Examples of transudate from increased hydrostatic pressure:**

1. **left heart failure (LHF)**— hydrostatic pressure in pulmonary vein overrides pulmonary capillary oncotic pressure
2. dependent pitting edema in right heart failure (RHF)
3. volume overload from increase in isotonic saline (0.9%) or hypertonic saline (3%)

**Examples of transudate from decreased oncotic pressure:**

1. **nephrotic syndrome**—
   A. >3.5 g urine protein loss per day
   B. minimal change disease MCC in children
   C. membranous glomerulonephritis MCC in adults

2. **malabsorption**—
   A. celiac disease
   B. Crohn's disease

3. **hypertrophic gastritis**
4. **kwashiorkor:** decreased intake of protein but normal number of total calories
5. dependent pitting edema in cirrhosis
Example of transudate from both increase in hydrostatic pressure and decrease in oncotic pressure: ascites in cirrhosis—
1. increased portal vein pressure—portal vein hypertension
2. decreased oncotic pressure—hypalbuminemia from decreased synthesis

Body fluid compartments:
1. total body water (TBW)—
   A. ~60% body weight in kg: e.g., 70 kg x 0.60 = 42 liters
   B. distributed between intracellular fluid (ICF, ~40%) and extracellular fluid (ECF) compartments (~20%)
   C. ICF ~2/3 larger than ECF
   D. total body potassium (TxBK+) is primarily located in ICF compartment
2. ECF—
   A. interstitial fluid compartment: ~2/3 larger than vascular compartment
   B. vascular compartment: heart, arteries, arterioles, capillaries, venules, veins
   C. total body sodium (TBNa+) is limited to ECF compartment:
      (1) Na+ kept out of ICF compartment by the Na+/K+ ATPase pump
      (2) most of the TBNa+ is located in the interstitial compartment: an increase of TBNa+ in this compartment results in pitting edema

Plasma osmolality (POsm):
1. formula for POsm—POsm = 2\(^{\circ}\) (serum Na\(^+\)) + serum glucose/18 + serum blood urea nitrogen (BUN)/2.8 = 275–295 mOsm/kg
2. impermeant solutes (limited to ECF)—
   A. sodium: most important impermeant solute
   B. glucose
   C. alterations in sodium (increased or decreased)/glucose (increased only) set up osmotic gradients that control water movements between ECF and ICF by law of osmosis: water moves from low concentration to high concentration
3. permeant solutes (freely move between ECF and ICF)—
   A. urea
   B. alcohol
   C. permeant solutes cannot establish osmotic gradients for water movements: osmolality the same in ECF and ICF
4. effective osmolality (EOsm)—
   A. refers to impermeant solutes that control water movements: normally, serum Na\(^+\) most important
   B. in hyperglycemia, glucose overrides serum Na\(^+\) as the main osmotic force
   C. EOsm = 2 (serum Na\(^+\)) + glucose/18
   D. EOsm reflects the tonicity of the ECF
Types of tonicity in ECF:
1. Tonicity primarily depends on the serum Na⁺ and glucose concentrations
2. Isotonic condition (normal EOsM)
   A. Occurs when both the serum sodium/glucose are normal
   B. No osmotic gradient
3. Hypotonic condition (low EOsM)
   A. Refers to hyponatremia
   B. Osmotic gradient directs water into the ICF (expanded)
4. Hypertonic condition (high EOsM)
   A. Causes:
      (1) Hyponatremia
      (2) Hyperglycemia: MCC
   B. Osmotic gradient directs water from the ICF into the ECF
   C. Hyperglycemia effect on serum Na⁺: Water added to the ECF produces a dilutional hyponatremia
   D. Correction for dilutional effect on serum Na⁺ when hyperglycemia is present:
      (1) Corrected serum Na⁺ = measured serum Na⁺ + (serum glucose/100 x 1.6)
      (2) E.g., serum Na⁺ = 130 mEq/L, serum glucose = 1000 mg/dL: Corrected serum Na⁺ = 130 - (1000/100 x 1.6) = 146 mEq/L
      (3) Corrected serum Na⁺ represents what the concentration of Na⁺ would be if the serum glucose was normal

Factors controlling ECF volume:
1. Thirst
   A. Increased POsm due to hyponatremia, hyperglycemia
   B. Presence of angiotensin II from the renin-angiotensin-aldosterone (RAA) system
2. RAA system – see below
3. Antidiuretic hormone (ADH)
   A. Stimuli for ADH release in the CNS:
      (1) Increased POsm
      (2) Volume depletion (overrides POsm as the major stimulus for ADH release)
      (3) Direct reflexes from left atrium in the presence of volume depletion
   B. Inhibition of ADH:
      (1) Low POsm
      (2) Atrial natriuretic peptide (ANP): Present when atria are volume expanded as in left and right heart failure
4. Renal Na⁺ reabsorption – see below

Concept of effective arterial blood volume (EABV):
1. Definition – Amount of total circulating volume required to stimulate baroreceptors in the aortic arch and carotid sinus: correlates with stroke volume and cardiac output
2. Usually parallels ECF volume
   A. E.g., isotonic loss of fluid contracts ECF compartment and decreases EABV
   B. Exception:
      (1) Starling's force alterations trap transudate in the interstitial space (expanded) →
      (2) Increases total ECF volume →
      (3) Decreases EABV, since the venous return to the right heart is decreased
      (4) Examples:
         a. Right heart failure with an increase in venous hydrostatic pressure causes a movement of fluid (transudate) into the interstitial space: EABV is decreased
b. cirrhosis is associated with hypoalbuminemia, which causes a movement of fluid (transudate) into the interstitial space: EABV is decreased

3. baroreceptors—
   A. low pressure baroreceptors: left atrium/major thoracic veins
   B. high pressure baroreceptors: carotid sinus/aortic arch innervated by IX and X cranial nerves

Physiologic events with a decrease in EABV:
1. clinical examples—
   A. hypovolemia:
      (1) blood loss
      (2) other fluid loss: diarrhea, sweat
   B. decreased cardiac output: e.g., myocardial infarction

2. underfilling of arterial vessels—
   A. inhibits cranial nerves IX and X innervating the high pressure baroreceptors
   B. increases sympathetic activity and catecholamine release

3. catecholamine functions—
   A. tachycardia: chronotropic effect
   B. increases cardiac contractility:
      (1) raises systolic blood pressure (BP)
      (2) inotropic effect
   C. peripheral vasoconstriction: raises diastolic BP
   D. systemic venoconstriction: increases return of blood to right heart
   E. stimulates hypothalamic synthesis/posterior pituitary release of antidiuretic hormone (ADH):
      (1) increases reabsorption of free water in the collecting tubules of the kidneys
      (2) vasoconstriction of peripheral resistance arterioles
   F. activates the renin/angiotensin/aldosterone (RAA) system: direct sympathetic stimulation

4. RAA system activation—
   A. activation of juxtaglomerular (JG) apparatus (modified smooth muscle) in afferent arteriole:
      (1) direct stimulation by the sympathetic nervous system
      (2) reduced renal blood flow
      (3) activation of macula densa (see below)
   B. renin (enzyme not a hormone) released from JG apparatus: angiotensinogen converted into angiotensin I (AT I)
   C. angiotensin converting enzyme (ACE) in the lungs converts AT I into angiotensin II (AT II): example of noncompetitive inhibition
   D. AT II stimulates synthesis/release of aldosterone in zona glomerulosa by activating 18-hydroxylase: corticosterone converted into aldosterone

5. AT II functions—
   A. vasoconstriction of peripheral resistance arterioles: increases diastolic BP
   B. stimulation of aldosterone synthesis/release
   C. stimulates thirst center
   D. constricts mesangial cells in the glomerulus: decreases glomerular filtration rate by reducing the overall surface area for filtration
   E. constricts efferent arteriole: peritubular capillaries are the run-off vessels originating from the efferent arterioles

6. aldosterone functions—
   A. increases renal Na⁺ reabsorption
   B. increases renal K⁺ and H⁺ secretion
7. Role of atrial natriuretic peptide (ANP) in volume control—
   A. released from left/right atrium with atrial distention; e.g., left/right heart failure
   B. inhibits ADH release; increased ANP does not override stimulus for ADH release by
      increased POsm or volume depletion (USMLE question)
   C. inhibits all AT II functions
   D. inhibits renal reabsorption of Na⁺: direct natriuretic effect
8. Role of kidney-derived prostaglandin E₂ in volume control—
   A. inhibits ADH
   B. inhibits renal Na⁺ reabsorption
   C. intrarenal vasodilator of afferent arterioles; offsets intrarenal vasoconstrictive effects of
      AT II on efferent arteriole
9. Increased renal reabsorption of Na⁺—
   A. increased proximal tubule reabsorption of Na⁺:
      (1) isosmotic reabsorption (same urine osmolality after reabsorption)
      (2) increased glomerular filtration fraction (FF): ↑FF = ↓glomerular filtration
           rate/↓renal plasma flow, therefore, more Na⁺ is filtered
      (3) peritubular capillary hydrostatic pressure (Pₜ) is lower than peritubular capillary
           oncotic pressure (Pₒ)
           a. decrease in renal blood flow automatically decreases Pₜ
           b. results in massive isosmotic reabsorption of Na⁺ and water back into the
              ECF
   B. increased aldosterone-enhanced reabsorption of Na⁺: see below
   C. tonicity of fluid reabsorbed by the kidneys that returns to the ECF is slightly hypotonic: 
      slightly more water than salt

Physiologic events that occur with an increase in EABV:
1. Clinical examples—
   A. isotonic gain of fluid: patient given too much isotonic (0.9%, normal) saline
   B. primary aldosteronism: benign tumor in zona glomerulosa → Conn's syndrome
   C. inappropriate ADH syndrome (SIADH)
   D. hypertonic gain of fluid:
      (1) 3% hypertonic saline infusion
      (2) overzealous NaHCO₃ infusions to correct metabolic acidosis
2. No inhibition of high pressure baroreceptors—no catecholamine effects
3. No stimulus for ADH release—
   A. loss of free water in the urine: normal dilution
   B. exception is SIADH where free water is reabsorbed when it should be excreted
4. No activation of RAA system—
   A. no AT II or aldosterone effect
   B. renal blood flow is increased
5. ↑ANP—natriuretic effect
6. Decreased glomerular filtration fraction:
   A. ↓FF = ↑glomerular filtration rate/↑↑renal plasma flow
   B. decrease in the filtered load of Na⁺
7. Pₜ > Pₒ—
   A. no proximal tubule reabsorption of Na⁺
   B. all other solutes normally reabsorbed in the proximal tubule are also lost in the urine

Effect of infusion of 3% hypertonic saline (USMLE):
1. Increase POsm—due to hypernatremia
2. Increase in serum ADH—
A. increase in POsm stimulates its release
B. increased POsm overrides effect of ANP release on inhibiting ADH
C. schematic

Serum ADH

1. A = dilution in a normal person with low POsm inhibiting ADH
2. B = patient with diabetes insipidus with high POsm and low ADH
3. C = patient given 3% hypertonic saline with high POsm and high ADH: could also represent normal concentration
4. D = patient with SIADH with low POsm and high ADH

Physiologic effects of hemorrhage: sequence as described for decrease in EABV

Proximal renal tubule functions (see nephron diagram):

1. primary site for Na⁺ reabsorption
2. primary site for reclamation of HCO₃⁻:
   A. H⁺ ions in the tubule are exchanged with Na⁺ in the urine
   B. H⁺ in proximal tubule lumen combines with filtered HCO₃⁻ to form H₂CO₃
   C. brush border carbonic anhydrase dissociates H₂CO₃ into H₂O and CO₂, which are reabsorbed back into the proximal tubule
   D. H₂CO₃ is reformed in the proximal renal tubule cell with the aid of intracellular carbonic anhydrase
   E. H₂CO₃ in the proximal renal tubule, dissociates into H⁺ and HCO₃⁻ anions
   F. HCO₃⁻ is reabsorbed into the peritubular capillaries
   G. H⁺ ions reclaim more bicarbonate
   H. note that this is not a mechanism for excreting H⁺ ions, since they are reused to reclaim more bicarbonate
3. site for type II proximal renal tubular acidosis (RTA)–:
   A. renal threshold for reclaiming HCO₃⁻ is lowered from the normal of 24 mEq/L to ~15 mEq/L
   B. filtered HCO₃⁻ is lost in the urine (urine pH >5.5)
   C. HCO₃⁻ anions lost in the urine as NaHCO₃ are replaced by Cl⁻ anions leading to a normal anion gap metabolic acidosis
4. primary nephron site for synthesis of ammonia–:
   A. glutamine (non-toxic vehicle for carry NH₄⁺ in blood) from the blood enters the proximal tubules
   B. in the proximal tubules, glutamine is enzymatically converted into NH₄⁺ + α-ketoglutarate
      1. α-ketoglutarate is used to synthesize glucose, which is metabolized to CO₂ and H₂O
      2. CO₂ + H₂O combine to form H₂CO₃, which dissociates into newly synthesized HCO₃⁻ + H⁺
      3. HCO₃⁻ is reabsorbed back into the blood, while H⁺ combines with NH₃ in the cell to form NH₄⁺
A = Aldosterone

\*H_2O\* = free water: mostly generated in Na^+\text{}/K^+\text{}/2Cl^- cotransport pump

ADH = antidiuretic hormone

TAL = thick ascending limb (diluting segment)

DCT = distal convoluted tubule

H^+ = hydrogen ion that can be secreted with HPO_4^{2-}\text{}/(H_3PO_4), which is titratable acidity or NH_3\text{}/(NH_4\text{}/Cl)

Proximal tubule: • carbonic anhydrate inhibitor—blocks reclamation of bicarbonate, which is excreted as NaHCO_3 or KHCO_3; • proximal renal tubular acidosis, • loss of K^+ and Na^+

Ascending tubule: • loop diuretic—blocks Na^+\text{}/K^+\text{}/2Cl^- cotransport pump; • impairs generation of free water, • calcium is also lost in the urine (Rx of hypercalcemia), • hyponatremia, hypokalemia, metabolic alkalosis; • thiazide diuretic—blocks Na^+\text{}/Cl^- pump; • allows calcium reabsorption with the help of parathormone (useful in calcium stone formers), • hyponatremia, hypokalemia, metabolic alkalosis

Distal/collecting tubule: • spironolactone—blocks aldosterone (A) pumps: • blocks Na^+\text{}/K^+ exchange pump, • blocks H^+\text{}/K^+ ATPase exchange pump, • K^- sparing, • normal anion gap metabolic acidosis

Functional Aspects of the Nephron
(4) \( \text{NH}_4^+ \) is secreted into the lumen of the tubule (substitutes for \( \text{H}^+ \) in the \( \text{Na}^+ / \text{H}^+ \) exchange mechanism); reabsorbed in the thick ascending limb in the medulla and cortex (\( \text{NH}_4^+ \) substitutes for \( \text{K}^+ \) in the \( \text{Na}^+ / \text{K}^+ / 2\text{Cl}^- \) cotransport pump) and then secreted into the collecting duct for final excretion in the urine as \( \text{NH}_4\text{Cl} \)

5. site for reabsorption of-
   A. glucose: cotransport with \( \text{Na}^+ \)
   B. urea
   C. amino acids
   D. phosphate: inhibited by parathormone

6. carbonic anhydrase inhibitors-
   A. acetazolamide blocks the enzyme
   B. \( \text{HCO}_3^- \) cannot be reclaimed: combines with \( \text{Na}^+ / \text{K}^+ \) to form \( \text{NaHCO}_3 / \text{KHCO}_3 \) which are lost in the urine
   C. acts as a proximal tubule diuretic
   D. produces normal anion gap metabolic acidosis: see below

Functions of thin descending limb:
1. only permeable to water
2. urine becomes hypertonic (maximum of 1200 mOsm/kg) by the time it reaches the loop of Henle

Functions of thin ascending limb:
1. impermeable to water but permeable to \( \text{Na}^+ \) and \( \text{Cl}^- \)
2. UOsm decreases

Functions of thick ascending limb (TAL medullary segment):
1. generation of free water via the active \( \text{Na}^+ / \text{K}^+ / 2\text{Cl}^- \) co-transport pump-
   A. water in the urine up to this pump is obligated: 20 mL of water must accompany every solute excreted
   B. free water is solute free: essential for normal dilution and concentration of urine
   C. every \( \text{Na}^+ \), \( \text{K}^+ \), \( \text{Cl}^- \) reabsorbed leaves behind its obligated water in the tubule lumen: now it is free water
   D. UOsm ~150 mOsm/kg after leaving TAL medullary segment: most of the water is now free water
2. loop diuretics block this co-transport pump—
   A. ability to generate free water is impaired
   B. hyponatremia occurs, since dilution requires the loss of free water in the urine
   C. what should be free water is still obligated water when a patient is on a diuretic
3. pump also reabsorbs calcium (not PTH-enhanced)— loop diuretics are a mainstay to Rx hypercalcemia
4. reabsorbs some of \( \text{NH}_4^+ / \text{NH}_3 \) secreted by the proximal tubule—
   A. substitutes for \( \text{K}^+ \) in the \( \text{Na}^+ / \text{K}^+ / 2\text{Cl}^- \) cotransport pump
   B. \( \text{NH}_4^+ / \text{NH}_3 \) enters the medullary interstitial tissue
   C. \( \text{NH}_3 \) eventually diffuses into the collecting ducts where it is excreted into the urine and combines with \( \text{H}^+ \) to form \( \text{NH}_4\text{Cl} \)

Functions of the cortical TAL segment:
1. \( \text{Na}^+ / \text{Cl}^- \) pump in early distal tubule— \( \text{Na}^+ \) and \( \text{Ca}^{++} \) (PTH-enhanced reabsorption) cations share the same channel for reabsorption
2. \( \text{Na}^+ \) channel is blocked by thiazides—
   A. channel is open for PTH-enhanced \( \text{Ca}^{++} \) reabsorption
   B. potential for hypercalcemia
C. thiazides are used in removing Ca\(^{2+}\) from urine in hypercalciuric patients who are stone formers
D. thiazides are a commonly used diuretic in the Rx of congestive heart failure and hypertension

3. a small amount of free water is generated in the pump

Functions of the macula densa:
1. interacts with the juxtaglomerular (JG) apparatus on afferent arteriole—
   A. modified chemoreceptor
   B. senses volume and Na\(^+\) alterations in the distal tubule
2. increased Na\(^+\) in the urine inhibits renin release and vice versa

Functions of aldosterone-enhanced ATPase Na\(^+\)K\(^+\) exchange pump in distal collecting tubule and collecting ducts:
1. Na\(^+\) is reabsorbed in exchange for K\(^+\):
   A. main site for K\(^+\) excretion
   B. if K\(^+\) is depleted, Na\(^+\) exchanges with H\(^+\), the latter reclaiming HCO\(_3\)\(^-\): potential for metabolic alkalosis
2. effect of increased distal delivery of Na\(^+\) from more proximal acting diuretics (e.g., loop diuretic or thiazide diuretics)
   OR (A inhibits)
   A. augmented Na\(^+\)/K\(^+\) exchange leads to hypokalemia
   B. hypokalemia is prevented if the patient takes K\(^+\) supplements
   C. if Na\(^+\) exchanges with H\(^+\) due to depletion of K\(^+\), bicarbonate is reclaimed and metabolic alkalosis is produced
3. aldosterone blocker—(Same effect seen in Addison's disease)
   A. spironolactone inhibits aldosterone function on the pump — binds to basolateral side; only in presence of aldosterone
   B. Na\(^+\) is lost in the urine: diuretic effect
   C. K\(^+\) is retained in the blood:
      (1) good for people on diuretics who cannot take K\(^+\) supplements ("K\(^+\) sparer")
      (2) danger of hyperkalemia — can cause cardiac arrest in diuretics
   D. H\(^+\) is retained: metabolic acidosis
   E. used with ACE inhibitors in Rx of congestive heart failure: (Gold Standard Rx)
      (1) increases survival of patients
      (2) maintains ACE inhibitor block of aldosterone
4. triamterene/amiloride—(K\(^+\) sparing)
   A. block Na\(^+\) channel
   B. not true aldosterone blockers

Functions of the aldosterone enhanced H\(^+\)/K\(^+\) ATPase pump and H\(^+\) ATPase pumps in the α-intercalated cells in the collecting ducts:
1. primary sites for excretion of excess H\(^+\) ions—
   A. H\(^+\) ions in the tubule exchange for K\(^+\) in the lumen in one of the two pumps
   B. H\(^+\) from both pumps enters the lumen and combines with HPO\(_4\)\(^2-\) to produce NaH\(_2\)PO\(_4\): called titratable acidity
   C. H\(^+\) combines with NH\(_3\) and Cl\(^-\) to form NH\(_4\)Cl: causes acid pH of urine
2. regeneration of HCO\(_3\)\(^-\):
   A. CO\(_2\) from the blood enters the collecting duct cells
   B. CO\(_2\) combines with H\(_2\)O with the aid of carbonic anhydrase to produce H\(_2\)CO\(_3\)
   C. H\(_2\)CO\(_3\) dissociates into H\(^+\) and HCO\(_3\)\(^-\):
      (1) newly synthesized HCO\(_3\)\(^-\) is reabsorbed back into the blood
      (2) H\(^+\) exchanges for K\(^+\) and is excreted in the urine or is excreted into the urine by the H\(^+\) ATPase pump
3. aldosterone blocker (e.g., spironolactone) effect—
   A. cannot excrete H⁺ ions → they will combine with Cl⁻
   B. develop a normal anion gap metabolic acidosis

4. site for type I distal RTA—
   A. dysfunctional pump
   B. H⁺ ions cannot be excreted and combine with Cl⁻ anions: produce normal anion gap metabolic acidosis
   C. cannot regenerate HCO₃⁻
   D. urine cannot be acidified after infusing NH₄Cl into the patient: urine pH > 5.5
   E. K⁺ is lost in the urine: severe hypokalemia with muscle weakness

5. collecting tubules are the site for diffusion of NH₃ from the medullary interstitial tissue (see #17) into the lumen where it combines with H⁺ to produce NH₄Cl

Normal dilution of urine:
1. UOsm in late distal collecting tubule/collecting duct is ~150 mOsm/kg—primarily contains free water and a little obligated water that must accompany solute
2. when P0sm is low, ADH is inhibited—
   A. absence of ADH causes loss of free water in the urine
   B. low UOsm
3. positive free water clearance (know how to calculate for USMLE)—
   A. \( CH₂O = V \cdot COsm \), where \( CH₂O \) = free water clearance, \( V \) = volume of urine in mL/min, \( COsm \) = obligated water
   B. to calculate COsm: COsm = UOsm x V/P0sm
   C. a positive CH₂O indicates dilution (free water is lost in the urine): it could also indicate acute tubular necrosis and absence of normal renal dilution/concentration
   D. example: urine volume 10 mL, P0sm 250 mOsm, UOsm 150 mOsm: COsm = 150 x 10/250 = 6 mL, CH₂O = 10 - 6 = +4 mL

4. effect of diuretics on CH₂O—
   A. loop diuretics inhibit the generation of free water by blocking the Na⁺/K⁺/2Cl⁻ cotransport pump: Na⁺ remains in the urine with its obligated water
   B. patients with unrestricted intake of water are not able to generate enough free water to eliminate in the urine: develop hyponatremia

5. summary of normal dilution—
   A. low UOsm: maximum dilution is 50 mOsm/kg
   B. absence of ADH
   C. positive CH₂O

Normal concentration of urine:
1. increase in P0sm is a stimulus for ADH release
2. ADH renders the late distal and collecting ducts permeable to free water (not Na⁺, cannot reabsorb obligated water)—
   A. urine is concentrated
   B. maximum of UOsm of 1200 mOsm/kg
3. negative CH₂O (free water is reabsorbed back into the blood)—e.g., urine volume 10 mL, P0sm 300 mOsm/kg, UOsm 900 mOsm/kg: COsm = 900 x 10/300 = 30 mL, CH₂O = 10 - 30 = -20 mL
4. ability to concentrate urine is the first abnormality in renal failure
5. summary of normal concentration—
   A. high UOsm
   B. presence of ADH
   C. negative CH₂O
Factors controlling serum Na⁺ concentration (NOTE—arrows represent degrees of magnitude):

1. serum Na⁺ - TBNa⁺/TBW -
   A. TBNa⁺ = total body sodium
   B. TBW = total body water
   C. daily serum Na⁺ concentration reflects TBW status:
      (1) hyponatremia usually indicates a gain in TBW
      (2) hypernatremia usually indicates a loss in TBW
   D. daily weight reflects TBNa⁺ status: increased weight usually indicates an increase in TBNa⁺

2. physical exam approximates TBNa⁺ status -
   A. ↓TBNa⁺:
      (1) signs of volume depletion
      (2) dry mucous membranes
      (3) decreased skin turgor (skin tenting)
      (4) drop in BP/increase in pulse when rising from supine position (positive tilt test)
   B. ↑TBNa⁺:
      (1) dependent pitting edema
         a. most of the Na⁺ is located in interstitial fluid compartment
         b. reason for pitting edema
         c. it is not possible to have pitting edema solely due to an increase in water in the interstitial space
      (2) body effusions: e.g., ascites
   C. normal TBNa⁺: normal skin turgor

Clinical examples and treatment (Rx) of isotonic loss of fluid:

1. clinical—most cases of adult diarrhea
2. pathophysiology—
   A. no osmotic gradient: equal loss of Na⁺ and water
   B. ↓EABV
   C. normal serum Na⁺: ⇔serum Na⁺ = ↓TBNa⁺/↓TBW
   D. ECF contracted (interrupted lines in schematic): signs of volume depletion
   E. normal ICF compartment
3. Rx—
   A. IV crystalloid solutions:
      (1) 0.9% normal saline
         a. contains 154 mEq/L of NaCl per liter
         b. distributed in plasma, which is 93% water
         c. final concentration in plasma is 0.93 x 154 = 143 mEq/L, which is isotonic
      (2) Ringer's lactate
         a. most physiologic IV solution
         b. contains K⁺, bicarbonate (lactate converted into bicarbonate by oxidation reactions)
         c. primarily used in Rx of volume depletion from diarrhea
   B. only isotonic fluids remain in ECF compartment and raise blood pressure (USMLE)
   C. 5% dextrose and water or 0.45% saline cannot raise the blood pressure: they are hypotonic solutions
   D. requires ~3 liters of normal saline for 1 liter to remain in vascular compartment:
      (1) 1 liter in vascular compartment
      (2) 2 liters in interstitial fluid compartment
Clinical example and Rx of isotonic gain of fluid:

1. **clinical**—excessive IV administration of 0.9% normal saline or Ringer's lactate
2. **pathophysiology**—
   A. no osmotic gradient: equal gain of Na⁺ and water,
   B. normal serum Na⁺: \( \text{serum Na}^+ = \text{TBNa}^+/\text{TBW} \)
   C. ↑EABV
   D. ECF expanded:
      1. dependent pitting edema/pulmonary edema
      2. TBNa⁺ is increased in interstitial compartment
   E. normal ICF compartment: no osmotic gradient
3. **Rx**—
   A. restrict salt/water intake
   B. diuretics

Pathogenesis of hyponatremia:

1. **decreased serum Na⁺ concentration**—<136 mEq/L
2. **generally indicates a problem with dilution** (inability to lose free water in the kidneys)—
   A. gain of pure water in the ECF must be countered by a loss of pure water in the urine
   B. loss of obligated water is not the same as losing pure water
3. **clinical manifestations**—
   A. mainly CNS due to cerebral edema from water movement into cells:
      1. mental status alterations
      2. seizures
   B. neuromuscular system: muscle cramps

Hyponatremia due to a hypertonic loss of fluid:

1. **clinical**—
   A. diuretics: MCC (Loops)
   B. Addison's disease—
      1. loss of aldosterone effect
      2. same pathophysiology as aldosterone blocker
   C. Also, 21- hydroxylase deficiency (same as Addison's)
NORMAL

\[ \frac{\text{ICF}}{\text{ECF}} \]

Correlates with serum Na\(^+\)

Volume

**ISOTONIC LOSS:** \( \leftrightarrow \) SERUM Na\(^+\) = \( \downarrow \text{TBNa}^+ / \downarrow \text{TBW} \)

Normal POsm

ICF normal

Volume contracted

- Adult diarrhea

**ISOTONIC GAIN:** \( \leftrightarrow \) SERUM Na\(^+\) = \( \uparrow \text{TBNa}^+ / \uparrow \text{TBW} \)

Normal POsm

ICF normal

Volume expanded

- Excessive isotonic saline
2. Pathophysiology—
   A. osmotic gradient favoring water movement into the ICF
   B. ↓EABV
   C. ↓serum Na⁺ = ↓TBNa⁺/↑TBW
   D. ECF contraction:
      (1) signs of volume depletion
      (2) TBNa⁺ is decreased
   E. ICF expansion: osmotic gradient is present

3. Rx—
   A. 0.9% normal saline
   B. 3% hypertonic saline rarely used
   C. rapid intravenous fluid correction of hyponatremia with saline may result in central pontine myelinolysis: irreversible demyelinating syndrome

Hyponatremia due to a hypotonic gain of water with salt:
1. Clinical— dependent pitting edema states
   A. congestive heart failure
   B. cirrhosis

2. Pathogenesis of hyponatremia in right heart failure— increased hydrostatic pressure in venous system in right heart failure:
   A. ↓EABV from decrease in cardiac output
   B. hypotonic gain of fluid from kidneys (see #10)
   C. hyponatremia
      (1) ↓serum Na⁺ = ↑TBNa⁺/↑↑TBW
      (2) ↑TBNa⁺ distributes in ECF leading to pitting edema
      (3) ↑↑TBW distributes in ECF and ICF, the latter by osmosis
   D. hypotonic fluid reabsorbed from kidneys is redirected into interstitial compartment by increased hydrostatic pressure in venous system

3. Pathogenesis of hyponatremia in cirrhosis— decrease in synthesis of albumin in cirrhosis:
   A. decrease in oncotic pressure
   B. transudate containing excess Na⁺ is redirected into interstitial space (dependent pitting edema)
   C. ↓venous return to heart leads to:
      (1) ↓EABV
      (2) hypotonic gain of fluid from kidneys
   D. hyponatremia: ↓serum Na⁺ = ↑TBNa⁺/↑↑TBW
   E. hypotonic fluid from kidney is redirected into the interstitial space due to the decreased oncotic pressure

4. Rx—
   A. restrict intake of salt and water
B. diuretics:
   (1) loop diuretics for CHF
   (2) spironolactone safer than loop diuretics in cirrhosis (see hepatobiliary notes)
C. heart failure:
   (1) decrease afterload: e.g., vasodilators
   (2) decrease preload: e.g., diuretics
   (3) ACE inhibitors decrease both afterload (block ATII) and preload (block aldosterone)

\[ \downarrow \text{POsm} \]
\[ \uparrow \text{ICF} \quad \uparrow \text{ECF} \]
Volume expanded

ECF expanded, pitting edema due to \( \uparrow \text{TBNa}^+ \)

\( \checkmark \) Hyponatremia due to a gain in pure water:
1. **clinical**—syndrome of inappropriate ADH (SiADH):
   A. ectopic secretion in small cell carcinoma of lung: MCC of SiADH
   B. drugs
      (1) chlorpropamide (sulfonylureas) \( \rightarrow \text{enhance activity of ADH} \)
      (2) cyclophosphamide
      (3) morphine
   C. CNS injury
   D. lung infections: TB

2. **pathophysiology of SiADH**—
   A. hypotonic gain of pure water: ECF/ICF expanded (see schematic)
   B. \( \downarrow \text{serum Na}^- = \text{TBNa}^+/\uparrow \text{TBW} \)
   C. normal skin turgor since TBNa\(^+\) is normal:
      (1) \( \uparrow \text{TBW} \) alone cannot produce pitting edema
      (2) majority of water is directed into ICF
         a. severe mental status abnormalities
         b. chance for herniation
   D. \( \uparrow \text{EABV} \):
      (1) \( \text{P}_{\text{H}} > \text{P}_{\text{O}} \): increase in renal blood flow
      (2) loss of Na\(^-\) in urine
         a. random UNa\(^+\) > 40 mEq/L
         b. proximal tubule cannot reabsorb any filtrate
         c. urea and uric acid also lost in urine: reason for low serum urea and uric acid
         d. low serum BUN and uric acid
   E. \( \uparrow \text{UOsm} \):
      (1) presence of ADH causes increased concentration of urine due to constant reabsorption of free water
      (2) patient should be diluting urine with a gain in water but patients with SiADH are concentrating urine due to inappropriate presence of ADH

3. **Rx**—
   A. restrict water
   B. demeclocycline for small cell cancer patients:
      (1) produces nephrogenic diabetes insipidus
      (2) no need to restrict water
HYPERTONIC LOSS: \( \downarrow \text{SERUM Na}^+ = \downarrow \text{TBNa}^+ / \downarrow \text{TBW} \)

- Diuretics
- Addison's disease

HYPOTONIC GAIN: \( \downarrow \text{SERUM Na}^+ = \uparrow \text{TBNa}^+ / \uparrow \uparrow \text{TBW} \)

- Congestive heart failure
- Cirrhosis

\[ \text{Serum Na}^+ : \frac{\text{TBNa}^+}{\text{TBW}} \]
HYPOTONIC GAIN: $\downarrow$SERUM $\text{Na}^+ = \text{TBNa}^+ / \uparrow\uparrow\text{TBW}$

- ICF expanded
- ECF expanded, no pitting edema since TBNa$^+$ is normal

- Inappropriate ADH syndrome
- Excessive water intake

HYPOTONIC LOSS: $\uparrow$SERUM $\text{Na}^+ = \text{TBNa}^+ / \downarrow\downarrow\text{TBW}$

- ICF contraction
- ECF contraction

- Slight ECF contraction, no signs volume depletion due to normal TBNa$^+$

- Diabetes insipidus
- Insensible water loss (e.g., fever)
Pathophysiology of hypernatremia:
1. **Definition**— serum Na⁺ concentration >147 mEq/L.
2. **Pathophysiology**—
   A. Loss of pure water: *purists call this dehydration* when there is only a loss of water and no salt
   B. Mixed loss of hypotonic fluid
   C. Hypertonic gain of Na⁺
   D. Patient usually has no access to water: cannot increase TBW, which would alter serum Na⁺ concentration
3. **Clinical**— CNS signs and symptoms:
   A. Convulsions
   B. Increased reflexes

Hypernatremia due to a pure water loss:
1. **Clinical**—
   A. Central and nephrogenic diabetes insipidus: lack ADH or tubule refractory to ADH
   B. Loss of insensible water: fever with evaporation of water from mucous membranes
2. **Pathophysiology**—
   A. Hypotonic loss of pure water: ↑serum Na⁺ = TBNa⁺/↓↓TBW
   B. EABV slightly decreased: not enough to show signs of volume depletion
   C. ECF slightly contracted: not enough to show signs of decreased skin turgor
   D. ICF contraction: osmotic gradient is present
   E. Normal hydration/skin turgor: no signs of volume depletion since TBNa⁺ is normal
3. **Rx**—
   A. Water by mouth if possible
   B. IV 5% dextrose and water
   C. Rapid correction of fluid losses in hypernatremia may result in brain herniation and death
Hypernatremia due to a hypertonic gain of Na⁺:
1. clinical–
   A. excess 3% hypertonic saline
   B. excess NaHCO₃
   C. IV infusion of Na⁺ containing antibiotics
2. pathophysiology–
   A. hypertonic gain of more salt than water: ↑serum Na⁺ = ↑↑TBNa⁺/↑TBW
   B. ↑EABV
   C. ECF expanded:
      (1) dependent pitting edema/pulmonary edema
      (2) TBNa⁺ is increased
   D. ICF contracted: osmotic gradient is present
3. Rx–
   A. restrict Na⁺
   B. diuretics

Hypernatremia due to mixed loss of hypotonic fluid:
1. clinical–
   A. sweating
   B. osmotic diuresis:
      (1) glucosuria in diabetic ketoacidosis or hyperosmolar nonketotic coma
      (2) use of mannitol
      (3) increased urine urea: obstruction of urine flow (prostate hyperplasia), increase in protein intake
   C. baby diarrhea: hypotonic loss rather than isotonic loss as in adults
2. pathophysiology–
   A. loss of more water than salt:
      (1) ↑serum Na⁺ = ↓TBNa⁺/↓↓TBW
      (2) ↓EABV
      (3) ECF contracted greater than with pure water loss due to ↓TBNa⁺: signs of volume depletion
      (4) ICF contracted: osmotic gradient is present
3. Rx–
   A. baby diarrhea:
      (1) give hypotonic salt solutions available in stores
      (2) if volume depleted, give 0.9% normal saline first to raise BP, then give 0.45% normal saline
   B. osmotic loss of fluid or sweating:
      (1) give 0.9% saline to restore blood pressure
HYPERTONIC GAIN: $\text{SERUM Na}^+ = \uparrow\text{TBNa}^+/\uparrow\text{TBW}$

- ECF expanded, pitting edema present due to $\uparrow\text{TBNa}^+$

  - Hypertonic saline (e.g., 3%)

HYPOTONIC LOSS: $\text{SERUM Na}^+ = \downarrow\text{TBNa}^+//\downarrow\text{TBW}$

- ECF contracted greater than with pure water loss due to $\downarrow\text{TBNa}^+$

  - Sweating
  - Osmotic diuresis (e.g., glucosuria)
  - Baby diarrhea

Oral treatment of cholera: Na$^+$ + glucose solution

They are reabsorbed together
Types of shock:
1. **hypovolemic shock**—
   A. hemorrhage: MCC of shock
   B. excessive fluid loss:
      1. sweat
      2. diarrhea
      3. severe burns
      4. vomiting
2. **cardiogenic shock**—e.g., acute myocardial infarction
3. **septic (endotoxic) shock**—e.g., gram negative endotoxic shock
4. **neurogenic shock**—e.g., loss of vasomotor tone in venules/small veins:
   A. fainting
   B. spinal cord injury

**Massive blood loss:**
1. loss of >20% of the blood volume (about 1000 ml) results in hypovolemic shock
2. hemoglobin (Hb)/hematocrit (Hct) changes—
   A. no initial effect due to loss of whole blood: loss of equal amounts of plasma and RBCs
   B. vascular contraction around the reduced volume of blood
   C. plasma replaced first and uncovers RBC deficit in hours to days
   D. infusion of crystalloid solutions immediately uncovers RBC deficit
3. **changes in pulmonary capillary wedge pressure (PCWP)**—
   A. measured with Swan-Ganz catheter (SGC) threaded into right heart
   B. PCWP indicates left ventricular end-diastolic pressure
   C. decreased PCWP in hypovolemic shock
4. **mixed venous oxygen content (MVO₂)**—
   A. measured with SGC in right heart
   B. **best indicator of tissue hypoxia**
   C. indicates how much or how little oxygen was extracted from the blood delivered to tissue
   D. decreased in hypovolemic shock: decreased cardiac output allows tissue to extract more O₂ than usual
5. **clinical**—
   A. cold/clammy skin: vasoconstriction of vessels in skin from catecholamine release
   B. hypotensive
   C. rapid weak pulse; compensatory response
6. **kidney in hypovolemic shock**—
   A. renal medulla most adversely affected in shock
   B. ischemic acute tubular necrosis common
7. Rx - IV crystalloid solutions while waiting for whole blood

Cardiogenic shock:
1. clinical - similar clinical findings as in hypovolemic shock
2. changes in pulmonary capillary wedge pressure (PCWP) - increased PCWP owing to a back-up of hydrostatic pressure into the pulmonary venous system
3. mixed venous oxygen content (MVO₂):
   A. decreased in cardiogenic shock
   B. decreased cardiac output allows tissue to extract more O₂ than usual
4. kidney in cardiogenic shock - same as in hypovolemic shock

Septic shock:
1. pathogenesis -
   A. endotoxins are lipid component of cell wall of gram negative bacteria:
      (1) endotoxins bind to the CD₁₄ receptors on leukocytes/endothelial cells
      (2) direct injury and/or release of chemical mediators
   B. interleukin (IL)-1/tumor necrosis factor (TNF) released from macrophage activation:
      increases neutrophil adhesion to vessels
   C. nitric oxide is released from damaged endothelial cells: vasodilator of peripheral resistance arterioles
   D. activation of alternative complement pathway:
      (1) release of anaphylotoxins C3a and C5a
      (2) cause histamine release and vasodilatation
   E. pancreatic release of myocardial depressant factor
   F. warm skin: peripheral arteriolar vasodilation from above vasodilators
   G. increased blood flow through microcirculation:
      (1) reduced O₂ exchange in tissue → tissue hypoxia
      (2) increased return of blood to heart → high output cardiac failure
2. clinical -
   A. E. coli sepsis from indwelling urinary catheter MCC
   B. urinary retention secondary to prostate hyperplasia also common cause
3. differences from hypovolemic/cardiacogenic shock -
   A. warm skin
   B. increased cardiac output
   C. increased MVO₂: tissue cannot extract O₂ from increased flow rate
4. complications -
   A. multiorgan dysfunction MC COD
   B. disseminated intravascular coagulation (DIC)
   C. ARDS: ( Vinci P. C.)
      (1) from neutrophil-injury
      (2) endotoxic shock is MCC of ARDS
   D. ischemic acute tubular necrosis
   E. severe absolute neutropenia: increased synthesis of adhesion molecules stimulated by endotoxin

Acid-base physiology:
1. primary alterations in the arterial PCₐₐₐ -
   A. respiratory acidosis:
      (1) ↑PaCO₂
      (2) ↓pH → ↑HCO₃⁻/↑PaCO₂
B. respiratory alkalosis:
   (1) ↓PaCO₂
   (2) ↑pH ~ ↓HCO₃⁻/↓↓PaCO₂

2. primary alterations in arterial HCO₃⁻
   A. metabolic acidosis:
      (1) ↓HCO₃⁻
      (2) ↓pH ~ ↓↓HCO₃⁻/↓PaCO₂
   B. metabolic alkalosis:
      (1) ↑HCO₃⁻
      (2) ↑pH ~ ↑↑HCO₃⁻/↑PaCO₂

Compensation:
1. brings arterial pH close to but not usually into the normal range of 7.35–7.45
2. pH 7.40 = ratio of HCO₃⁻/PCO₂ ~20/1–
   A. compensation always moves in the same direction as the primary disorder:
      (1) increase bicarbonate (metabolic alkalosis) must be compensated by an increase in PCO₂ (respiratory acidosis)
      (2) decrease in PCO₂ (respiratory alkalosis) must be compensated by a decrease in HCO₃⁻ (metabolic acidosis)
   B. compensation for primary metabolic alkalosis is respiratory acidosis
   C. compensation for primary metabolic acidosis is respiratory alkalosis
   D. compensation for primary respiratory acidosis is metabolic alkalosis
   E. compensation for primary respiratory alkalosis is metabolic acidosis

3. types of compensation–
   A. uncompensated: compensation for that disorder is still in the normal range
   B. partially compensated: compensation is outside its normal range and the pH is moving towards normal range
   C. fully compensated:
      (1) compensation brings pH into the normal range (rarely occurs)
      (2) chronic respiratory alkalosis in high altitude residents is the only known exception for full compensation

Respiratory acidosis:
1. alveolar hypoventilation–
   A. reduced ventilation results in hypercapnia: retain CO₂
   B. PaCO₂ >45 mm Hg: normal is 33–45 mm Hg
2. acute respiratory acidosis–
   A. PaCO₂ >45 mm Hg
   B. serum HCO₃⁻ ≤30 mEq/L:
      (1) indicates no renal compensation has occurred
      (2) requires 2–4 d for renal compensation to occur
3. chronic respiratory acidosis–
   A. PaCO₂ >45 mm Hg
   B. serum HCO₃⁻ >30 mEq/L: indicates renal compensation has occurred
4. causes–
   A. depression of CNS medullary respiratory center:
      (1) barbiturates
      (2) narcotics
      (3) CNS trauma
B. upper airway obstruction:
(1) acute epiglottitis (*H. influenzae*)/laryngotracheobronchitis (parainfluenza virus)
(2) café coronary (food obstruction)
C. chest bellows dysfunction related to weakness/paralysis of muscles of respiration (e.g., diaphragm):
(1) amyotrophic lateral sclerosis (ALS)
(2) polio
(3) Guillain Barré
(4) myasthenia gravis
(5) brachial plexus injury involving phrenic nerve (C 4)
D. primary lung disease:
(1) COPD (smoking) (chronic bronchitis → “blue blather”)
(2) cystic fibrosis
(3) severe pneumonia
(4) ARDS

5. S/S or respiratory acidosis—
A. somnolence
B. increased intracranial pressure: respiratory acidosis increases cerebral vessel dilatation/permeability
C. benign intracranial hypertension

6. additional lab findings—
A. hypoxemia: low PaO 2
B. hypochloremia due to exchange of Cl - anions (chloride shift) for HCO 3 - anions leaving cells and entering ECF for non-renal compensation
C. hyperkalemia due to excess K + ions enter cells for buffering in exchange for K + to maintain electroneutrality
D. secondary polycythemia due to erythropoietin stimulation of erythropoiesis

7. examples of acute and chronic respiratory acidosis—
A. pH 7.20 acidemia (<7.35), PCO 2 74 mm Hg respiratory acidosis (>45 mm Hg), HCO 3 - 28 mEq/L normal:
   (1) interpretation is acute respiratory acidosis
   (2) uncompensated (HCO 3 - is not outside the normal range)
B. pH 7.33 acidemia (<7.35), PCO 2 60 mm Hg respiratory acidosis (>45 mm Hg), HCO 3 - 31 mEq/L metabolic alkalosis (>28 mEq/L):
   (1) interpretation is chronic respiratory acidosis (HCO 3 - >30 mEq/L)
   (2) partially compensated metabolic alkalosis

Respiratory alkalosis:
1. alveolar hyperventilation (hypocapnia)—
   A. PaCO 2 <33 mm Hg
   B. blowing off more CO 2 than normal
2. acute respiratory alkalosis—
   A. HCO 3 - ≥18 mEq/L
   B. no renal compensation
3. chronic respiratory alkalosis—
   A. HCO 3 - <18 mEq/L but >12 mEq/L
   B. renal compensation is present
4. causes—
   A. CNS medullary respiratory center stimulation:
      (1) anxiety
(2) * normal pregnancy (estrogen/progestrone effect)
(3) * high altitude
(4) * salicylates  \(\rightarrow\) and metabolic acidosis \(\text{(mixed disorder)}\)
(5)  endotoxins
(6)  cirrhosis (toxic products)

B.  primary lung disease:
(1)  pulmonary embolus: tachypnea (rapid, shallow breathing)
(2)  restrictive lung disease: e.g., sarcoidosis
(3)  mild to moderate bronchial asthma: \textit{respiratory acidosis means patient is tiring and must be intubated}

5.  \textbf{S/S of respiratory alkalosis}—tetany
A.  alkalosis increases negative charges on albumin
B.  albumin binds more ionized calcium without altering the total calcium

6.  \textbf{additional lab abnormalities}—
A.  \textbf{hyperchloremia} due to intracellular exchange of \(\text{Cl}^-\) anions for \(\text{HCO}_3^-\) entering cells in non-renal compensation
B.  \textbf{hypokalemia} due to \(\text{H}^+\) ions leaving cells to lower the \(\text{pH}\) and \(\text{K}^+\) moving into cells to maintain electroneutrality
C.  \textbf{hypophosphatemia}, since alkalosis stimulates glycolysis leading to increased phosphorylation of glucose
D.  \textbf{low ionized calcium concentration} in the presence of a normal total calcium

7.  \textbf{examples of acute and chronic respiratory alkalosis}—
A.  \(\text{pH} 7.56\)  alkalemia \(>7.45\), \(\text{PCO}_2\) \(24\) mm Hg  respiratory alkalosis \(<33\) mm Hg), \(\text{HCO}_3^-\) \(21\) mEq/L  metabolic acidosis \(<22\) mEq/L):
\(\text{(1)}\)  interpretation is acute respiratory alkalosis
\(\text{(2)}\)  partially compensated metabolic acidosis \(\text{(HCO}_3^-\)  is outside the normal range but the \(\text{pH}\) is not normal)
B.  \(\text{pH} 7.48\)  alkalemia \(>7.45\), \(\text{PCO}_2\) \(20\) mm Hg  respiratory alkalosis \(<33\) mm Hg), \(\text{HCO}_3^-\) \(14\) mEq/L  metabolic acidosis \(<22\) mEq/L):
\(\text{(1)}\)  interpretation is chronic respiratory alkalosis \(\text{(HCO}_3^-\)  \(<18\) but \(>12\) mEq/L)
\(\text{(2)}\)  partially compensated metabolic acidosis

\(\Rightarrow\)  \textbf{Metabolic alkalosis:}

1.  \textbf{loss of \(\text{H}^+\) ions or a gain in \(\text{HCO}_3^-\) anions}—
A.  serum \(\text{HCO}_3^-\) \(>28\) mEq/L
B.  normal is \(22\)–\(28\) mEq/L

2.  \textbf{pathogenesis}—
A.  initial generation of metabolic alkalosis:
\(\text{(1)}\)  loss of \(\text{H}^+\) ions
\(\text{a.}\)  vomiting
\(\text{b.}\)  diuretics
\(\text{c.}\)  mineralocorticoid excess
\(\text{(2)}\)  gain in \(\text{HCO}_3^-\)
\(\text{a.}\)  excessive intake of \(\text{HCO}_3^-\)
\(\text{b.}\)  oxidative metabolism of acetate, lactate, citrate into \(\text{HCO}_3^-\)
B.  \textbf{maintenance of increased serum \(\text{HCO}_3^-\) in metabolic alkalosis:}
\(\text{(1)}\)  volume depletion must occur to maintain metabolic alkalosis\(\rightarrow\)
\(\text{(2)}\)  \(\downarrow\text{EABV}\) increases the proximal reabsorption of \(\text{Na}^+\) in exchange for \(\text{H}^+\) ions\(\rightarrow\)
\(\text{(3)}\)  increased \(\text{Na}^+/\text{H}^+\) exchange raises the renal threshold for reclaiming \(\text{HCO}_3^-\)\(\rightarrow\)
\(\text{(4)}\)  allows reclamation of most of the increase in filtered \(\text{HCO}_3^-\) load
3. causes (discussed separately below) --
   A. diuretics: MCC
   B. vomiting
   C. primary aldosteronism

4. S/S of metabolic alkalosis --
   A. increased risk for ventricular arrhythmias
   B. hypoxia occurs in myocardial tissue from a left shifted \( O_2 \) dissociation curve induced by alkalosis
   C. hypoxemia also occurs due to compensation of metabolic alkalosis by respiratory acidosis

5. example of metabolic alkalosis --
   A. \( 7.50 \) alkalemia (>7.45), \( PCO_2 \) 47 mm Hg respiratory acidosis (>45 mm Hg), \( HCO_3^- \) 35 mEq/L metabolic alkalosis (>28 mEq/L)
   B. interpretation is metabolic alkalosis
   C. partially compensated respiratory acidosis: \( PCO_2 \) is outside the normal range and the pH is not in the normal range

Pathogenesis of metabolic alkalosis due to vomiting:
1. parietal cells in body/fundus --
   A. normally synthesize and secrete \( H^+ \) ions into the stomach
   B. corresponding \( HCO_3^- \) anions move into the blood: called the alkaline tide

2. initial generation of metabolic alkalosis --
   A. every mEq of HCl lost in vomitus is counterbalanced by a mEq gain of \( HCO_3^- \) in the blood
   B. there is an accumulation of unneutralized \( HCO_3^- \) in the blood when HCl is lost from vomiting

3. maintenance of metabolic alkalosis --
   A. initially, the filtered load of \( HCO_3^- \) surpasses the proximal renal tubule threshold for reclaiming \( HCO_3^- \):
      (1) urine is alkaline as \( HCO_3^- \) excess is excreted as \( NaHCO_3 \)
      (2) there is a significant renal loss of \( Na^+ \) as \( NaHCO_3 \): random \( UNa^+ > 20 \) mEq/L
   B. loss of \( Cl^- \) anions in HCl decreases serum \( Cl^- \) concentration (hypochloremia) and the amount of chloride anions filtered in the urine: random \( UCl^- < 20 \) mEq/L
   C. excessive vomiting leads to:
      (1) volume depletion →
      (2) ↓EABV →
      (3) increased proximal tubule reabsorption of \( Na^+ \) in exchange for \( H^+ \) ions → further \( \uparrow \) alkalosis
      (4) increased renal threshold for reclaiming \( HCO_3^- \) →
      (5) urine pH becomes acid: called paradoxical aciduria

4. Rx --
   A. correction of volume depletion with 0.9% normal saline supplemented by KCl: reason why it is called chloride-responsive metabolic alkalosis
   B. corrects volume deficit and replaces \( Cl^- \) lost as HCl in the vomitus

Pathogenesis of metabolic alkalosis due to loop/thiazide diuretics:
1. MCC of metabolic alkalosis --
2. increased distal delivery of \( Na^+ \) leads to the following --
   A. augmented exchange of \( Na^+ \) in the urine for \( K^+ \) in the tubule at the \( Na^+ / K^+ \) aldosterone-enhanced pump
   B. hypokalemia occurs from the increased exchange
C. Na⁺ exchanges with H⁺ ions when K⁺ is depleted:
   (1) increases distal reclamation of HCO₃⁻ →
   (2) metabolic alkalosis

3. **Rx**–
   A. 0.9% normal saline to replace volume deficits
   B. KCl by mouth or in infusion
   C. correcting hypokalemia prevents metabolic alkalosis: enough K⁺ is available to exchange with Na⁺

**Pathogenesis of metabolic alkalosis due to primary aldosteronism (Conn’s syndrome):**

1. **causes**–
   A. MCC is a benign adenoma in the zona glomerulosa
   B. primary hyperplasia is a less common cause

2. **pathogenesis**–
   A. continual enhancement of distal Na⁺/K⁺ aldosterone pump
   B. increased Na⁺ reabsorption:
      (1) mild hypernatremia
      (2) increased loss of K⁺ in the urine from the enhanced Na⁺ exchange causes hypokalemia
   C. K⁺ depletion causes Na⁺ to exchange with H⁺ ions:
      (1) increased distal reclamation of HCO₃⁻ →
      (2) metabolic alkalosis

3. **effect of excess Na⁺ reabsorption into the ECF**–
   A. ECF volume increases: increases stroke volume and raises the systolic blood pressure
   B. excess Na⁺ enters smooth muscle cells of peripheral resistance arterioles
      (1) Na⁺ opens up calcium channels leading to vasoconstriction of smooth muscle cells
      (2) increases total peripheral resistance →
      (3) raises the diastolic blood pressure

4. **reason for the lack of pitting edema in primary aldosteronism**–
   A. ↑EABV from excess Na⁺ and water in the ECF compartment
   B. increased peritubular capillary hydrostatic pressure (Pₜ) prevents proximal tubule reabsorption of Na⁺:
      (1) majority of Na⁺ normally reabsorbed in the proximal tubule is lost in the urine
      (2) Na⁺/K⁺ aldosterone-enhanced pump is already maximally functioning and cannot reabsorb the Na⁺: called "escape mechanism"
      (4) increased renal loss of Na⁺ from the proximal tubule almost offsets the amount of Na⁺ reabsorbed by aldosterone
      (5) slight increase in TBNa⁺, though present, is not clinically detectable as pitting edema

5. **S/S of primary aldosteronism**–
   A. severe muscle weakness: due to hypokalemia (muscle cannot repolarize)
   B. diastolic hypertension
   C. tetany: from alkalotic state (see previous explanation)
   D. polyuria:
      (1) severe hypokalemia causes tubular refractoriness to ADH: called vacuolar nephropathy
      (2) acquired nephrogenic diabetes insipidus

6. **summary of lab findings**–
   A. low plasma renin activity:
      (1) increase in renal arterial blood flow inhibits renin release
      (2) increased aldosterone inhibits renin release
B. mild hypernatremia
C. severe hypokalemia
D. severe metabolic alkalosis

Metabolic acidosis:
1. definition—serum HCO₃⁻ concentration <22 mEq/L (22–28 mEq/L): could be venous or arterial blood
2. pathophysiology—
   A. addition of exogenous or endogenous acid: increased anion gap (AG) type
   B. loss of HCO₃⁻: normal AG type
3. concept of the anion gap—
   A. \( AG = Na^+ - (Cl^- + HCO_3^-) \)
   B. when the most common anions (Cl⁻ and HCO₃⁻) are subtracted from the most common cation (Na⁺), an apparent AG is present: AG represents unaccounted for anions not in the formula
   (1) albumin
   (2) phosphate
   (3) sulfate
   (4) lactate
C. in increased AG metabolic acidosis, the anion of the acid (e.g., lactate, acetoacetate) replaces the HCO₃⁻ lost to buffering the H⁺ ions of the acid:
   (1) electroneutrality is preserved
   (2) every 1 mEq/L of HCO₃⁻ that is lost by buffering H⁺ ions of the acid is replaced by the anion of the acid
D. example of a patient with diabetic ketoacidosis:
   (1) serum Na⁺ = 128 mEq/L, serum Cl⁻ = 89 mEq/L, serum HCO₃⁻ = 3.0 mEq/L
   (2) AG = 128 - (89 + 3) = 36
   (3) AG is 24 mEq/L above normal and is due to acetoacetate and β-hydroxybutyrate anions replacing the HCO₃⁻ ions lost to buffering of their respective H⁺ ions
E. in normal AG metabolic acidosis, HCO₃⁻ anions lost in stool or urine are replaced mEq for mEq by Cl⁻ anions, hence maintaining a normal AG and electroneutrality:
   (1) example serum Na⁺ = 128 mEq/L, serum Cl⁻ = 110 mEq/L, serum HCO₃⁻ = 6.0 mEq/L
   (2) AG = 128 - (110 + 6) = 12
   (3) note how Cl⁻ anions increased 1 mEq/L for every 1 mEq/L of HCO₃⁻ lost
   (4) called hyperchloremic normal AG metabolic acidosis
f. another method of expressing AG is to subtract unmeasured cations (e.g., calcium, magnesium, potassium) from the unmeasured anions (e.g., albumin, phosphate, sulfate, organic acids):
   (1) \( AG = \text{Unmeasured anions (UA)} - \text{Unmeasured cations (UC)} \)
   (2) \( \uparrow \text{AG by} \uparrow \text{UA (e.g., lactate)} \) or \( \downarrow \text{UC (e.g., hypocalcemia)} \)
   (3) \( \downarrow \text{AG by} \downarrow \text{UA (e.g., albumin)} \) or \( \uparrow \text{UC (e.g., hypercalcemia)} \)
4. causes of increased and normal AG—separately listed below
5. S/S of metabolic acidosis—
   A. hyperventilation: Kussmaul’s breathing (deep, rapid respirations)
   B. negative inotropic effect on myocardial tissue
   C. osteoporosis: bone buffers excess H⁺ ions
   D. warm shock: acidosis vasodilates peripheral resistance arterioles (warm skin)
6. example of metabolic acidosis—
   A. pH 7.28 acidemia (<7.35), PCO₂ 28 mm Hg respiratory alkalosis (<33 mm Hg), \( \text{HCO}_3^- \) 13 mEq/L metabolic acidosis (<22 mEq/L)
   B. interpretation is metabolic acidosis
   C. partially compensated respiratory alkalosis; PCO₂ is outside the normal range but the pH is not in the normal range

Increased AG metabolic acidosis:
1. lactic acidosis—causes:
   A. end-product of anaerobic glycolysis in tissue hypoxia
   B. alcoholism (see cell injury)
   C. liver disease: liver normally converts lactic acid into pyruvate in the Cori cycle
   D. phenformin and phenformin-like drugs used in treating type II diabetes
2. ketoacidosis—causes:
   A. diabetic ketoacidosis: type I diabetes with an excess in \( \text{AcAc} \) and \( \beta\text{-OHB} \)
   B. alcoholism: excess in \( \beta\text{-OHB} \)
   C. starvation: starvation ketosis
3. renal failure—retention of organic acids like phosphoric and sulfuric acid
4. salicylate intoxication—
   A. salicylic acid is an acid
   B. salicylates unCouple oxidative phosphorylation
      (1) tissue hypoxia
      (2) additional component of lactic acidosis
5. ethylene glycol poisoning—
   A. ethylene glycol is in antifreeze
   B. ethylene glycol is converted into glycolic and oxalic acid by alcohol dehydrogenase: example of competitive inhibition
   C. oxalate anions combine with calcium to form calcium oxalate crystals: crystals obstruct renal tubules and produce oliguric renal failure
   D. Rx with infusion of ethanol:
      (1) ethanol is metabolized by the same enzyme that metabolizes ethylene glycol (alcohol dehydrogenase)
      (2) unmetabolized ethylene glycol is removed by dialysis: recall that in competitive inhibition, increasing the substrate (ethanol) reverses the inhibition
6. methyl alcohol poisoning—
   A. present in:
      (1) window shield washer fluid
      (2) solvents for paints
   B. methyl alcohol is converted into formic acid by alcohol dehydrogenase: another example of competitive inhibition
      (1) damages the optic nerve (optic neuritis)
      (2) could lead to permanent blindness
   C. Rx similar to ethylene glycol
7. example of increased AG metabolic acidosis—serum Na⁺ 135 mEq/L (135–147 mEq/L), serum Cl⁻ = 98 mEq/L (95–105 mEq/L), serum HCO₃⁻ = 13 mEq/L (22–28 mEq/L), AG = 23 mEq/L (8–16 mEq/L)

Normal AG metabolic acidosis:
1. losing \( \text{HCO}_3^- \) and \( \text{HCO}_3^- \) is replaced by an equal number of \( \text{Cl}^- \) anions—hyperchloremic normal AG metabolic acidosis
2. **diarrhea**—
   A. **MCC of normal AG metabolic acidosis**
   B. lab findings:
      (1) isotonic loss of Na⁺ (normal serum Na⁺)
      (2) hypokalemia
      (3) normal AG metabolic acidosis

3. **distal type I renal tubular acidosis**—
   A. dysfunctional aldosterone-mediated H⁺/K⁺ ATPase pump in collecting ducts:
      (1) retain H⁺ ions, which combine with Cl⁻ ions in the blood to form HCl
      (2) cannot regenerate HCO₃⁻ (see above discussion)
      (3) cannot acidify urine (urine pH > 5.5)
   B. causes:
      (1) amphotericin B
      (2) Bence Jones protein
   C. Rx: increase bicarbonate intake

4. **proximal type II (proximal)**—
   A. lower threshold for HCO₃⁻ reclamation:
      (1) normal of threshold of 24 mEq/L is lowered to ~15 mEq/L
      (2) HCO₃⁻ is lost in the urine (urine pH > 5.5)
      (3) loss of HCO₃⁻ stops when the serum HCO₃⁻ equals the new renal threshold of 15 mEq/L
   B. causes:
      (1) heavy metals: e.g., lead
      (2) **Fanconi syndrome** with loss of—
         a. HCO₃⁻
         b. uric acid (hypouricemia)
         c. glucose (hypoglycemia)
         d. amino acids
         e. K⁺ (hypokalemia)
         f. phosphate (hypophosphatemia)
      (3) primary hyperparathyroidism: excess PTH blocks HCO₃⁻ reclamation
      (4) nephrotoxic drugs (aminoglycosides)
   C. Rx:
      (5) **Ca²⁺ inhibitors**
      (1) thiazides are given to produce volume depletion
      (2) volume depletion raises the renal threshold for reclaiming HCO₃⁻

5. **type IV renal tubular acidosis**—
   A. due to **destruction of the juxtaglomerular apparatus** in the afferent arteriole leading to low renin and low aldosterone: **hyperreninemic hypoaldosteronism**
   B. causes:
      (1) **MCC is hyaline arteriolosclerosis of the afferent arteriole** in diabetic nephropathy
      (2) interstitial nephritis: drugs, *Legionella pneumophila*
   C. lab findings relate to low aldosterone:
      (1) hyponatremia
      (2) hypokalemia: only RTA with hypokalemia
      (3) normal AG metabolic acidosis
   D. Rx: weak mineralocorticoid

6. example of normal anion gap metabolic acidosis—serum Na⁺ 135 mEq/L (135–147 mEq/L), serum Cl⁻ = 110 mEq/L (95–105 mEq/L), serum HCO₃⁻ = 13 mEq/L (22–28 mEq/L), AG = 12 mEq/L (8–16 mEq/L)
Lab Dx of mixed acid-base disorders:

1. blend of two or more acid-base disorders occurring at the same time—
   A. e.g., a patient with diabetic ketoacidosis (increased AG metabolic acidosis) is vomiting (metabolic alkalosis)
   B. in the above case, pH, PaCO₂, and HCO₃⁻ are all normal since the 2 conditions are exact opposites

2. final pH, PaCO₂, and HCO₃⁻ concentration depends on the sum of the expected values for each component—
   A. e.g., cardiorespiratory arrest with no breathing (acute respiratory acidosis) and cardiac standstill (metabolic acidosis from lactic acidosis)
   B. note: arrows represent degrees of magnitude

\[
\begin{align*}
\text{Respiratory acidosis} & \quad \downarrow \quad \uparrow \uparrow \text{(primary)} \\
\text{(compensation)} & \quad \downarrow \quad \downarrow \text{(compensation)} \\
\text{Metabolic acidosis} & \quad \downarrow \quad \downarrow \text{(primary)} \\
\text{Final blood gas} & \quad \downarrow \downarrow \text{(extreme acidemia)} \quad \uparrow \quad \downarrow
\end{align*}
\]

3. clues suggesting a mixed disorder—
   A. normal pH in the presence of an abnormal PaCO₂ or HCO₃⁻
   B. implies full compensation, which is extremely rare
   C. usually indicates a primary acidosis and a primary alkalosis
   D. e.g., salicylate intoxication:
      (1) pH 7.42 normal (7.35–7.45), PaCO₂ 16 mm Hg respiratory alkalosis (<33 mm Hg), HCO₃⁻ 10 mEq/L metabolic acidosis (<22 mEq/L), B. extreme acidemia:
      (2) e.g., primary metabolic acidosis + primary respiratory acidosis in a patient who is in cardiorespiratory arrest

Potassium:

1. general—
   A. maintained within a narrow range of 3.5–5.0 mEq/L
   B. major intracellular fluid (ICF) cation
   C. maintains cell volume and resting membrane potential

2. K⁺ alterations with pH (called transcellular shift)—
   A. acidosis (see schematic):
      (1) excess H⁺ ions enter RBCs/other cells and K⁺ exits RBCs/cells to maintain electroneutrality→
      (2) hyperkalemia
   B. alkalosis (see schematic):
      (1) H⁺ ions exit RBCs/other cells and K⁺ enters RBCs/cells→
      (2) hypokalemia
   C. exceptions to above:
      (1) diarrhea (ble of K⁺ loss in stool)
      (2) renal tubular acidosis (RTA)
      (3) there is acidosis and hypokalemia in both conditions indicating that more is lost in the body fluid than is gained by a shift out of cells
Hypokalemia:
1. <3.5 mEq/L (3.5–5.0 mEq/L)
2. decreased intake– uncommon
3. transcellular shift–
   A. alkalosis: see above discussion
   B. insulin Rx:
      (1) insulin enhances Na⁺/K⁺ ATPase pump
      (2) insulin is used in the Rx of hyperkalemia
   C. β₂ agonists (catecholamines and albuterol):
      (1) enhance the Na⁺/K⁺ ATPase pump
      (2) albuterol is used in the Rx of hyperkalemia
4. increased excretion–
   A. GI losses:
      (1) diarrhea
      (2) vomiting
   B. renal losses:
      (1) diuretics: MCC of hypokalemia
      (2) primary aldosteronism
      (3) proximal/distal renal RTA
5. S/S of hypokalemia–
   A. muscle weakness
   B. polyuria:
      (1) collecting tubules become refractory to ADH
      (2) acquired nephrogenic diabetes insipidus
6. ECG finding in hypokalemia–
   A. U wave
   B. positive wave after T wave
7. Rx– oral/IV K⁺ supplements

Transcellular shift of K⁺ in alkalosis

Hyperkalemia:
1. >5.0 mEq/L (3.5–5.0 mEq/L)
2. increased tissue breakdown–
   A. rhabdomyolysis: rupture of muscle
   B. iatrogenic hemolysis of RBCs:
      (1) pseudohyperkalemia
      (2) MC non-pathologic cause of hyperkalemia
3. transcellular shift–
   A. acidosis: see above discussion
   B. drugs:
      (1) digitalis overdose: blocks Na⁺/K⁺ ATPase pump
      (2) succinylcholine (muscle relaxant)
      (3) β-blockers (e.g., propranolol)
4. decreased excretion—
   A. renal failure: MC pathologic cause of hyperkalemia
   B. aldosterone deficiency:
      (1) drugs (spironolactone)
      (2) Addison's disease: loss of aldosterone effect
      (3) destruction of JG apparatus
         a. called hyporeninemic hypoaldosteronism or type IV RTA
         b. common in diabetic nephropathy

5. S/S of hyperkalemia—
   A. cardiac arrhythmias
   B. heart stops in diastole (USMLE)

6. ECG finding in hyperkalemia— peaked T wave

7. Rx—
   A. first protect the heart with IV calcium gluconate
   B. then redistribute K⁺:
      (1) insulin with glucose infusion
      (2) infusion NaHCO₃: create alkaloic state, which drive K⁺ into cells
      (3) albuterol
      C. then eliminate K⁺:
         (1) loop diuretics
         (2) cationic exchange resins
         (3) dialysis

![Transcellular shift of K⁺ in acidosis](image)

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Thrombosis:

1. definition of thrombus—
   A. intravascular mass attached to the vessel wall
   B. composed of varying proportions of coagulation factors, RBCs and platelets

2. pathogenesis of thrombi—
   A. stasis of blood flow: usually venous thrombosis
   B. turbulent blood flow: usually arterial thrombosis composed of platelets overlying an atheromatous plaque
   C. hypercoagulability— usually venous thrombosis
   D. postmortem clot: not attached to vessel wall

3. composition of venous thrombi—
   A. dark red mass of fibrin (red thrombus) within which are entrapped RBCs, white blood cells, and a few platelets
      (1) coagulation factors are used up in the clot
      (2) fibrinogen (factor I), prothrombin (factor II), V, VIII are consumed in a venous clot
   B. heparin and warfarin inhibit formation of venous clots since these drugs are anticoagulants
   C. not prevented by aspirin

4. composition of arterial thrombi—
   A. composed of platelets held together by fibrin strands
B. appear firm and pale:
(1) pale thrombus
(2) relative absence of entrapped RBCs
C. prevented by aspirin: decreases platelet aggregation
D. ticlopidine is used if patients are allergic to aspirin
E. heparin or warfarin do not prevent arterial thrombi composed of platelets
F. mural thrombus in the heart after a myocardial infarction are a combination of a platelet and "venous" clot
   (1) platelet part of the clot is that portion attached to the damaged endocardial surface
   (2) "venous" part of the clot is built on top of the platelet clot
   (3) aspirin and heparin/warfarin prevent these mixed clots

5. risk factors for venous thrombosis—
A. surgery: hip replacement worst
B. immobility: post-operative state
C. obesity
D. congestive heart failure (CHF)
E. malignancy: hypercoagulable due to an increase in fibrinogen, V, and VIII
F. oral contraceptives:
   (1) hypercoagulable
   (2) decreased antithrombin III
   (3) increased fibrinogen, V, VIII

6. risk factors for arterial thrombosis—
A. atherosclerosis: most important
B. smoking: chemicals damage vessels
C. hypertension
D. diabetes mellitus
E. LDL ≥160 mg/dL
F. HDL ≤35 mg/dL
G. family history of premature acute myocardial infarction and/or stroke
H. increased plasma homocysteine: folate deficiency MCC

7. MC site for venous thrombosis— deep veins of the calf
8. MC site for arterial thrombosis— coronary arteries
9. natural history of venous thrombi—
A. thromboembolization: potential for infarction
B. dissolution: role of fibrinolytic system
C. organization/possible recanalization: restoration of blood flow
D. infection of thrombus: potential for septic embolization and "metastatic" abscess formation

10. natural history of arterial thrombi—
A. infarction
B. dissolution by fibrinolytic system
C. embolization

Embolism:
1. definition— vessel occlusion by a mass (e.g., clot, fat, gas) with subsequent movement of the mass to a distant site
2. site of origin of pulmonary embolus—
A. proximal veins in thigh followed by pelvic veins:
B. deep veins of the calf are the MC site for thrombosis: they are not the MC site for embolization
3. site of origin for arterial embolization—
   A. left heart: MC site
      (1) left atrial thrombus in mitral stenosis
      (2) mural thrombus in an acute myocardial infarction
      (3) vegetations on aortic/mitral valve
      (4) cardiac myxoma in left atrium
   B. atherosclerotic plaque material in elastic arteries

4. paradoxical emboli—arise in the venous system and pass through an atrial septal defect (ASD) into the systemic circulation

5. fat embolization—
   A. traumatic fractures of the long bones: particularly femoral shaft and pelvis
   B. pathogenesis:
      (1) microglobules of fat from the bone marrow and/or surrounding adipose tissue enter the circulation and lodge in the microvasculature throughout the body
      (2) fatty acids damage vessel endothelium resulting in thrombosis and cause platelet adherence leading to thrombocytopenia
   C. S/S of fat embolization—
      (1) usually delayed 24–72 hs after trauma
      (2) CNS damage
         a. ischemia
         b. hemorrhage
         c. necrosis
      (3) respiratory failure: hypoxemia due to microglobules of fat in pulmonary capillaries interfering with gas exchange
      (4) severe dyspnea
      (5) thrombocytopenia: petechia over the upper half of the body and conjunctiva
   D. Rx—
      (1) oxygen
      (2) corticosteroids

6. amniotic fluid embolization—
   A. complication during a difficult labor/delivery
   B. S/S amniotic fluid embolism:
      (1) dyspnea
      (2) cardiovascular collapse
      (3) shock due to DIC: amniotic fluid is rich in thromboplastin
      (4) lanugo hair and/or fetal skin in the right side of the heart on pulmonary artery catheterization
   C. 80% mortality rate

7. air embolism—
   A. complicates head and neck surgery or catheter insertion into the jugular or subclavian veins
   B. air mixes with blood in the right heart causing frothy material that blocks pulmonary blood flow

8. *decompression sickness (Caisson’s disease)*—
   A. inert gases, like nitrogen, dissolve in tissues and come out of physical solution when environmental pressure drops too rapidly (rapid ascent from diving or rapid ascent in an airplane)
   B. most commonly occurs in scuba diving, but also may occur in rapid ascent in airplanes up to 18,000 feet
      (1) atmospheric pressure increases by 1 for every 33 feet of descent
(2) Nitrogen gas (normally 80% of inspired air) under increased pressure moves from the alveoli, through the blood, into the tissues; obesity predisposes to decompression sickness due to increased gas solubility.

(3) Rapid ascent forces nitrogen gas bubbles to develop in the tissue and blood vessels:
   a. S/S usually occur within minutes to hours after a dive
   b. Partial pressure of nitrogen in blood increases

(4) Bubbles develop in tissue and block blood vessels; acute findings include:
   a. "Bends" from nitrogen gas around joints
   b. Pruritus and mottling of skin
   c. Sinus/ear barotrauma: rupture of tympanic membrane
   d. Pneumomediastinum due to subcutaneous emphysema
   e. Hemiparesis
   f. Bladder and bowel dysfunction

(5) Chronic changes:
   a. Demyelination in the dorsal and lateral columns of inferior thoracic spinal cord rather than upper cord or brain
   b. Lower limb, bladder, and rectal paralysis
   c. Aseptic necrosis in bones

(6) Bubbles also active complement, produce platelet aggregation, and release vasoactive chemicals leading to ischemia

(7) Partial pressure of nitrogen in the blood increases

C. Rx: recompression in a hyperbaric chamber with 100% oxygen

**Questions used during the board review:**

Which of the following characterizes early endotoxic (septic) shock rather than hypovolemic or cardiogenic shock?

A. Warm skin
B. Decreased cardiac output
C. Low mixed venous oxygen content
D. Increased total peripheral resistance
E. Decreased venous return to the heart

A

Which of the following edema conditions represents a transudate secondary to an decrease in oncotic pressure?

A. Patient with pneumonia who has a pleural effusion
B. Patient with cirrhosis who has dependent pitting edema
C. Patient with edema of the arm post-modified radical mastectomy
D. Patient with a pulmonary infarction who has a left pleural effusion
E. Patient with congestive heart failure with bilateral pleural effusions

B
Items 3-4

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>PaCO₂</th>
<th>HCO₃⁻</th>
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<tbody>
<tr>
<td>A.</td>
<td>7.22</td>
<td>69</td>
<td>27</td>
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<tr>
<td>B.</td>
<td>7.26</td>
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<td>11</td>
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<tr>
<td>C.</td>
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<tr>
<td>D.</td>
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<tr>
<td>E.</td>
<td>7.51</td>
<td>48</td>
<td>38</td>
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</table>

A 56 year old patient who has been vomiting
answer: E (metabolic alkalosis)

A 51-year-old woman with rheumatoid arthritis has salicylate intoxication
answer: D mixed: respiratory alkalosis + metabolic acidosis
other ABG answers: A = acute respiratory acidosis, B = metabolic acidosis, C = chronic respiratory acidosis

In treating a patient with right heart failure who has dependent pitting edema, which of the following would be the MOST APPROPRIATE management of the patient’s sodium and water intake?

<table>
<thead>
<tr>
<th></th>
<th>Sodium intake</th>
<th>Water intake</th>
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</thead>
<tbody>
<tr>
<td>A.</td>
<td>No change</td>
<td>Decrease</td>
</tr>
<tr>
<td>B.</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>C.</td>
<td>Decrease</td>
<td>No change</td>
</tr>
<tr>
<td>D.</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>E.</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

D

A 58-year-old man with a small cell carcinoma of the lung presents with mental status abnormalities. A CT scan of the brain reveals cerebral edema but no space occupying lesions. Serum electrolytes exhibit a serum sodium of 110 mEq/L (136–145 mEq/L). There is no evidence of pitting edema or volume depletion. Which of the following is the BEST non-pharmacologic treatment of this patient?

<table>
<thead>
<tr>
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<th>Water intake</th>
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<tbody>
<tr>
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<td>Decrease</td>
<td>Decrease</td>
</tr>
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<td>B.</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>C.</td>
<td>Decrease</td>
<td>No change</td>
</tr>
<tr>
<td>D.</td>
<td>No change</td>
<td>Decrease</td>
</tr>
<tr>
<td>E.</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

D (SiADH)

Electrolyte patterns discussed in lecture

<table>
<thead>
<tr>
<th></th>
<th>Serum sodium</th>
<th>Serum potassium</th>
<th>Serum chloride</th>
<th>Serum bicarbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td>118</td>
<td>3.0</td>
<td>88</td>
<td>21</td>
</tr>
<tr>
<td>B.</td>
<td>152</td>
<td>2.8</td>
<td>110</td>
<td>33</td>
</tr>
<tr>
<td>C.</td>
<td>125</td>
<td>2.9</td>
<td>80</td>
<td>36</td>
</tr>
<tr>
<td>D.</td>
<td>126</td>
<td>5.8</td>
<td>86</td>
<td>18</td>
</tr>
</tbody>
</table>

A = inappropriate ADH syndrome, B = primary aldosteronism, C = diuretic therapy or vomiting, D = Addison’s disease
A 45-year-old man with diastolic hypertension presents with muscle weakness and tetany. Laboratory studies reveal mild hypernatremia, hypokalemia, and metabolic alkalosis. There is no evidence of pitting edema or volume depletion. The patient most likely has...

A. Addison's disease
B. chronic renal failure
C. primary aldosteronism
D. been taking a loop diuretic
E. type I renal tubular acidosis

C (primary aldosteronism)
Top three causes of death in the United States in descending order:
1. in descending order they are—
   A. heart disease
   B. cancer
   C. stroke
2. effect of dietary factors on the above—high-fat, low-fiber diets contribute to all of these disorders

Macronutrients:
1. definition—
   A. proteins
   B. fats
   C. carbohydrates
2. assessment—
   A. total body composition: body weight
   B. body fat composition: skin fold calipers
   C. immunocompetence testing:
      (1) total lymphocyte count: bad sign if reduced
      (2) cutaneous sensitivity to Candida: called anergy
   D. lean body mass (somatic protein): urine creatinine
   E. visceral protein mass:
      (1) albumin
      (2) transferrin
      (3) prealbumin (transthyretin)
      (4) retinol-binding protein (best test)

Micronutrients:
1. definition—
   A. vitamins
   B. trace elements
2. assessment—
   A. “static” tests: e.g., serum folate
   B. functional tests: effect on transketolase activity after thiamine pyrophosphate is added

Anorexia nervosa:
1. distorted body image—leads to significant weight loss due to lack of eating
2. clinical—
   A. secondary amenorrhea:
      (1) loss of body fat/weight <15% of normal in women→
      (2) reduces hypothalamic gonadotropin releasing hormone (GnRH) secretion→
      (3) low FSH/LH (gonadotropins in anterior pituitary)→
      (4) low estrogen levels→
      (5) secondary amenorrhea
   B. osteoporosis: from estrogen lack
   C. increased lanugo hair on face (USMLE): not androgen-dependent hair
   D. ventricular arrhythmias: MC cause of death (COD)
3. lab findings—
   A. increased stress hormones:
      (1) cortisol
4. **USMLE scenarios**
   A. danger of weight loss syndrome/anorexia nervosa: osteoporosis due to lack of estrogen
   B. MC COD in anorexia: ventricular arrhythmias

**Bulimia nervosa:**
1. **MC in young women**
2. **voluntary vomiting of food**— "binge" and then vomit food
3. **clinical**—
   A. body weight usually normal
   B. body image not as distorted as in anorexia
   C. complications of vomiting:
      (1) acid injury to tooth enamel: brown discoloration due to loss of enamel and exposure of dentine
      (2) knuckle bruising (Russell's sign)
      (3) salivary gland enlargement
      (4) Mallory-Weiss syndrome: laceration of esophageal/stomach mucosa
      (5) Boerhaave's syndrome: rupture of stomach/distal esophagus
      (6) electrolyte disturbances: hypokalemic metabolic alkalosis

4. **USMLE scenarios**
   A. enamel injury in young woman: bulimia
   B. acid-base disturbance in bulimia: metabolic alkalosis from vomiting

**Obesity:**
1. **definition**—
   A. **body mass index (BMI)** $> 30$ kg/m$^2$: weight in kilograms divided by the height in meters squared
   B. **morbid obesity**: BMI $> 40$ kg/m$^2$

2. **pathogenesis**—
   A. hereditary factors (50–75%):
      (1) e.g., gene inactivation of leptin protein in adipose
      (2) leptin is normally released from adipose and inhibits the hypothalamic satiety center
   B. ethnicity:
      (1) Native Americans (Pima Indians)
      (2) Hispanics
      (3) African-Americans
   C. psychological factors: e.g., depression
   D. biological factors: e.g., hypothyroidism

3. **clinical**—
   A. cardiovascular:
      (1) hypertension (MC complication)
      (2) left ventricular hypertrophy: related to hypertension
      (3) thromboembolism
      (4) increased LDL/VLDL
      (5) decreased HDL
   B. abdominal obesity (waist-to-hip ratio approaching 1) increases incidence of:
      (1) coronary artery disease (CAD)
      (2) hypertension
(3) stroke
(4) diabetes mellitus: down regulation of insulin receptors as adipose increases
(5) cholesterol gallstones
(6) cancers of breast/endometrium

C. respiritory:
(1) obstructive sleep apnea
(2) Pickwickian syndrome: omental adipose hinders diaphragm movement

D. GI:
(1) cancer risks
   a. colorectal
   b. pancreas
   c. gallbladder
(2) CH gallstones: more CH in bile
(3) fatty change in liver

E. musculoskeletal: osteoarthritis
F. endocrine: type II DM
G. reproductive: cancer risk includes
(1) breast
(2) endometrium
(3) ovary
(4) prostate

4. Rx-
   A. behavior modification
   B. low calorie diets
   C. exercise
   D. medication: amphetamine type drugs
   E. surgery

5. COD in calorie restricted diets- ventricular arrhythmias

Protein-energy malnutrition (PEM):
1. definition- supply of protein and/or calories is inadequate for body demands
2. kwashiorkor-
   A. decreased protein intake:
      (1) hypoproteinemia/hypoalbuminemia
      (2) normal total caloric intake (all carbohydrates)
   B. fatty liver: decreased synthesis of apolipoproteins . TAG's are trapped in liver
   C. pitting edema: due to hypoalbuminemia
   D. flaky paint dermatitis
   E. anemia
   F. low lymphocyte count
   G. anergy
   H. diarrhea:
      (1) loss of brush border enzymes
      (2) parasitic infestations
   I. flag sign: red hair from copper deficiency
   J. growth failure
3. marasmus-
   A. decreased total caloric intake
   B. loss of muscle mass
   C. broomstick extremities
   D. growth failure
4. **USMLE scenario**—know differences between kwashiorkor and marasmus

**Vitamin overview:**

1. **fat soluble vitamins**—A, D, E, K
2. **water soluble**
   - A. $B_1$: thiamine
   - B. $B_2$: riboflavin
   - C. $B_3$: niacin
   - D. $B_6$: pyridoxine
   - E. folate
   - F. $B_{12}$: cobalamin
3. **USMLE scenario**—
   - A. what vitamin supplements for cystic fibrosis: all the fat soluble vitamins
   - B. pancreatic malabsorption of fat and fat soluble vitamins
4. **reabsorption of vitamins**—
   - A. proximal small intestine
   - B. exception is vitamin $B_{12}$ in the terminal ileum
5. **functions**—
   - A. biochemical reactions:
     - (1) reducing agents: vitamin C
     - (2) cofactors in oxidative decarboxylation (remove CO$_2$)
       - a. thiamine
       - b. pyridoxine
     - (3) oxidative phosphorylation
       - a. riboflavin
       - b. niacin
     - (4) carboxylase (add CO$_2$): biotin
     - (5) transamination: pyridoxine
     - (6) components of coenzyme A: pantothenic acid
     - (7) DNA synthesis: folate and $B_{12}$
   - B. cell growth/differentiation:
     - (1) vitamin A
     - (2) folate and $B_{12}$
   - C. antioxidants:
     - (1) $\beta$-carotene
     - (2) vitamin E
     - (3) ascorbic acid
   - D. hormones: vitamin D
   - E. hemostasis:
     - (1) vitamin C
     - (2) vitamin K
     - (3) vitamin E

6. **toxicity**—MC with fat soluble vitamins

**Vitamin A:**

1. **functions**—
   - A. vision:
     - (1) retinol maintains rhodopsin in rods for night vision
     - (2) iodopsin maintains cones for daytime vision
     - (3) thyroxine enhances intestinal conversion of $\beta$-carotene to retinol→
       - a. retinol binds to retinol-binding protein (RBP)→
b. stored as retinol esters in liver
B. spermatogenesis
C. normal growth
D. wound healing

2. causes of deficiency—
   A. MCC is malabsorption
   B. liver disease
   C. diets lacking β-carotene: e.g., due to decreased intake of green vegetables
   D. drugs: e.g., cholestyramine

3. S/S of vitamin A deficiency—
   A. night blindness (nyctalopia): first sign
   B. squamous metaplasia of corneal epithelium:
      (1) called Bitot's spots
      (2) corneal softening (keratomalacia)/ulcers/infection/blindness: very common cause of global blindness
   C. bronchitis/pneumonia:
      (1) squamous metaplasia
      (2) lung cancer
   D. growth retardation: decreased epiphyseal bone formation
   E. follicular hyperkeratosis: squamous metaplasia in hair follicles
   F. poor wound healing

4. causes of vitamin A toxicity—
   A. eating bear liver
   B. common in big game hunters/Eskimos

5. S/S of vitamin A toxicity—
   A. increased intracranial pressure:
      (1) MC complication
      (2) papilledema:
         a. picture of papilledema on USMLE
         b. could be malignant hypertension, space occupying lesion in brain, Pb poisoning, hypervitaminosis A depending on stem of question
      (3) convulsions
      (4) bulging fontanelles in infants: increased intracranial pressure
   B. liver toxicity: elevated transaminases
   C. bone pain: periostitis
   D. hypercalcemia

6. β-carotenemia—
   A. drinking too much carrot juice
   B. no toxicity: toxicity is due to increased intake of retinoic acid
   C. white sclera/yellow skin (USMLE)
   D. yellow skin discoloration noted in primary hypothyroidism

Vitamin D:
1. sources—
   A. sunlight: most important source
   B. diet:
      (1) USMLE question on colostrum in milk
      (2) vitamin D is absent in colostrum of breast milk

2. metabolism—
   A. skin-derived 7-dehydrocholesterol converted to vitamin D₃→
(1) both skin/diet-derived vitamin D hydroxylated in liver to 25-(OH)-D$_3$ (cholecalciferol or calcidiol) →
(2) 25-(OH)-D$_3$ undergoes second hydroxylation (1α-hydroxylase) in proximal tubules to form 1,25-(OH)$_2$-D$_3$ (calcitriol)
B. PTH/hypophosphatemia enhance 1α-hydroxylase synthesis
C. 1,25-(OH)$_2$-D$_3$/hyperphosphatemia inhibit 1α-hydroxylase: 25-(OH)-D$_3$ converted into an inactive metabolite called 24,25-(OH)$_2$-D$_3$

3. **functions of vitamin D**—
A. vitamin D receptors are located in the duodenum and on osteoblasts
B. reabsorption of calcium/phosphorous
C. osteoblast:
   (1) releases alkaline phosphatase →
   (2) establishes high solubility product →
   (3) mineralization of cartilage/bone

4. **functions of parathormone (PTH)**—
A. reabsorbs calcium from kidney
B. increases reabsorption of calcium/phosphate from bowel: indirect function related to vitamin D
C. decreases phosphorous/bicarbonate reabsorption in proximal tubule
D. PTH attaches to receptors on osteoblasts:
   (1) interleukin-1 (osteoclast activating factor) released →
   (2) IL-1 activates osteoclasts →
   (3) release of calcium into the blood maintains the ionized calcium level (main function)
E. 1,25-(OH)$_2$-D$_3$ and PTH stimulate conversion of bone marrow macrophages into osteoclasts

5. **functions of calcitonin**—
A. synthesized in parafollicular cells in thyroid
B. activation of receptors on osteoclasts by calcitonin inhibits their activity
C. clinical uses of calcitonin:
   (1) Rx of hypercalcemia
   (2) Rx of Paget's disease of bone
   (3) Rx of osteoporosis

6. **physiologic events that occur when 1,25-(OH)$_2$-D$_3$ is decreased**—
A. hypocalcemia/hypophosphatemia →
B. increased PTH (stimulus of hypocalcemia) from secondary hyperparathyroidism →
C. unfavorable solubility product for bone mineralization →
D. increased PTH increases bone resorption by osteoclasts →
E. rickets in children/osteomalacia in adults

7. **physiologic events that occur when 1,25-(OH)$_2$-D$_3$ is increased**—
A. hypercalcemia/hyperphosphatemia (increases solubility product, metastatic calcification in soft tissue/kidneys) →
B. suppression of PTH release by hypercalcemia/hyperphosphatemia/increased 1,25-(OH)$_2$-D$_3$ →
C. excess bone resorption due to increased 1,25-(OH)$_2$-D$_3$ stimulation of marrow macrophages into osteoclasts →
D. excessive bone resorption,
E. note: either an increase or decrease in vitamin D results in excess bone resorption
8. causes of vitamin D deficiency—
   A. chronic renal failure (CRF):
      (1) MCC
      (2) lack of 1α-hydroxylase
   B. poor diet:
      (1) alcoholism
      (2) elderly
   C. malabsorption: e.g., celiac disease
   D. liver disease:
      (1) e.g., cirrhosis
      (2) decreased first hydroxylated
   E. drugs enhancing cytochrome P-450 system:
      (1) increases metabolism of 25-(OH)-D₃
      (2) e.g., alcohol, phenytoin, barbiturates
   F. hypoparathyroidism/hyperphosphatemia: decreased 1α-hydroxylase synthesis
   G. genetic diseases:
      (1) enzyme deficiency (type I vitamin D-dependent rickets)
      (2) deficiency of vitamin D receptors in target tissue (type II vitamin D-dependent rickets)

9. S/S of vitamin D deficiency in both rickets/osteomalacia—
   A. loss of bone density:
      (1) osteopenia
      (2) pathologic fractures (bone pain)
   B. excess in normal osteoid
   C. Looser's lines:
      (1) metaphyseal blood vessels push aside soft, unmineralized osteoid producing linear lines resembling a fracture
      (2) also called pseudofractures or milkman's fractures
   D. bowed legs: due to soft osteoid yielding under stress

10. S/S of vitamin D deficiency in rickets only—
    A. defective mineralization of cartilage in epiphyseal growth plates: growth failure
    B. abnormal calcification of osteoid at the bone/osteoid interface: adults have defective mineralization of the diaphysis
    C. skeletal deformities
    D. widening of osteoid seams in the epiphyses of the ribs: rachitic rosary
    E. craniofibas: excess osteoid in the skull produces increased elastic recoil on palpation

11. lab measurement of vitamin D—
    A. serum 25-(OH)-D₃:
       (1) best evaluates vitamin D status due to long circulating half-life of 3 wks
       (2) represents non-renal generated vitamin D from diet/photoformation
    B. serum 1,25-(OH)₂-D₃:
       (1) limited usefulness due to short half-life of 4–6 hours
       (2) most useful in differentiating type I vs type II vitamin D dependent rickets—
          a. decreased in type I (enzyme deficiency)
          b. increased in type II (receptor deficiency)

12. lab findings in vitamin D deficiency of non-renal origin (e.g., malabsorption)—
    A. low serum calcium
    B. low serum phosphorous
    C. high serum alkaline phosphatase: due to secondary hyperparathyroidism
    D. high serum PTH: due to the stimulus of hypocalcemia
E. low serum 25-(OH)-D$_3$
F. low serum 1,25-(OH)$_2$-D$_3$

13. **lab findings in vitamin D deficiency due to chronic renal failure**--
   A. low serum calcium
   B. **high serum phosphorous**: normalizes when secondary hyperparathyroidism occurs
   C. high serum alkaline phosphatase: due to secondary hyperparathyroidism
   D. high serum PTH: stimulus of hypocalcemia
   E. **normal serum 25-(OH)-D$_3$
   F. **low serum 1,25-(OH)$_2$-D$_3$
   G. Rx with active form of vitamin D

14. **lab findings in vitamin D deficiency due to type I vitamin D-dependent rickets (low 1α-hydroxylase)**--
   A. low serum calcium
   B. low serum phosphorous
   C. high serum alkaline phosphatase: due to secondary hyperparathyroidism
   D. high serum PTH: stimulus of hypocalcemia
   E. **normal serum 25-(OH)-D$_3$
   F. **low serum 1,25-(OH)$_2$-D$_3$

15. **lab findings in vitamin D deficiency due to type II vitamin D-dependent rickets (absent receptors for vitamin D)**-- same as type I except for a **high serum 1,25-(OH)$_2$-D$_3$**: no receptor to take it up

16. **lab findings in vitamin D deficiency due to hypoparathyroidism**--
   A. low serum calcium
   B. high serum phosphorous
   C. high serum alkaline phosphatase: due to secondary hyperparathyroidism
   D. low serum PTH
   E. **normal serum 25-(OH)-D$_3$
   F. low serum 1,25-(OH)$_2$-D$_3$: no 1α-hydroxylase due to low PTH

17. **cause of hypervitaminosis D**-- vitamin faddists

18. **S/S of vitamin D toxicity**--
   A. hypercalcemia
   B. metastatic calcification in kidneys: renal failure
   C. renal stones

19. **USMLE scenarios**--
   A. why is there hypocalcemia in CRF?
   B. loss of 1α-hydroxylase enzyme leads to hypovitaminosis D → hypocalcemia

**Vitamin E:**

1. **α-tocopherol most active form**

2. **functions**--
   A. antioxidant
   B. prevents free radical catalyzed-lipid peroxidation of polyunsaturated fatty acids in cell membranes

3. **causes of vitamin E deficiency**--
   A. chronic fat malabsorption: cystic fibrosis MCC
   B. abetalipoproteinemia: malabsorption due to absent apolipoprotein B

4. **S/S of vitamin E deficiency**--
   A. spinocerebellar ataxia
   B. posterior column disease
   C. peripheral neuropathy
D. hemolytic anemia: membrane defect
E. retinopathy
F. "brown bowel syndrome":
   (1) mainly seen in cystic fibrosis patients
   (2) increase in lipofuscin from increased lipid peroxidation

5. S/S of vitamin E toxicity—
   A. hemorrhagic diathesis:
      (1) decreases synthesis of vitamin K dependent coagulation factors
      (2) potentiates warfarin effects
   B. possible USMLE scenario;
      (1) man post recovery myocardial infarction is on warfarin and hemorrhages from GI tract
      (2) taking excess vitamin E as an antioxidant

\textit{Vitamin K:}

1. source—
   A. K\textsubscript{1} in plants converted by colonic bacteria to less active vitamin K\textsubscript{2}
   B. K\textsubscript{2} must be reconverted back to K\textsubscript{1} by epoxide reductase for it to function

2. function—
   A. K\textsubscript{1} is a coenzyme for activation of liver-derived vitamin K-dependent factors:
      (1) II (prothrombin)
      (2) VII
      (3) IX
      (4) X
      (5) proteins C/S
   B. biochemical reaction is posttranslational \(\gamma\)-carboxylation of their glutamic acid residues: allows calcium to bind the vitamin K dependent factor in the formation of a clot

3. causes of vitamin K deficiency—
   A. broad spectrum antibiotics:
      (1) MCC in a hospitalized patient
      (2) kills colonic bacteria
   B. malabsorption syndromes:
      (1) chronic pancreatitis
      (2) bile salt deficiency
      (3) small bowel disease
   C. newborns:
      (1) no colonic bacteria
      (2) very little vitamin K in breast milk
      (3) reason for intramuscular injection of vitamin K at birth (low levels after 3–5th d)
   D. drugs/chemicals:
      (1) warfarin inhibits epoxide reductase
      (2) rat poison (warfarin)

4. S/S of vitamin K deficiency— hemorrhagic disorder with multiple factor deficiencies
   A. ecchymoses
   B. GI bleeding

5. lab testing for vitamin K deficiency—
   A. prothrombin time (PT):
      (1) best test
      (2) covers all vitamin K dependent factors except IX
   B. partial thromboplastin time (PTT) is also prolonged but it is not the most sensitive test
6. **USMLE scenarios**

A. how to Rx child who ate rat poison: give IM vitamin K

B. why is heparin given at the same time as warfarin:
   1. heparin immediately anticoagulates the patient by enhancing antithrombin III
   2. warfarin prevents any further γ-carboxylation of coagulation factors but those that have been activated have half-lives
      a. factor VII ~6 h
      b. factor II (prothrombin) ~3–4 d

C. cause of **hemorrhagic skin necrosis** with warfarin:
   1. patient is heterozygous for protein C or S deficiency: has ~50% factor levels
   2. both factors have a very short half-life like factor VII (~6 hs)
   3. in ~6 hs after starting warfarin, activated C/S factors are gone and the patient has 0 factor levels→ leads to vessel thrombosis in skin
   4. **Rx with heparin and very small incremental doses of warfarin**

D. comparison of mature breast milk with cow’s milk:
   1. cows milk has more vitamin K (very little in breast milk)
   2. cows milk has more vitamin B₁₂ (less in breast milk)
   3. cows milk has more casein: whey is the primary protein in breast milk
   4. cows milk has less ascorbic acid: more in breast milk
   5. breast milk is low in iron but it is absorbed very well in the babies duodenum

**Vitamin C (ascorbic acid):**

1. **sources**—
   A. citrus fruits
   B. green vegetables

2. **functions**—
   A. reducing agent:
      1. posttranslational hydroxylation of proline/lysine in collagen synthesis
      2. reduction of iron from ferric to ferrous state (occurs in GI tract)
      3. keeps tetrahydrofolate in the reduced form
      4. antioxidant (traps free radicals)
      5. synthesis of catecholamines

   B. prevents nitrosamination: important in preventing stomach cancer due to nitrosamines

3. **causes of vitamin C deficiency**—
   A. poor diet: common in elderly, adolescents, and alcoholics
   B. smoking: lower vitamin C levels than non-smokers

4. **S/S of vitamin C deficiency (scurvy)**—
   A. poor wound healing: lack of hydroxylation leaves no binding site for cross-bridges
   B. bone pain:
      1. subperiosteal bleeding
      2. hemarthroses
   C. hemostasis abnormalities:
      1. ecchymoses (vessel instability)
      2. hemarthroses
      3. **perifollicular hemorrhage** (USMLE)
   D. scurbutic rosary
      1. rib enlargement in children
      2. increase in structurally abnormal osteoid
   E. corkscrew hairs
   F. bleeding gums after brushing teeth
   G. periodontitis/loss of teeth: loss of teeth
H. painful glossitis: smooth, red tongue
I. anemias: iron/folate deficiency
J. increased bleeding time

5. **S/S of vitamin C excess**
   A. false-negative urine dipstick reactions:
      (1) blood
      (2) glucose
      (3) bilirubin
      (4) nitrites
      (5) leukocyte esterase
   B. diarrhea
   C. calcium oxalate/urate acid renal stones (USMLE)

6. **USMLE scenario**— elderly woman with tea and toast diet has bleeding gums after brushing teeth, burning tongue, and perifollicular hemorrhages: scurvy

**Thiamine (B<sub>1</sub>):**

1. **sources**—
   A. meats
   B. wheat

2. **functions**—
   A. thiamine pyrophosphate (TPP) is a **cofactor in oxidative decarboxylation**:
      (1) **pyruvate dehydrogenase complex**
          a. converts pyruvate into acetyl-CoA,
          b. acetyl-CoA combines with oxaloacetate to produce citrate
          c. NAD<sup>+</sup> to NADH<sub>2</sub> reaction generates 6 ATP
      (2) cofactor in **α-ketoglutarate dehydrogenase reaction**
          a. converts α-ketoglutarate to succinyl CoA in TCA cycle
          b. NAD to NADH<sub>2</sub> reaction generates 6 ATP
      (3) cofactor in **α-keto acid dehydrogenase complex**
          a. branched-chain amino acid metabolism
          b. absence of this enzyme results in maple syrup urine disease
      (4) cofactor in **RBC transketolase enzyme reactions**: two-carbon transfer reactions in pentose phosphate pathway
   B. **note importance of thiamine in generating ATP**

3. **causes of thiamine deficiency**—
   A. **alcoholism (MCC):** poor diet
   B. polished rice: Far East
   C. renal dialysis/diuretics
   D. high carbohydrate diet: uses up TTP in dehydrogenase reactions

4. **S/S of thiamine deficiency**—
   A. related to ATP deficiency
   B. wet beriberi: congestive cardiomyopathy
      (1) dilated type
      (2) left/right heart failure
      (3) dependent pitting edema
   C. dry beriberi:
      (1) demyelination syndromes
      (2) peripheral neuropathy: distal sensorimotor neuropathy
      (3) Wernicke’s encephalopathy
          a. confusion
          b. ataxia
c. ophthalmoplegia (eye muscle palsies)
d. nystagmus

(4) Korsakoff’s psychosis
  a. inability to remember new/old information
  b. confabulation

(5) hemorrhage into mamillary bodies and periventricular areas of the brain

5. **USMLE scenario**— patient given IV with glucose and develops Wernicke’s encephalopathy:
   A. glucose converted to pyruvate and pyruvate to acetyl CoA
   B. uses up remaining thiamine
   C. precipitates attack
   D. always infuse IV thiamine before giving a patient glucose

**Riboflavin (B₂):**
1. **sources**—
   A. dairy products
   B. green leafy vegetables
   C. synthesized by colonic bacteria

2. **functions**—
   A. component of flavin mononucleotide (FMN)/flavin adenine dinucleotide (FAD): important in oxidative phosphorylation reactions
   B. component of glutathione reductase in pentose phosphate shunt: produces reduced glutathione, a potent antioxidant

3. **S/S of riboflavin deficiency**—
   A. corneal neovascularization: MC sign
   B. facial dermatitis
   C. fissuring/dry scaling of vermilion borders of lips (cheilosis) and angles of the mouth (angular cheilosis/stomatitis)
   D. glossitis: magenta-colored tongue

**Niacin (B₃), or nicotinic acid:**
1. **sources**—
   A. meats/fish/vegetables/nuts
   B. synthesized by colonic bacteria
   C. endogenously synthesized from tryptophan: essential amino acid

2. **functions**—
   A. niacin and nicotinamide
      (1) diet-derived and then converted into nicotinic acid
      (2) required for synthesis of NAD⁺/NADH₂ and NADP⁺/NADPH
        a. cofactors for majority of oxidation reduction reactions
        b. NADH₂ reactions are usually catabolic
        c. NADPH reactions are usually catabolic
   B. NAD⁺ to NADH₂ reactions include (know these for USMLE):
      (1) glycerolaldehyde 3-phosphate→ 1,3-diphosphoglycerate: glycolysis
      (2) lactate → pyruvate
        a. Cori cycle: muscle and RBCs give liver lactate for its conversion into glucose
        b. gluconeogenesis
      (3) malate → oxaloacetate:
        a. gluconeogenesis
b. OAA cannot exit the mitochondria, so it must be converted to malate or aspartate, which are able to exit the mitochondria and be reconverted back into OAA

(4) pyruvate $\rightarrow$ acetyl CoA
a. glycolysis
b. TCA cycle
c. one way reaction: underscores why acetyl CoA is not a substrate for gluconeogenesis

(5) $\beta$-oxidation of fatty acids: 3 ATP per NADH$_2$

C. NADH to NAD$^+$ (know these for USMLE)
(1) dihydroxyacetone phosphate (DHAP) $\rightarrow$ glycerol 3-phosphate
a. glycolysis
b. VLDL synthesis: glycerol 3-phosphate is the carbohydrate backbone for synthesis of VLDL

(2) acetoacetate $\rightarrow$ $\beta$-hydroxybutyrate: ketone synthesis

D. NADP$^+$ to NADPH reactions (know these for USMLE): (1) glucose 6-phosphate $\rightarrow$ 6-phosphogluconate
a. pentose phosphate pathway
b. major site for synthesis of NADPH
c. synthesis of glutathione, an antioxidant

(2) malate $\rightarrow$ pyruvate
a. occurs in the synthesis of fatty acids
b. second MC reaction for generation of NADPH

(3) molecular oxygen $\rightarrow$ superoxide free radical
a. oxygen-dependent myeloperoxidase system using NADPH oxidase
b. microbicidal system

(4) cytochrome P 450 pathway
a. drug metabolism
b. drug free radicals
c. aromatization reactions
d. synthesis of vitamin D and steroid hormones

(5) fatty acid synthesis

(6) cholesterol $\rightarrow$ pregnenolone: steroid synthesis

(7) cholesterol synthesis

(8) ribonucleotides $\rightarrow$ deoxyribonucleotides: using thioredoxin reductase

3. causes of niacin deficiency—
A. diets high in corn (USMLE):
(1) deficient in tryptophan
(2) MCC of niacin deficiency

B. tryptophan deficiency:
(1) carcinoid syndrome: serotonin comes from tryptophan
(2) Hartnup's disease
a. AR disease
b. decreased intestinal/renal reabsorption of neutral amino acids, including tryptophan

4. S/S of niacin deficiency (pellagra)—
A. diarrhea
B. dementia
C. dermatitis:
(1) increased skin pigmentation in sun-exposed areas
(2) e.g., Casal's necklace
D. glossitis

5. **USMLE scenarios**
   A. niacin relation to nicotinic acid:
      (1) lowers lipids (both TG/CH)
      (2) inhibition of lipolysis in adipose tissue
      (3) reduces release of fatty acids and lipid synthesis
      (4) vasodilatation mediated by prostaglandins: prevented by taking aspirin
   B. diet of corn relationship with tryptophan deficiency and pellagra
   C. primary site for synthesis of NADPH:
      (1) pentose phosphate shunt (main source)
      (2) malate to pyruvate

\[\text{Pyridoxine (B}_6\text{):}\\
1. \text{sources—}\\
   A. most foods
   B. not present in goat's milk
2. \text{functions—}\\
   A. cofactor in the form of pyridoxal phosphate
   B. heme synthesis: glycine + succinyl-CoA + B6 $\rightarrow$ 8-aminolevulinic acid
   C. transamination reaction involving alanine:
      (1) alanine $\leftrightarrow$ pyruvate: removal of amino group from alanine produces $\alpha$-keto acid (pyruvate)
      (2) addition of amino group to pyruvate produces alanine
      (3) important in gluconeogenesis and amino acid metabolism
   D. transamination reaction involving aspartate:
      (1) aspartate $\leftrightarrow$ oxaloacetate
         a. removal of amino group from aspartate produces oxaloacetate
         b. important in gluconeogenesis and amino acid metabolism
      (2) oxaloacetate + amino group produces aspartate: aspartate can exit the mitochondria and be reconverted into OAA
   E. deamination reactions: serine $\rightarrow$ pyruvate + ammonia
   F. decarboxylation reactions: histidine $\rightarrow$ histamine + CO$_2$
   G. niacin synthesis from tryptophan
   H. neurotransmitter synthesis:
      (1) $\gamma$-aminobutyric acid
      (2) serotonin
      (3) norepinephrine
3. causes of pyridoxine deficiency—
   A. isoniazid (INH) therapy for TB: MCC of B6 deficiency
   B. alcoholism
   C. birth control pills
   D. pregnancy
4. S/S of pyridoxine deficiency—
   A. cheilosis/stomatitis/glossitis
   B. sideroblastic anemia with ringed sideroblasts
   C. peripheral neuropathy
   D. abnormal electroencephalogram
   E. convulsions: particularly in infants
5. S/S of pyridoxine toxicity—
   A. convulsions
B. excess porphyrin synthesis: photosensitive skin lesions

\textbf{Pantothenic acid}: functions—
1. component of coenzyme A—transfers acyl groups
2. component of fatty acid synthase—key enzyme complex in fatty acid synthesis

\textbf{Biotin}:
1. function—
   A. carboxylation reactions
   B. pyruvate carboxylase reaction: e.g., pyruvate $\rightarrow$ oxaloacetate
2. \textbf{cause of biotin deficiency}—
   A. eating raw eggs (USMLE question)
   B. avidin in raw egg whites prevents its absorption in the small bowel
3. S/S of biotin deficiency—alopecia

\textbf{Vitamin B}_{12}\text{ (cobalamin) and folate (see schematic on following page)}:
1. sources of B\textsubscript{12}—
   A. meat/dairy products
   B. not present in vegetables/fruits
2. sources of folate—
   A. beer: cannot become folate deficient by drinking too much beer
   B. fruits/vegetables
   C. grains
3. functions of both folate and B\textsubscript{12}—DNA synthesis
4. functions of B\textsubscript{12} only—
   A. propionate metabolism: propionyl-CoA $\rightarrow$ methylmalonyl-CoA + B\textsubscript{12} $\rightarrow$ succinyl-CoA
   B. succinyl CoA used in:
      (1) TCA cycle as a substrate for gluconeogenesis
      (2) heme synthesis
5. function of folate only—1-carbon transfers to other intermediates for the synthesis of:
   A. amino acids
   B. purines
   C. pyrimidines
6. B\textsubscript{12} metabolism—
   A. B\textsubscript{12} requires intrinsic factor (IF) for reabsorption in the terminal ileum: IF is synthesized in parietal cells located in the body/fundus
   B. B\textsubscript{12} is initially bound to R factor in saliva: R factor prevents gastric acid destruction of B\textsubscript{12}
   C. pancreatic enzymes cleave off R factor: this allows B\textsubscript{12} to bind to IF
   D. B\textsubscript{12}-IF complex is reabsorbed in the terminal ileum
   E. B\textsubscript{12} is bound to transcobalamin in the plasma: delivered to metabolically active cells or stored in the liver (6–9 y supply)
7. folate metabolism—
   A. folate is in a polyglutamate form in vegetables/grains $\rightarrow$
      (1) converted into monoglutamates in GI by intestinal conjugase: enzyme is inhibited by phenytoin $\rightarrow$
      (2) monoglutamate is reabsorbed in jejunum: reabsorption blocked by alcohol and birth control pills $\rightarrow$
      (3) folate circulates in blood as methyltetrahydrofolate
   B. 3–4 mths supply of folate in liver:
      (1) dietary deficiency common in alcoholics
\[ \text{Methionine} \xrightarrow{\text{Methyltransferase}} \text{Cbl} \xrightarrow{\text{N}^2\text{-Methyl-FIG}} \text{(plasma)} \]

\[ \text{Homocysteine} \xrightarrow{\text{Methyl-Cbl}} \text{FIG} \xrightarrow{\text{replenished by serine and FIG}} \text{FIGlu} \]

\[ \text{Dihydrofolate reductase (inhibited by methotrexate, trimethoprim)} \]

\[ \text{Dihydrofolate (oxidized form)} \]

\[ \text{Citrovorum factor replenishes} \rightarrow \text{N}^{5,10}\text{methylene FIG} \]

\[ \text{Thymidylate synthetase} \rightarrow \text{dUMP} \rightarrow \text{dTMP} \rightarrow \text{DNA} \]

\[ \text{Vitamin B} \text{12 in propionate metabolism} \]

\[ \text{Propionyl CoA} \rightarrow \text{Methylmalonyl CoA} \rightarrow \text{Succinyl CoA} \]

\[ \text{↑ urine methylmalonic acid (B} \text{12 deficiency only)} \]

- Methyl-FIG - methyltetrahydrofolate
- FIGlu - formaminoglutamic acid
- FIG - tetrahydrofolate
- Cbl - cobalamin (B12)
- Methyl-Cbl - methylcobalamin (B12)
- dUMP - deoxyuridine monophosphate

(reduced synthesis in both B12 and folate deficiency)
(2) woman must be on folate before pregnancy in order to prevent open neural tube defects

8. **B₁₂/folate in DNA synthesis (see schematic)**—B₁₂ removes methyl group from methyltetrahydrofolate
   A. methyl transferred to homocysteine: homocysteine converted into methionine
   B. methyltetrahydrofolate becomes tetrahydrofolate (THF)
   C. THF converted into N⁵,¹⁰-methylene tetrahydrofolate →
   D. N⁵,¹⁰-methylene THF + thymidylate synthetase + deoxyuridine monophosphate → dihydrofolate (DHF)
   E. DHF (oxidized form of THF) + deoxythymidine monophosphate (used for DNA synthesis) →
   F. DHF is converted by dihydrofolate reductase back into THF (reduced form)

9. **causes of B₁₂ deficiency**—
   A. pernicious anemia (PA):
      (1) MCC
      (2) autoimmune destruction of parietal cells
      (3) autoantibodies against IF and parietal cells
      (4) loss of IF leads to B₁₂ deficiency
      (5) achlorhydria: increases serum gastrin levels
      (6) chronic atrophic gastritis of body/fundus: predisposition to gastric adenocarcinoma
   B. pure vegan diet
   C. chronic pancreatitis: cannot cleave off R factor
   D. fish tapeworm
   E. bacterial overgrowth in small bowel:
      (1) bacteria destroy B₁₂-IF complex
      (2) also destroy bile salts leading to malabsorption of fats
   F. terminal ileal disease (normal site for B₁₂-IF reabsorption): Crohn's disease

10. **causes of folate deficiency**—
    A. alcoholism:
       (1) MCC of folate deficiency
       (2) not deficient in folate in a beer drinking alcoholic
    B. poor diet: elderly/alcoholics
    C. pregnancy/lactation: uses up folate
    D. disseminated cancer: uses up folate
    E. phenytoin: blocks intestinal conjugase
    F. birth control pills/alcohol: block uptake of monoglutamates in jejunum
    G. **inhibition of dihydrofolate reductase**:
       (1) methotrexate
       (2) trimethoprim

11. **S/S of B₁₂/folate deficiency**—
    A. macrocytic anemia: delayed nuclear maturation of hematopoietic cells
    B. glossitis
    C. diarrhea:
       (1) malabsorption
       (2) affects duplication of stem cells in the intestine

12. **S/S unique to B₁₂ deficiency**—
    A. subacute combined degeneration:
       (1) posterior column demyelination
          a. lack proprioception
          b. lack vibratory sensation
c. positive Romberg’s test
(2) lateral corticospinal tract demyelination
   a. positive Babinski
   b. upper motor neuron disease
   c. spasticity
(3) dementia

13. S/S unique to PA–
   A. achlorhydria
   B. chronic atrophic gastritis body/fundus
   C. gastric adenocarcinoma
   D. autoantibodies against parietal cells and IF
   E. correction of Shilling’s test with addition of IF

14. lab findings in B12/folate deficiency–
   A. large nucleated cells with immature nuclear features: cells are called megaloblastic
   B. pancytopenia: megaloblastic cells in the bone marrow are destroyed by macrophages
      before they enter the bone marrow sinusoids
   C. hypersegmented neutrophils:
      (1) >5 nuclear lobes
      (2) excellent marker for B12/folate deficiency
   D. increased plasma homocysteine levels: no methyl group to transfer to homocysteine
      to produce methionine if either B12 or folate deficient

15. lab findings unique to folate deficiency–
   A. increased formiminoglutamic acid (FIGlu): usually metabolized by THF
   B. decreased serum folate
   C. decreased RBC folate: best test for folate deficiency

16. lab findings unique to B12 deficiency–
   A. decreased serum B12
   B. increased urine methylmalonic acid: build-up methylmalonyl-CoA proximal to the block
   C. increased propionates (odd chained fatty acids) cause demyelination and CNS findings

17. Schilling’s test–
   A. non radioactive B12 is first given to bind to all available transcobalamin in the peripheral
      blood:
      (1) prevents any reabsorbed radioactive B12 from binding to transcobalamin
      (2) forces it to be excreted in the urine,
   B. radioactive B12 given by mouth followed by 24 h urine for % radioactive B12 reabsorbed:
      no radioactive B12 in 24 h urine confirms B12 deficiency,
   C. if corrected with addition of IF to oral radioactive B12: patient has pernicious anemia
   D. if corrected after antibiotic therapy: patient has bacterial overgrowth
   E. if corrected with addition of pancreatic extract followed by intake oral radioactive B12:
      patient has chronic pancreatitis

18. Rx of folate deficiency–
   A. folate
   B. folate in pharmacologic doses can correct B12 deficiency but not the neurologic
      abnormalities

19. Rx of B12 deficiency– IM B12

20. USMLE scenarios–
   A. MC vitamin deficiency in alcoholics:
      (1) folate
      (2) also MCC of macrocytic anemia
B. woman is a pure vegan and is breast feeding her baby and the baby develops anemia: B₁₂ deficiency

C. when to give folate to prevent open neural tube defects:
   (1) before pregnancy
   (2) neural tube is already developed before the patient knows she is pregnant

D. interpretation of a Schilling's test corrected with IF: PA

E. drug causing a macrocytic anemia in a patient with severe rheumatoid arthritis: methotrexate, which blocks dihydrofolate reductase

F. drug young woman with hypertension and a macrocytic anemia is taking:
   (1) birth control pills
   (2) estrogen increases angiotensinogen
   (3) estrogen blocks reabsorption of monoglutarate

G. anemia in an infant that develops when switched from cow’s milk to goat’s milk:
   (1) goat’s milk is low in folate, B₆ (pyridoxine), iron
   (2) high in potassium, chloride, arachidonic acids, and linoleic acids when compared to cow’s milk

H. prevention of macrocytic anemia in patients on methotrexate:
   (1) leucovorin rescue (citrovorum factor)
   (2) replenishes N⁵,₁₀-methylene THF: substrate necessary for thymidylate synthesis

Trace element disorders:

1. functions—
   A. micronutrients
   B. serve as cofactors in enzymes or are components of prosthetic groups

2. lab test—atomic absorption spectrophotometry is the gold standard

3. causes of trace metal deficiency—
   A. total parenteral nutrition: MCC of trace metal deficiency
   B. decreased absorption:
      (1) malabsorption
      (2) phytates in diet
   C. increased excretion: chelation therapy
   D. increased requirement:
      (1) due to old age
      (2) diabetes mellitus
         a. zinc
         b. chromium

4. chromium—
   A. function: potentiates insulin activity
   B. S/S of chromium deficiency:
      (1) glucose intolerance
      (2) peripheral neuropathy

5. copper—
   A. majority is bound to ceruloplasmin:
      (1) synthesized in liver
      (2) most of the total copper is that copper bound to ceruloplasmin (very little is free)
   B. functions:
      (1) cofactor in lysyl oxidase: cross-links collagen to increase tensile strength
      (2) cofactor in cytochrome c oxidase: electron transport system
      (3) cofactor in superoxide dismutase: antioxidant that neutralizes superoxide free radicals
      (4) cofactor in ferroxidase: converts ferric to ferrous iron for binding to transferrin
(5) cofactor in tyrosinase
   a. converts tyrosine to dopa in melanin synthesis
   b. missing in albinism
C. S/S of copper deficiency:
   (1) wound healing: role in cross-bridging collagen
   (2) dissecting aortic aneurysms
   (3) skin depigmentation: tyrosinase-relationship
   (4) microcytic anemia
      a. iron deficiency
      b. ferroxidase relationship
   (5) Menkes kinky hair syndrome
   (6) flag sign in kwashiorkor
   (7) osteoporosis
D. S/S of copper excess: Wilson's disease
   (1) defect in copper excretion into bile→
   (2) chronic liver disease→
   (3) decrease in ceruloplasmin synthesis→
   (4) low ceruloplasmin→
   (5) low total copper levels→
   (6) increase in free copper levels in blood→
   (7) copper deposits in Descemet's membrane in the eye (Kayser-Fleischer ring) and lenticular nuclei (dementia, choreoathetosis)
6. fluorine—
A. function: incorporated into bone and tooth enamel
B. S/S of fluorine deficiency: dental caries
C. S/S of fluorine excess:
   (1) mottled teeth
   (2) calcification of ligaments/tendons
   (3) increased brittleness of bone
7. manganese—
A. function:
   (1) cofactor for superoxide dismutase
   (2) cofactor for glycosyltransferases: mucopolysaccharide synthesis
B. S/S of manganese deficiency:
   (1) decreased synthesis of vitamin K-dependent factors: hemorrhagic diathesis
   (2) pigmentary changes in hair
8. molybdenum—
A. function: cofactor in xanthine oxidase involved in uric acid synthesis in purine metabolism
B. S/S of molybdenum deficiency:
   (1) headache
   (2) night blindness
9. selenium—
A. functions:
   (1) cofactor in glutathione peroxidase
      a. synthesis of glutathione
      b. potent antioxidant against peroxides located in cytosol
      c. vitamin E neutralizes peroxides in cell membranes
   (2) cofactor in iodosines: peripheral conversion of T4 to T3
   (3) stimulates immune system
B. S/S of selenium deficiency:
   (1) muscle pain/weakness
   (2) cardiomyopathy

10. zinc–
   A. functions:
      (1) cofactor for carbonic anhydrase: bicarbonate reclamation in the kidneys
      (2) cofactor for superoxide dismutase: neutralizes superoxide free radicals
      (3) cofactor for alkaline phosphatase: bone mineralization
      (4) cofactor for collagenases: replaces type III collagen with type I collagen
      (5) cofactor for alcohol dehydrogenase: ethanol metabolism
      (6) role in immune functions: macrophage function
      (7) role in nucleic acid/protein synthesis
      (8) role in spermatogenesis
      (9) role in normal growth

B. causes of zinc deficiency:
   (1) TPN
   (2) diabetes mellitus
   (3) alcoholism
   (4) acrodermatitis enteropathica
      a. AR disease
      b. decreased intestinal reabsorption of zinc
   (5) birth control pills

C. S/S of zinc deficiency:
   (1) dysgeusia: decreased taste sensation (USMLE)
   (2) poor wound healing (USMLE)
   (3) rash around the eyes/mouth (USMLE)
   (4) growth retardation
   (5) hypogonadism

Dietary fiber:
1. types/function–
   A. insoluble fiber:
      (1) nonfermentable
      (2) e.g., wheat bran, wheat germ
      (3) absorbs water
      (4) binds potential carcinogen: e.g., lithocholic acid
      (5) stool eliminated faster: protects against constipation and diverticulosis

B. soluble fiber:
   (1) fermentable
   (2) e.g., oat bran, psyllium seeds, fruits
   (3) lowers serum cholesterol
   (4) increases fecal bacterial mass
   (5) hypoglycemic effect: improves carbohydrate metabolism in diabetes

C. fiber in general:
   (1) reduces stool pH: keeps secondary bile acids like lithocholic acid in a protonated state, which enhances elimination
   (2) reduces deconjugation of estrogen delivered in bile
      a. less hormone reabsorbed back into the circulation
      b. protective effect against breast, endometrial, ovarian cancers

2. fiber reduces cancer risk–
   A. colorectal
B. endometrial
C. ovarian
D. prostate
E. breast

3. **fiber and polyunsaturated fats + ω6 fatty acids**–
   A. fiber prevents the adverse effects of polyunsaturated fats which include:
      1. increase amount of free estrogen and estrogen metabolites: danger of excess unopposed estrogen and cancer
      2. saturated fats are converted in secondary bile acids: lithocholic acid is carcinogenic
   B. **recommendation for fiber in diet**—20–30 grams of fiber/day

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Diet and cancer:

1. refer to above discussion

2. **foods preventing cancer**–
   A. cruciferous vegetables: e.g., broccoli, cauliflower
   B. fruits/vegetables containing β-caroteneoids
   C. vitamin C
   D. vitamin E

3. **aflatoxins**–
   A. molds
   B. increase risk for hepatocellular carcinoma: especially in conjunction with preexisting postnecrotic cirrhosis from HBV

4. **free radicals and cancer**–
   A. enhances cancer risk in the following areas:
      1. initiation (irreversible mutation)
      2. promotion (clonal expansion of initiated cell)
      3. progression (subspecialization of cancer cells)
   B. effect of reactive oxygen molecules (e.g., superoxide):
      1. directly mutagenic to DNA
      2. activate chemical procarcinogens into their active form
   C. factors that inhibit free radicals:
      1. free-radical scavengers
      2. antioxidants such as β-carotene, vitamin C, vitamin E, selenium

5. **recommendations to prevent cancer**–
   A. avoid obesity
   B. decrease total fat intake to 30% of total calories (ideally <25%)
   C. decrease saturated fat intake to <10% of the calories (ideally <7%)
   D. increase intake of whole-grain foods
   E. increase intake of green, yellow, orange vegetables rich in β-carotenes/vitamin C
   F. increase intake of cruciferous vegetables
   G. eliminate salt-cured/smoked meats and nitrite-cured foods
   H. avoid/reduce alcohol intake
   I. stop smoking
   J. exercise

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Nutrition and aging (**know this well for USMLE**):

1. **normal changes**–
   A. decrease in body weight
   B. loss in skeletal muscle mass
   C. relative increase in fat
   D. decline in energy requirements
2. **variables contributing to dietary problems**—
   A. drug interactions with nutrients:
      (1) cholestramine
      (2) phytates in diet
   B. reduced renal function: decrease in glomerular filtration rate
   C. malabsorption of nutrients: problems with reduced gastric acidity

3. **dietary inadequacies**—
   A. pyridoxine (B₆)
   B. calcium/vitamin D: taking these supplements slows the rate of bone loss
   C. folate

4. **supplements not recommended**—
   A. iron:
      (1) lack of menses eliminates need for iron supplements
      (2) iron produces free radicals
   B. vitamin A:
      (1) livers ability to clear retinoic acid from blood is reduced
      (2) danger of hypervitaminosis A

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**Special diets:**

1. **sodium restriction**—
   A. reduces blood pressure
   B. nonpharmacologic Rx for:
      (1) congestive heart failure
      (2) chronic renal disease
      (3) cirrhosis

2. **protein-restricted diets**—
   A. purpose: reduce the formation of urea and ammonia
   B. restrict in chronic renal/liver disease

3. **vegan diets**—
   A. Ornish diet:
      (1) vegan diet low in saturated fats/high in fiber
      (2) reverses calcified atherosclerotic plaques in coronary vessels
   B. soybean products excellent source of:
      (1) proteins
      (2) calcium (hard tofu)
      (3) bioavailable iron
   C. proven benefits of vegan diets:
      (1) decrease incidence of CAD/hypertension
      (2) decrease cancer risk: lung, oropharyngeal, laryngeal, esophageal, breast, colorectal, endometrial
      (3) fewer deaths from type II DM, renal disease
   D. nutrients that may be lacking in pure vegan diets:
      (1) vitamin B₁₂
      (2) calcium
      (3) vitamin D
      (4) zinc: particularly true in pregnant women or those who are lactating

4. **USMLE scenarios**—
   A. prenatal vitamins:
      (1) iron: women only have 400 mg of iron stores and lose 500 mg in pregnancy
      (2) folate: only 3–4 mth supply in liver
(3) note: B₁₂ is not necessary unless a woman is a pure vegan
B. most cost effective way of preventing hepatic coma in cirrhotics: reduce protein intake
C. diet requirements in pregnant woman who is a pure vegan:
   (1) iron
   (2) calcium
   (3) B₁₂ (most important)

Questions used during the board review:

A 25-year-old woman has not had her period for the last 8 months. She is 5' 2" and weighs 90 pounds. A urine pregnancy test is negative. She states that she has been trying to lose weight for her upcoming wedding. You order a battery of tests and give the patient an intramuscular injection of progesterone. Ten days later the patient returns to your office and reports that she had no withdrawal bleeding. Laboratory tests reveal the following: serum prolactin is normal, serum FSH and LH are low, serum TSH is normal, serum estradiol is low, and serum cortisol is increased. Based on these findings, you strongly suspect the patient has...
A. primary ovarian disease
B. hypopituitarism
C. secondary hypothyroidism
D. weight loss syndrome
E. Cushing's syndrome

D (anorexia nervosa)
Follicular hyperkeratosis, night blindness, and a hemorrhagic diathesis are expected in a patient...
A. with cystic fibrosis
B. with scurvy
C. with hypothyroidism
D. who is a pure vegan
E. who is bulimic

A (vitamin A deficiency, vitamin K deficiency as well)
Which of the signs or symptoms characterize a fat soluble rather than a water soluble vitamin deficiency?
A. Perifollicular hemorrhage
B. Bone pain and tetany
C. Peripheral neuropathy
D. Ophthalmoplegia, confusion, and ataxia
E. Hyperpigmentation in sun-exposed areas

B (vitamin D deficiency, choice A is scurvy, choice C is pyridoxine, choice D is thiamine deficiency, choice E is pellagra from niacin deficiency)
Which of the signs or symptoms are more prominently found in marasmus than kwashiorkor?
A. Hepatomegaly
B. Pitting edema
C. Reduced total lymphocyte count
D. Flaky paint dermatitis
E. Broomstick extremities
Pellagra will MOST LIKELY develop in a patient...
A. who is taking isoniazid
B. whose diet primarily consists of corn
C. who is a pure vegan
D. who is taking nicotinic acid to lower lipids
E. with malabsorption secondary to chronic pancreatitis

B (choice A is pyridoxine, choice C is B₁₂ deficiency, choice D is a by-product of niacin, choice E- malabsorption will cause fat soluble vitamin deficiencies A, D, E, K)

Which of the following is more often associated with anorexia nervosa than bulimia nervosa?
A. Hypokalemia
B. Metabolic alkalosis
C. Normal body image
D. Normal serum gonadotropins
E. Osteoporosis

Which of the following laboratory test abnormalities would you MOST expect in a patient with morbid obesity?
A. Increased serum TSH
B. Increased 24-h urine for free cortisol
C. Increased fasting glucose
D. Increased 24-h urine for 17-ketosteroids
E. Increased serum DHEA-sulfate

Which of the following vitamin deficiencies would you expect in a child maintained on unfortified goat's milk?
A. Ascorbic acid
B. Thiamine
C. Niacin
D. Riboflavin
E. Folate

E (folate deficiency, also causes pyridoxine deficiency)

Which of the following vitamins would be deficient in a newborn child with anemia whose mother is a pure vegan?
A. Ascorbic acid
B. Thiamine
C. Niacin
D. Pyridoxine
E. B₁₂

A 65-year-old woman complains of bleeding gums after brushing her teeth, easy bruising, and pain in her legs when walking. Her platelet count is normal. The pathogenesis of her disease is MOST CLOSELY related to...
A. a deficiency of ATP
B. a cofactor deficiency in collagenase
C. lack of hydroxylation of lysine and proline
D. a cofactor deficiency in lysyl oxidase
E. platelet dysfunction

C (scurvy)
A 30 year-old man develops an acute onset of confusion, ataxia, nystagmus, and ophthalmoplegia shortly after the administration of an intravenous solution containing 5% glucose and normal saline. The pathogenesis of this patient's neurologic disorder is most closely related to...

A. central pontine myelinolysis
B. thiamine deficiency
C. Purkinje cell atrophy
D. viral encephalitis
E. B₁₂ deficiency

B (acute Wernicke's encephalopathy)
Genetics

Diagnostic techniques used in genetics:
1. history
2. pedigree analysis—maps out the distribution of an inherited disease
3. physical exam
4. prenatal testing—
   A. amniocentesis beginning at 16 weeks
   B. chorionic villous sampling beginning at 9–12 weeks
   C. fetal blood sampling
   D. ultrasound: R/O open tube defects
   E. maternal screening tests:
      (1) alpha fetoprotein (AFP)
         a. high in open neural tube defects
         b. causally related to folate deficiency
         c. low in Down syndrome
         d. must correlate with gestational age
      (2) β-hCG: high in Down syndrome
      (3) urine for unconjugated estriol: low in Down syndrome
F. nucleic acid probes:
   (1) probes contain specific amino acid sequences of portions of DNA
   (2) sequences are spliced into DNA strands
   (3) allowed to hybridize with a corresponding segment of DNA from a patient sample
   (4) use of polymerase chain reactions (PCR) for probes
      a. amplifies DNA fragments that harbor abnormal gene loci
      b. enzyme used is DNA polymerase (USMLE question)
G. restriction fragment length polymorphism (RFLP, USMLE):
   (1) technique used when the exact site of an abnormal gene is unknown
   (2) abnormal genetic sites must be linked to a harmless marker gene on the same chromosome
   (3) DNA fragments on the abnormal chromosome (DNA cleaved by restriction endonucleases) from both normal family members and those with the disease are studied for variations in fragment lengths in order to detect abnormal genetic sites
   (4) future children compared with normal/affected family members

Chromosomes:
1. 46 chromosomes—
   A. 22 pairs of autosomes: somatic chromosomes
   B. two sex chromosomes:
      (1) XX = female
      (2) XY = male

2. meiosis—
   A. only occurs in germ cells
   B. gametes contain the haploid number of chromosomes (23)

3. Lyon’s hypothesis—
   A. 1 of the 2 X chromosomes in a female is randomly inactivated:
      (1) ~50% X chromosomes are maternal
      (2) ~50% X chromosomes paternal
      (3) inactivated X chromosome becomes a Barr body (USMLE); projection from the nucleus counted in squamous cells obtained by scrapings from the buccal mucosa
(3) most cases involve sex chromosomes: e.g., gonadal dysgenesis with XO/XX, XO/XY

3. chromosome mutation–

A. 1:180 births
B. e.g., Down syndrome with 46 chromosomes
C. causes:
   (1) translocations
   (2) deletions
   (3) duplications
   (4) inversions: can only be identified with high resolution chromosome studies

D. **translocation** is where one part of a chromosome is transferred to a non-homologous or homologous chromosome:
   (1) called a **balanced translocation** if the translocated fragment is functional

E. **Robertsonian translocation** in Down syndrome (USMLE):
   (1) type of balanced translocation with a reciprocal translocation between 2 homologous chromosome
   (2) produces 1 long chromosome 21: really 2 chromosomes fused together
   (3) one of the parents of the Down child must have 45 chromosomes (usually mother), with only 1 long chromosome 21
      a. really 2 functional 21s
      b. parent is normal, since both translocated fragments are functional
   (4) Down child of one of these parents receives 1 normal chromosome 21 from the uninvolved parent (usually father) and 1 long fused chromosome from the affected parent (usually mother) for a total of 46 chromosomes
      (a) really 3 functioning chromosome 21s

   ![Diagram of Robertsonian translocation in Down syndrome]

   **parent: 45 chromosomes**
   **(2) chromosome 21s fused**
   **Down syndrome: 46 chromosomes**
   **(3) functional chromosome 21s**

F. deletion syndrome:
   (1) cri-du-chat (USMLE)
   (2) deletion of short arm of chromosome 5
   (3) mental retardation
   (4) cry like a cat
   (5) association with ventricular septal defect

G. **microdeletion syndromes** (USMLE): **genomic imprinting**
   (1) loss of a small portion from 1 chromosome can only identified with high resolution techniques
   (2) microdeletion on chromosome 15 may result in the Prader-Willi syndrome
      a. chromosome 15 deletion is of **paternal origin**
      b. obesity / **short stature**
      c. hypogonadism
      d. mental retardation
   (3) microdeletion on chromosome 15 may result in Angelman syndrome
      a. chromosome 15 deletion is of **maternal origin**
      b. "happy puppy" syndrome
      c. child always happy/laughing but cannot talk
   (4) term applied to these syndromes is **genomic imprinting** (USMLE question)
Risk of recurrence of genetic disorders:
1. Mendelian disorders have the greatest risk of recurrence— AR diseases have a 25% recurrence rate
2. trisomy 21 has a 1% recurrence
3. multifactorial inheritance has a 2–10% recurrence rate

Genetics and ethnicity/sex:
1. genetic disorders in African-Americans—
   A. sickle cell trait/disease: 8–10% prevalence
   B. α-β-thalassemia
   C. glucose 6-phosphate dehydrogenase (G6PD) deficiency
   D. hereditary persistence of HbF
2. genetic disorders in Ashkenazi Jews—
   A. factor XII deficiency
   B. Gaucher’s disease
   C. Tay-Sachs disease
3. genetic disorder in Northern Europeans—
   A. cystic fibrosis:
   B. MC genetic disease interfering with the patient’s ability to reproduce owing to early death or problems with fertility
      (1) e.g., absent vas deferens in male (USMLE)
      (2) thick cervical mucus in females
4. genetic disorders in Mediterranean peoples—
   A. G6PD deficiency
   B. sickle cell trait/disease
   C. β-thalassemia
   D. note: all of these conditions protect patients from contracting Plasmodium falciparum infections
5. genetic disorder in Southeast Asians— α-thalassemia
6. MC genetic syndrome associated with advanced maternal age— trisomy 21
7. genetic syndromes associated with advanced paternal age—
   A. Marfan’s syndrome
   B. achondroplasia
   C. increased paternal age leads to a greater number of cell divisions in germ cells, hence the greater risk for new mutations: majority are AD diseases

Down syndrome (USMLE):
1. pathogenesis—
   A. trisomy 21:
      (1) 95% of all cases
      (2) 47 chromosomes
      (3) maternal origin for extra chromosome
   B. translocation:
      (1) 4% of all cases
      (2) 46 chromosomes in child
      (3) one parent with 45 chromosomes: usually mother
      (4) usually Robertsonian type (USMLE question)
   C. mosaicism: 1% of all cases
2. incidence—
   A. 1/800
   B. MC genetic cause of mental retardation: IQ 25–50 in 80%

3. physical findings—
   A. epicanthal folds with upward slanting
   B. Brushfield spots in the eyes
   C. simian palmar crease
   D. flat facial profile
   E. poor reflexes/hypotonicity

4. clinical findings—
   A. cardiovascular:
      (1) endocardial cushion defects: combined ASD and VSD
      (2) major determining factor for survival in early infancy and childhood (USMLE)
   B. GI:
      (1) duodenal atresia
         a. polyhydramnios
         b. vomits bile at birth
         c. double bubble sign on x-ray
      (2) Hirschsprung’s disease: do not pass meconium at birth
   C. hematologic: increased incidence of leukemia
   D. CNS (USMLE):
      (1) Alzheimer's disease
      (2) chromosome 21 codes for β-proteins
         a. converted into amyloid
         b. toxic to neurons
      (3) universal finding by age 35: any patient with Alzheimer's disease under 40 is a patient with Down syndrome
      (4) major factor for longevity in older Down's patients
   E. reproductive:
      (1) all males are sterile
      (2) females have 50% chance of having a child with Down's

5. longevity—>80% survive beyond 35 ys of age

6. laboratory—see maternal screening discussion

7. risk for future children with Down’s—
   A. 1–2% overall risk for trisomy 21
   B. maternal age: women >35 ys of age 1:385 risk
   C. 5–15% risk for parent with a balanced translocation of having another affected child
   D. karyotype of affected child should always be determined to evaluate risk for siblings to have affected children

**Trisomy 18 (Edward’s syndrome):**

1. pathogenesis—similar to Down syndrome
2. clinical—
   A. ~90% die in first month
   B. severe mental retardation
   C. clenched hands with overlapping 2nd and 5th fingers
   D. ventricular septal defect (VSD)
   E. rocker bottom feet
Trisomy 13 (Patau's syndrome):
1. pathogenesis— similar to Down’s syndrome
2. clinical—
   A. 100% lethal by 6 mths of age
   B. cleft lip/palate
   C. severe mental retardation
   D. polydactyly
   E. cystic kidneys
   F. VSD

Turner's syndrome (USMLE):
1. MC sex-chromosome disease recognizable at birth
2. pathogenesis—
   A. nondisjunction with 45 XO genotype: ~50–60%
   B. mosaics may also occur:
      (1) XO/XY
      (2) XO/XX: occasionally fertile
   C. no Barr body on buccal smear in XO type
3. clinical findings at birth—
   A. lymphedema of hands/feet
   B. webbed neck: redundant skin overlying dilated lymphatic channels called cystic hygroma
   C. short 4th metacarpal
   D. preductal coarctation: 30% with bicuspid aortic valve leading to heart failure
4. reproductive—
   A. MC genetic cause of primary amenorrhea
   B. streak gonads:
      (1) oocytes absent by 2 years of age: “menopause before menarche”
      (2) decreased estradiol: lack of secondary sex characteristics/menses
   C. no parental risk for having another affected child
   D. ovarian tumors:
      (1) increased risk for dysgerminoma
      (2) reason they are surgically removed
5. skeletal—
   A. dimple over the fourth metacarpal owing to a hypoplastic fourth metacarpal
   B. shield chest
   C. increased carrying angle of arms
6. intelligence— normal IQ but a slightly lower non-verbal IQ
7. lab findings—
   A. decreased estradiol and progesterone
   B. increased FSH and LH

Klinefelter's syndrome (USMLE):
1. pathogenesis—
   A. nondisjunction in first step of meiosis resulting in an XXY genotype
   B. 1 Barr body
2. S/S of Klinefelter's syndrome—
   A. normal appearance before puberty
   B. arms/legs disproportionately long
   C. hypogonadism
   D. female secondary sex characteristics:
(1) female hair distribution
(2) gynecomastia
(3) feminization due to increased aromatization of androgens into estrogens in hyperplastic Leydig cells

E. learning disabilities
F. atrophic testicles:
   (1) atrophy/fibrosis of seminiferous tubules:
      a. no spermatogenesis
      b. no Sertoli cells: no inhibin to feedback with FSH
   (2) Leydig cell hyperplasia

G. increased cancer risks:
   (1) malignant lymphoma
   (2) breast cancer

3. pathogenesis of hyperestrinism—
   A. aromatization of testosterone into estradiol in the Leydig cells
   B. Sertoli cells normally synthesize inhibin: negative feedback on FSH
   C. absence of inhibin→
      (1) increases FSH→
      (2) increases aromatase synthesis in Leydig cells→
      (3) increases conversion of androgens into estrogen

4. lab findings—
   A. low testosterone→ high LH
   B. low inhibin→ high FSH
   C. azoospermia: no sperm
   D. high serum estradiol

 Mendelian disorders:
1. types of Mendelian disorder in descending order of frequency—
   A. autosomal dominant (AD)
   B. autosomal recessive (AR)
   C. sex-linked recessive (SXr)
   D. sex-linked dominant (SXD)

2. alleles—
   A. alternative forms of the same gene
   B. if a gene on an autosome has two alleles (normal A, abnormal a), patients may be:
      (1) AA
      (2) Aa
      (3) aa
   C. patients with the same alleles are homozygous:
      (1) e.g., AA (normal)
      (2) aa (disease)
   D. patients with different alleles are heterozygous for that disorder: e.g., Aa

3. AD disorders—
   A. only 1 abnormal allele is necessary to express the disease:
      (1) "dominant gene"
      (2) e.g., aa (disease) or Aa (disease)
      (3) aa fetuses are usually aborted
   B. only one parent has to have the gene to pass it on to their children

4. AR disorders—
   A. both abnormal alleles must be present (homozygous) to express the disease:
      (1) aa (disease)
(2) Aa (heterozygote asymptomatic carrier)
B. both parents must have the abnormal allele:
   (1) 2 asymptomatic carriers (Aa and Aa)
   (2) patient with the disease has children with an asymptomatic carrier (Aa and aa)
   (3) 2 people with the disease have children (aa and aa)

5. SXR disorders—
   A. males with abnormal allele express disease:
      (1) males are "homozygous"
      (2) only have 1 X chromosome
   B. affected males transmit the disease to both daughters: daughters are usually asymptomatic carriers
   C. females with abnormal allele are usually (not always) asymptomatic:
      (1) 50% of maternal X chromosomes are normal
      (2) only 50% of paternally derived X chromosomes are abnormal
   D. female carrier transmits the disease to 50% of the boys

6. SXD disorders— males and heterozygous females both express the disease

AD disorders:
1. **gene is strong enough to express itself in a heterozygous state**—
   A. 1 normal allele and 1 abnormal allele is enough to express the disease
   B. homozygosity is usually incompatible with life
2. sibling risk— see schematics
   A. 50% of the siblings are affected
   B. 50% are normal when 1 parent is affected
      
      A
      a
      male with disease
      normal A  AA  Aa
      female A  AA  Aa
      (a is abnormal allele)

3. clinical features—
   A. associated with structural defects in proteins and receptors: enzyme deficiencies are uncommon
   B. AD disorders that are enzyme deficiencies:
      (1) acute intermittent porphyria (AIP): deficiency of uroporphyrinogen synthase
      (2) hereditary angioedema: C1 esterase inhibitor deficiency
   C. late manifestations of disease: e.g., Huntington's disease with chorea/dementia later in life
   D. exhibit penetrance (USMLE):
      (1) affected person never expresses the disease but does transmit the disease to their children
      (2) some AD disorders have 100% penetrance: e.g., familial polyposis, adult polycystic kidney disease
   E. exhibit variable expressivity: affected people have different levels of severity of the disease

4. mechanisms of AD disease without a family Hx—
   A. MCC is incomplete penetrance
   B. new mutation
   C. somatic mosaicism: gene defect in only some cells, including reproductive cells
   D. incorrect assignment of paternity

5. examples of AD diseases (in order of decreasing frequency)—
   A. von Willebrand's disease (VWD):
      (1) MC AD disorder
      (2) deficiency of VIII coagulant, antigen, adhesion factor
ROBERTSONIAN TRANSLOCATION

Parent: 45 chromosomes (2) chromosome 21s fused

Down syndrome: 46 chromosomes (3) functional chromosome 21s

AUTOSOMAL DOMINANT

A       a

A       AA       Aa

A       AA       Aa

AUTOSOMAL DOMINANT

A       a

A       AA       Aa

a       Aa       aa
B. familial hypercholesterolemia:
   (1) absent LDL receptor
   (2) Achilles tendon xanthoma pathognomonic
C. adult polycystic kidney disease:
   (1) renal cysts develop in second decade
   (2) high penetrance
D. hypertrophic cardiomyopathy:
   (1) MCC cause of sudden death in young people
   (2) abnormal conduction pathways in interventricular septum
E. Huntington's disease: triplet repeat disorder
F. neurofibromatosis:
   (1) genetic disease with the greatest overall mutational rate in gametes
   (2) see discussion below
G. congenital spherocytosis:
   (1) defect in spectrin
   (2) hemolytic anemia
H. familial polyposis:
   (1) premalignant polyps begin in second decade
   (2) 100% penetrance
I. acute intermittent porphyria
J. osteogenesis imperfecta:
   (1) **MC hereditary bone disease**
   (2) defect in synthesizing type I collagen
   (3) pathologic fractures *from birth*
   (4) blue sclera → *blue sclera is thinner than normal & the underlying veins are visible

6. example of a **pedigree with complete penetrance (USMLE)**—

7. example of a **pedigree with incomplete penetrance (USMLE)**—

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Neurofibromatosis (NF):
1. AD
2. pathogenesis—
   A. type 1 NF (85–90%):
      (1) point mutation inactivating NF-1 suppressor gene on chromosome 17
      (2) ~50% arise from a new mutation
   B. type 2 NF: point mutation inactivating NF-2 suppressor gene on chromosome 22
3. S/S of neurofibromatosis regardless of type—
   A. ≥6 cafe-au-lait macules (USMLE):
      (1) coffee-colored flat lesions
      (2) long axes parallel underlying cutaneous nerve
   B. axillary or inguinal freckling
   C. Lisch nodules:
      (1) hamartomas in iris
      (2) not present in type 2
   D. pigmented neurofibromas:
      (1) benign tumors involving all peripheral nerve elements
      (2) first appear during puberty
   E. plexiform neurofibromas: grotesque overgrowth of soft tissue
   F. CNS tumors (USMLE):
      (1) optic nerve glioma
         a. MC CNS tumor associated with neurofibromatosis
         b. not present in type 2
      (2) meningiomas: associated with new onset epileptic seizures
      (3) acoustic neuroma
         a. nerve deafness
         b. usually unilateral in type 1 and bilateral in type 2
   G. skeletal deformities: kyphoscoliosis
   H. pheochromocytoma (USMLE): possible cause of hypertension in adult with neurofibromatosis check urine for metanephrines + VMA (vanillylmandelic acid)
   I. neurofibrosarcoma: usually involve large nerve trunks (e.g., sciatic nerve)
   J. Wilm’s tumor: possible cause of hypertension in a child with neurofibromatosis

Marfan syndrome (USMLE):
1. AD
2. pathogenesis—
   A. gene defect located on chromosome 15
   B. defect in fibrillin: component of elastin in elastic tissue
   C. abnormal fibrillin I:
      (1) due to missense mutation (USMLE)
      (2) abnormal fibrillin I disrupts assembly of the normal microfibrils making up elastic tissue: called a dominant negative
   D. ~20% arise by a new mutation
3. skeletal defects—
   A. eunuchoid proportions:
      (1) lower body length > upper body length
      (2) arm span > height
   B. arachnodactyly: spider hands
   C. scoliosis
4. cardiovascular abnormalities—
   A. dilatation of ascending aorta:
      (1) MC initial defect
      (2) may progress into an aortic dissection and/or aortic regurgitation
   B. mitral valve prolapse:
      (1) 85% of cases
      (2) MC valvular defect: may also involve tricuspid valve
      (3) common cause of sudden death in Marfan patients (USMLE)
      (4) mitral regurgitation often occurs
   C. aortic dissection:
      (1) may occur from trauma
      (2) aortic regurgitation is the MC murmur with a dissection: stretches the aortic valve ring

5. eye defect—
   A. dislocated lens
   B. defective suspensory ligament

6. lung defect— increased incidence of spontaneous pneumothorax from ruptured blebs in the pleura

7. MC COD—
   A. dissecting aortic aneurysm
   B. not a cause of sudden death: more likely to be MVP

**AR diseases (USMLE):**

1. abnormal allele must be present on both chromosomes (aa) to express the disease—
2. both parents must carry the abnormal gene—
   A. heterozygotes (Aa) are asymptomatic carriers → an exception is Sickle Cell Trait
   B. 2 asymptomatic carriers have a:
      (1) 25% chance of having a child with the disease
      (2) 50% chance of a child who is an asymptomatic carrier
      (3) 25% chance of a normal child (see additional schematics)
         A a asymptomatic male carrier
         A- AA Aa (a abnormal gene)
         carrier female a Aa aa (aa has the disease)

3. clinical features—
   A. no evidence of:
      (1) penetrance
      (2) variable expressivity
      (3) late manifestations
   B. most (not all) AR diseases are enzyme deficiencies: inborn errors of metabolism
   C. examples of those that are not enzyme deficiencies:
      (1) cystic fibrosis
      (2) sickle cell trait/disease
      (3) hemochromatosis
      (4) Wilson's disease
   D. examples of AR diseases (in order of decreasing frequency)—
      (1) non-classic 21-OHase deficiency:
      (2) hemochromatosis
      (3) sickle cell disease: 1:625 African-Americans
      (4) cystic fibrosis: 1:2500
      (5) α1-antitrypsin deficiency
      (6) phenylketonuria

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AUTOSOMAL RECESSIVE

A    a
A    AA    Aa
a    Aa    aa

AUTOSOMAL RECESSIVE

A    a
A    AA    Aa
A    AA    Aa

AUTOSOMAL RECESSIVE

a    a
A    Aa    Aa
A    Aa    Aa
Phenylketonuria (PKU):

1. **Pathogenesis**—
   A. AR disease
   B. deficiency of phenylalanine hydroxylase (see schematic):

   \[ \uparrow \text{phenylalanine (PHY)} \rightarrow \downarrow \text{tyrosine (TYR)} \]

   C. rising PHY levels in the newborn impairs brain development; severe mental retardation by 6 mths of age if left untreated

2. **S/S of phenylketonuria**—
   A. normal at birth:
      (1) must be exposed to milk containing PHY
      (2) screening performed a few days after birth and not on cord blood
   B. decreased TYR:
      (1) hypopigmentation
      (2) blonde hair: TYR is a substrate for melanin synthesis
   C. projectile vomiting: resembles congenital pyloric stenosis
   D. mousy odor: PHY is converted into phenylpyruvic acid, phenyllactic acid, phenylacetic acid, which impart a mousy odor to sweat

3. **Affected women on PHY-free diet**—can bear normal children

4. **Affected women who are not on PHY-free diet prior to conception**—
   A. homozygous children are born with profound mental retardation
   B. heterozygous carriers are also symptomatic at birth
   C. both are exposed in utero to high levels of PHY
   D. called maternal PKU

5. **Benign phenylalaninemia**—
   A. partial deficiency of phenylalanine hydroxylase,
   B. slight increase in PHY
   C. absence of neurologic abnormalities

6. **Rx of newborn with PKU**—
   A. PHY free diet
   B. TYR added to diet
   C. avoid Nutrasweet; contains aspartate and PHY (USMLE)

7. **PKU can be diagnosed by amniocentesis**

8. **Diet for pregnant woman with PKU**—
   A. low in PHY
B. high in TYR
C. avoid Nutrasweet

**Galactosemia:**

1. **pathogenesis**—
   A. AR disease
   B. deficiency of galactose-1-phosphate uridytransferase (GALT)
   C. galactose comes from lactose metabolism:
      \[
      \text{lactose} \rightarrow \text{glucose} + \text{galactose}
      \]
   D. biochemical reactions in galactose metabolism (see schematic):
      1. \( \text{galactose} + \text{galactokinase} \rightarrow \text{galactose 1-PO}_4 \)
      2. \( \text{galactose 1-PO}_4 + \text{GALT} + \text{UDP-glucose} \rightarrow \text{glucose 1-PO}_4 + \text{UDP-galactose} \)
      3. \( \text{glucose 1-PO}_4 + \text{phosphoglucomutase} \rightarrow \text{glucose 6-PO}_4 \)
      4. \( \text{glucose 6-PO}_4 + \text{glucose 6-phosphatase} \rightarrow \text{glucose} \)

2. **galactokinase deficiency**—
   A. benign disease:
      1. galactosemia
      2. galactosuria
      3. accumulation of galactitol (alcohol sugar of galactose)
   B. lab:
      1. positive urine Clinitest
      2. Clinitest detects all reducing sugars: sucrose is not a reducing sugar

3. **galactosemia due to GALT deficiency**—
   A. osmotic damage:
      1. excess galactose converted into the galactitol (polyol or alcohol sugar)
      2. damages lens (cataracts)
      3. damages nerve tissue
      4. damages CNS (mental retardation)
      5. damages liver
   B. excess galactose 1-PO4:
      1. toxic substance,
      2. liver damage
         a. neonatal cholestasis with jaundice
         b. cirrhosis
      3. CNS damage: mental retardation
      4. renal damage: aminoaciduria
      5. neonatal hypoglycemia: lack of glucose 6-PO4, a substrate for gluconeogenesis
   C. lab findings in galactosemia—
      1. galactosemia/galactosuria: positive urine Clinitest
      2. fasting hypoglycemia
      3. decreased GALT
   D. Rx of galactosemia—
      1. lactose free diet for the first two yrs
      2. pregnant women with galactosemia can synthesize lactose in their breast milk via
         the following reactions:
         a. UDP-glucose + UDP-hexose epimerase → UDP-galactose
         b. UDP-galactose + lactose synthetase → lactose + UDP

**Essential fructosuria/hereditary fructose intolerance:**

1. **pathogenesis**—
   A. AR diseases
B. essential fructosuria: deficiency of fructokinase
C. hereditary fructose intolerance: deficiency of aldolase B

2. fructose metabolism (see schematic)
   A. sucrose + sucrase → glucose + fructose
   B. fructose + fructokinase → fructose 1-PO₄
   C. fructose 1-PO₄ + aldolase B → glyceraldehyde 3-phosphate + dihydroxyacetone phosphate (DHAP): both are 3 carbon intermediates that are gluconeogenic substrates
   D. fructose can be synthesized from mannose (and vice versa) and sorbitol
   E. sorbitol, an osmotically active solute, is synthesized in those tissue containing aldose reductase.
      (1) aldose reductase is present in the lens, ova, seminal vesicles, Schwann cells, retina, and kidneys
      (2) aldose reductase converts glucose into sorbitol and sorbitol dehydrogenase converts sorbitol into fructose

      \[
      \begin{align*}
      \text{Glucose} & \quad \xrightarrow{\text{NADPH}} \quad \xrightarrow{\text{NADP}^+ \text{ NAD}^+} \quad \xrightarrow{\text{Fructose}} \\
      \text{aldose reductase} & \quad \text{sorbitol dehydrogenase} \\
      \end{align*}
      \]

      (3) in hyperglycemic states, like diabetes mellitus, there is an excess of sorbitol produced in the above tissues leading to osmotic damage:
      a. cataracts
      b. peripheral neuropathy: destruction of Schwann cells
      c. microaneurysms in retinal vessels: destruction of pericytes
      (5) fructose is an essential nutrient for sperm stored in the seminal vesicles, where all of the above reactions occur

3. S/S of essential fructosuria–
   A. benign disease: fructosuria
   B. lab: positive urine Clinitest

4. S/S of hereditary fructose intolerance–
   A. fructose 1-PO₄ is toxic to the liver:
      (1) neonatal cholestasis with jaundice at birth
      (2) liver failure
   B. fasting hypoglycemia: decrease in 3 carbon intermediates for gluconeogenesis
   C. severe hypophosphatemia:
      (1) excess fructose traps phosphate in cells
      (2) depletion of ATP→
         a. RBC hemolysis
         b. muscle weakness
         c. rhabdomyolysis
   D. gout: increased adenosine monophosphate (AMP), which is a purine, is converted into uric acid

5. lab findings in hereditary fructose intolerance:
   A. positive urine Clinitest
   B. decreased aldolase B: liver tissue assay
   C. fasting hypoglycemia
   D. Rx of hereditary fructose intolerance:
      (1) remove fructose and sucrose from the diet
      (2) honey is high in fructose
Homocystinuria:
1. pathogenesis–
   A. AR disease
   B. deficiency of cystathionine synthase (USMLE):  
      (1) methionine + ATP → S-adenosylmethionine (SAM) + methyl acceptors +  
          methyltransferase → S-adenosylhomocysteine + methylated products (donates  
          methyl groups for 1 carbon transfers)  
      (2) S-adenosylhomocysteine + H₂O → homocysteine + adenosine  
      (3) homocysteine + serine + cystathionine synthase → cystathionine
   C. both homocysteine and methionine increase in serum
2. S/S of homocystinuria–
   A. S/S that resemble Marfan syndrome: example of genetic heterogeneity
      (1) dislocated lens  
      (2) arachnodactyly  
      (3) eunuchoid
   B. distinctive features of homocystinuria:
      (1) increase in plasma homocysteine levels leads to vessel damage/thrombosis
      (2) mental retardation
      (3) osteoporosis
3. lab–
   A. increased urine homocysteine with a positive nitroprusside reaction
   B. increased serum/urine methionine
   C. prenatal detection of cystathionine synthase

Alcaptonuria:
1. AR disease
2. absence of homogentisate oxidase (USMLE)– see reactions below
   A. accumulation of black, homogentisate pigment in joints/cartilage leads to degenerative  
      joint disease
   B. urine turns black when oxidized upon exposure to light

Hereditary tyrosinosis (tyrosinemia):
1. pathogenesis–
   A. AR disease
   B. deficiency of fumarylacetoacetate hydrolase (USMLE)
2. metabolism (see schematic)–
   A. phenylalanine + phenylalanine hydroxylase (deficient in PKU) → tyrosine  
   B. tyrosine → 4-hydroxyphenyl pyruvate → homogentisate
   C. homogentisate + homogentisate oxidase (deficient in alkaptonuria) →  
      maleylacetoacetate
   D. maleylacetoacetate + fumarylacetoacetate hydrolase (deficient in hereditary tyrosinemia)  
      → fumarylacetoacetate
   E. fumarylacetoacetate → acetoacetate + fumarate (present in TCA cycle)
3. S/S of hereditary tyrosinosis–
   A. increase in serum tyrosine: cabbage-like odor
   B. cirrhosis
   C. renal disease (aminoaciduria)
   D. death in the first yr of life
Lysosomal storage diseases (USMLE):

1. definition—
   A. absence of degrading enzymes in lysosomes
   B. accumulation of complex substrates in lysosome:
      (1) sphingolipids
      (2) mucopolysaccharides
   C. most are AR diseases with the exception of two diseases, which are SXR:
      (1) Fabry’s disease
      (2) Hunter’s disease

2. biochemistry of lysosomes (see schematic)—
   A. lysosomes contain hydrolytic enzymes →
   B. enzymes are synthesized in the rough endoplasmic reticulum →
   C. enzymes are transported to the Golgi apparatus →
   D. enzymes undergo post-translational modification →
   E. enzymes are phosphorylated at one or more mannosyl residues to form mannose 6-phosphate (USMLE), which is attached to the side chains →
   F. mannose 6-phosphate receptors on the inner surface of the Golgi apparatus membranes bind to the mannose 6-phosphate residues on the targeted lysosomal enzymes →
   G. small transport vesicles are pinched off the Golgi membrane that contain the receptor-bound enzymes →
   H. the vesicles fuse and release enzymes into lysosomes located in the cytosol →
   I. receptors return to the Golgi apparatus to repeat the process over again

3. I cell disease (USMLE)—
   A. inability to phosphorylate the mannose residues of potential lysosomal enzymes located in Golgi apparatus
   B. empty lysosomes are unable to degrade their complex substrates
   C. substrates accumulate in the lysosomes
   D. patients have psychomotor retardation and an early death

Glycosaminoglycans (GAGs, USMLE):

1. definition—complexes of predominantly branched, strongly negatively charged polysaccharide chains with repeating units of amino sugars (D-glucosamine or D-galactosamine) and acid sugars (L-iduronic acid or D-glucuronic acid)

2. examples of GAGs (USMLE)—
   A. chondroitin sulfate:
      (1) most abundant GAG
      (2) important component in cartilage
   B. hepan sulfate: mainly responsible for negative charge of glomerular basement membrane
   C. heparin: anticoagulant
   D. keratan sulfate
   E. hyaluronic acid: major component of synovial fluid (joint lubricant)
   F. dermatan sulfate:
      (1) ground substance in heart valves
      (2) increased in mitral valve prolapse
      (3) increased in pretibial myxedema
   G. clinical disorders involving GAG accumulations are called mucopolysaccharidoses

3. Hurler’s disease (AR, USMLE)—
   A. enzyme deficiency: α-L-iduronidase
   B. metabolite accumulation: dermatan/heparan sulfate
C. clinical:
   (1) severe mental retardation
   (2) coarse facial features
   (3) hepatosplenomegaly
   (4) corneal clouding
   (5) **coronary artery disease**: lipid accumulates in coronary vessels
   (6) vacuoles in peripheral blood leukocytes

4. **Hunter’s disease (SX, USMLE)**
   A. enzyme deficiency: L-iduronosulfate sulfatase
   B. metabolite accumulation: dermatan/ heparan sulfate
   C. milder disease than Hurler’s

**Sphingolipids (USMLE):**
1. **biochemistry**–
   A. sphingolipids include:
      (1) sphingomyelin
      (2) cerebrosides
      (3) gangliosides
   B. sphingomyelin:
      (1) involved in the synthesis of cell membranes in nerve tissue
      (2) **sphingosine** is the backbone of sphingomyelin
      (3) sphingosine is used to produce **ceramides** (sphingosine + fatty acids → ceramide)
      (4) ceramide + phosphorylcholine→ sphingomyelin
      (5) ceramide + glucose or galactose→ gluco- or galactocerebrosides
      (6) ceramide + oligosaccharides → gangliosides

2. **Tay-Sachs disease (AR)**–
   A. GM₂ gangliosidosidosis
   B. enzyme deficiency: hexosaminidase (α-subunit)
   C. metabolite accumulation: GM₂ ganglioside
   D. clinical:
      (1) Ashkenazi Jews
      (2) normal at birth → severe mental retardation by 6 months
      (3) blindness
      (4) **cherry red spot in the macula** (picture on USMLE)
      (5) muscle weakness/flaccidity
      (6) **no hepatosplenomegaly** (USMLE)
      (7) electron microscopy exhibits whorled configurations in lysosomes that look exactly the same as lamellar bodies with surfactant in type II pneumocytes

3. **Niemann-Pick (AR)**–
   A. enzyme deficiency: sphingomyelinase
   B. metabolite accumulation: sphingomyelin (bubbly appearance in macrophages/ neurons)
   C. clinical:
      (1) mental retardation
      (2) hepatosplenomegaly
      (3) psychomotor dysfunction
      (4) fatal in early life
      (5) electron microscopy exhibits zebra bodies (USMLE picture) in lysosomes

4. **Gaucher disease (AR)**–
   A. enzyme deficiency: glucocerebrosidase
   B. metabolite accumulation: glucocerebroside
C. adult type:
   (1) glucocerebroside accumulates in macrophages (fibrillary appearance)/liver/spleen/bone marrow
   (2) massive hepatosplenomegaly
   (3) no CNS involvement
   (4) increase in serum total acid phosphatase derived from macrophages

5. metachromatic leukodystrophy (AR)–
   A. enzyme deficiency: arylsulfatase A
   B. metabolite accumulation:
      (1) sulfatide
      (2) results in abnormal myelin
      (3) sulfatides stain positive with metachromatic stains
   C. clinical:
      (1) mental retardation
      (2) peripheral neuropathy
      (3) urine arylsulfatase activity decreased/absent

6. Krabbe disease (AR)–
   A. enzyme deficiency: galactosylceramidase
   B. metabolite accumulation:
      (1) galactocerebroside
      (2) abnormal myelin
   C. clinical:
      (1) progressive psychomotor retardation
      (2) multinucleated globoid cells (histiocytes) in CNS

7. Fabry disease (SXR)–
   A. enzyme deficiency: α-galactocerebrosidase A
   B. metabolite accumulation: ceramide trihexoside
   C. clinical:
      (1) angiokeratomas on skin
      (2) hypertension
      (3) renal failure

Glycogenoses:
1. glycogen synthesis (glycogenesis) overview–
   A. occurs in fed state
   B. insulin enhanced
   C. synthesis:
      (1) glucose + glucokinase → G6-PO4
      (2) G6-PO4 + phosphoglucomutase → G1-PO4
      (3) G1-PO4 + UDP-glucose pyrophosphorylase → UDP-glucose + UTP + PPI
      (4) UDP-glucose + glycogen synthetase (insulin enhanced) →
      (5) glycogen: branched chain polysaccharide of D-glucose residues with α-1→4 linkages
   D. liver glycogen maintains blood glucose during the fasting state until its stores are depleted: gluconeogenesis is the most important factor maintaining glucose in the fasting state
   E. muscle glycogen is used only by muscle
   F. glycogen synthetase produces α-1,4 linkages between the glucose residues by adding linkages to an already existing glycogen primer
G. **glucosyl 4:6 transferase** makes branches by transferring 5–8 glucosyl residues from the non-reducing end of the linear glycogen chain to another residue on the chain and attaching it to the chain by a α-1,6 linkage.

H. Glycogen synthetase then adds glucose residues to the new non-reducing ends on the branches and to the old non-reducing ends.

2. **glycogenolysis**
   
   A. occurs in fasting state:
      
      (1) glucagon enhanced
      (2) glucagon only degrades liver glycogen
      (3) epinephrine is glycogenolytic in liver and muscle

   B. glycogenolysis:
      
      (1) glucagon/epinephrine activate adenylate cyclase → increases cyclic AMP (cAMP) →
      (2) cAMP activates protein kinase A
      (3) activated protein kinase A inhibits glycogen synthetase → prevents glycogenesis →
      (4) activated protein kinase A activates phosphorylase kinase →
      (5) activated phosphorylase kinase activates glycogen phosphorylase A →

      (6) activated glycogen phosphorylase A cleaves α1-4 bonds up to 4 glucose residues of a branch point →

      (7) **glucosyl (4:4) transferase** removes 3 of the outer glucose residues that are left on the branch and transfers them to the non-reducing end of another chain where glycogen phosphorylase A cleaves off more glucose 1-phosphates →
(8) amylase-α-1,6 glucosidase cleaves off the remaining 1 glucose on the chain leaving behind a free glucose (ratio of glucose 1-PO_4 to free glucose is ~10/1) →
(9) glucose 1-phosphate + phosphoglucomutase → glucose 6-phosphate
(10) glucose 6-phosphate + glucose 6 phosphatase (gluconeogenic enzyme) →
(11) glucose

C. small amounts of glycogen are degraded in lysosomes by α-1,4 glucosidase (acid maltase)

3. von Gierke’s (AR)-
   A. enzyme deficiency:
      (1) glucose 6 phosphatase (USMLE)
      (2) gluconeogenic enzyme
      (3) only in liver/kidney
   B. metabolite accumulation:
      (1) normal glycogen (USMLE)
      (2) increase in glucose 6-PO_4 proximal to enzyme block is used to synthesize normal glycogen
      (3) decreased fasting glucose (fasting hypoglycemia)
   C. clinical:
      (1) hepatorenomegal: sites where gluconeogenic enzymes are located
      (2) glycogen excess in renal tubules interferes with lactic acid excretion → increased anion gap metabolic acidosis
      (3) lactic acidosis interferes with uric acid excretion → hyperuricemia
   D. laboratory findings in von Gierke’s:
      (1) stimulation tests for gluconeogenesis using glucagon, fructose, galactose cannot increase blood glucose owing to the missing glucose 6-phosphatase (USMLE)
      (2) fasting hypoglycemia

4. Pompe’s disease (AR, USMLE)-
   A. lysosomal enzyme deficiency of α-1,4 glucosidase (acid maltase): only glycogenosis that is a lysosomal storage disease
   B. increase in lysosomal glycogen: glycogen structure is normal
   C. clinical:
      (1) restrictive cardiomyopathy
      (2) death at early age

5. McArdle’s disease (AR, USMLE)-
   A. enzyme deficiency:
      (1) muscle phosphorylase
      (2) muscle glycogen cannot be degraded
      (3) reduced amounts of glucose for muscle energy
   B. clinical:
      (1) early fatigue with exercise (no ATP)
      (2) muscle cramps
      (3) myoglobinuria
   C. laboratory findings in McArdle's disease:
      (1) absence of lactic acid in blood after exercise
      (2) normal blood glucose: muscle does not contribute to blood glucose
      (3) enzyme assay of muscle confirms diagnosis
PHENYLALANINE → TYROSINE

GALACTOSE METABOLISM

Lactose → glucose + galactose
Galactose + galactokinase → galactose 1-PO₄
Galactose 1-PO₄ + GALT + UDP-glucose → glucose 1-PO₄ + UDP-galactose
Glucose 1-PO₄ + phosphoglucomutase → glucose 6-PO₄
Glucose 6-PO₄ + glucose 6-phosphatase → glucose
UDP-glucose + UDP-hexose epimerase → UDP-galactose
UDP-galactose + lactose synthetase → lactose + UDP

FRUCTOSE METABOLISM

Sucrose + sucrase → glucose + fructose
Fructose + fructokinase → fructose 1-PO₄
Fructose 1-PO₄ + aldolase B → glyceraldehyde + DHAP
HOMOCYSTEINE METABOLISM

Methionine + ATP → S-adenosylmethionine (SAM)
S-adenosylmethionine + methyl acceptors + methyltransferase → S-adenosylhomocysteine + methylated products
S-adenosylhomocysteine + H₂O → homocysteine + adenosine
Homocysteine + serine + cystathionine synthase → cystathionine

PHENYLALANINE METABOLISM

Phenylalanine + phenylalanine hydroxylase → tyrosine
Tyrosine → 4-hydroxyphenyl pyruvate → homogentisate
Homogentisate + homogentisate oxidase → maleylacetoacetate
Maleylacetoacetate + fumarylacetoacetate hydrolase → fumarylacetoacetate
Fumarylacetoacetate → acetoacetate + fumarate
LYSOSOMAL ENZYME SYNTHESIS

- Lysosomal enzymes synthesized in rough endoplasmic reticulum
- Transported to Golgi apparatus
- Post-translational modification
- Mannose residues phosphorylated → mannose 6-phosphate
- Mannose 6-phosphate receptors bind mannose 6-phosphate
- Transport vesicles contain receptor-bound enzymes
- Vesicles fuse/release enzymes into lysosomes
- Receptors return to Golgi apparatus

GLYCOSAMINOGLYCANS

- Branched, (−) charged polysaccharide chains
- Amino sugars: D-glucosamine or D-galactosamine
- Acid sugars: L-iduronic acid or D-glucuronic acid

GLYCOSAMINOGLYCANS

- Chondroitin sulfate: cartilage
- Heparan sulfate: (1) (−) charge glomerular basement membrane, (2) anticoagulant
- Keratan sulfate
- Hyaluronic acid: joint lubricant
- Dermatan sulfate: (1) heart valves, (2) mitral valve prolapse, (3) pretibial myxedema
MUCOPOLYSACCHARIDOSES

- Hurler's disease (AR): (1) α-1-iduronidase, (2) dermatan/heparan sulfate
- Hunter's disease (SXR): (1) L-iduronosulfate sulfatase, (2) dermatan/heparan sulfate
- Clinical: (1) mental retardation, (2) corneal clouding, (3) coarse facial features, (4) coronary artery disease, (5) vacuoles in WBCs

SPHINGOLIPIDS

- Examples: (1) sphingomyelin, (2) cerebrosides, (3) gangliosides
- Sphingomyelin: (1) nerve cell membranes, (2) sphingosine backbone of sphingomyelin, (3) sphingosine produces ceramides: sphingosine + fatty acids → ceramide
  ♦ ceramide + phosphorylcholine → sphingomyelin
  ♦ ceramide + glucose → glucocerebrosides
  ♦ ceramide + oligosaccharides → gangliosides

TAY-SACHS (AR)

- GM₂ gangliosidosis
- Deficiency: hexosaminidase (α-subunit)
- Metabolite: GM₂ ganglioside
- Clinical: (1) Ashkenazi Jews, (2) mental retardation, (3) blindness, (4) cherry red macula, (5) EM: whorled configurations
NIEMANN-PICK (AR)

- Deficiency: sphingomyelinase
- Metabolite: sphingomyelin
- Clinical: (1) mental retardation, (2) hepatosplenomegaly, (3) fatal in early life, (4) EM: zebra bodies

GAUCHER DISEASE (AR)

- Deficiency: glucocerebrosidase
- Metabolite: glucocerebroside
- Adult type: (1) hepatosplenomegaly, (2) no CNS involvement, (3) increase in serum total acid phosphatase

METACHROMATIC DYSTROPHY (AR)

- Deficiency: arylsulfatase A
- Metabolite: (1) sulfatide, (2) results in abnormal myelin, (3) sulfatides stain positive with metachromatic stains
- Clinical: (1) mental retardation, (2) peripheral neuropathy, (3) urine arylsulfatase activity decreased/absent

KRABBE DISEASE (AR)

- Deficiency: galactosylceramidase
- Metabolite: (1) galactocerebroside, (2) abnormal myelin
- Clinical: (1) psychomotor retardation, (2) globoid cells (multinucleated histiocytes) in CNS
FABRY DISEASE (SX5R)
- Deficiency: α-galactocerebrosidase A
- Metabolite: ceramide trihexoside
- Clinical: (1) angiokeratomas on skin, (2) hypertension, (3) renal failure

GLYCOGENESIS

Glucose + glucokinase → G6-PO₄
G6-PO₄ + phosphoglucomutase → G1-PO₄
G1-PO₄ + UDP- glucose pyrophosphorylase → UDP-glucose + UTP + PPI
UDP-glucose + glycogen synthetase → glycogen

Glycogen synthetase: α-1,4 linkages
Glucosyl 4:6 transferase: branches with α-1,6 linkage
GLYCOGENOLYSIS

Glucagon/EPI activate adenylate cyclase: increases cAMP

cAMP activates protein kinase: (1) inhibits glycogen synthetase, (2) activates phosphorylase kinase

Phosphorylase kinase: activates phosphorylase A

Phosphorylase A: (1) cleaves α1-4 bonds up to 4 glucose residues of a branch point, (2) releases glucose 1-phosphate

Glucosyl (4:4) transferase: removes/transfers 3 of the outer glucose residues left on branch to non-reducing end of chain

Amylo- α-1,6 glucosidase: (1) cleaves off remaining 1 glucose → free glucose (2) ratio glucose 1-PO₄/free glucose = ~10/1

Glucose 1-phosphate + phosphoglucomutase → glucose 6-phosphate

Glucose 6-phosphate + glucose 6 phosphatase → glucose

VON GIERKE'S (AR)

- Deficiency: (1) glucose 6 phosphatase (2) gluconeogenic enzyme, (3) only in liver/kidney

- Metabolite accumulation: (1) normal glycogen, (2) increase in glucose 6-PO₄ → synthesize normal glycogen

- Clinical: (1) hepatorenomegaly, (2) lactic acidosis, (3) hyperuricemia, (4) no glucose response to gluconeogenesis stimulation tests (glucagon, galactose), (5) fasting hypoglycemia
POMPE’S DISEASE (AR)
- Lysosomal enzyme deficiency: (1) α-1,4 glucosidase (acid maltase), (2) increase in lysosomal glycogen
- Clinical: (1) restrictive cardiomyopathy, (2) death at early age

McARDLE'S DISEASE (AR)
- Deficiency: (1) muscle phosphorylase, (2) muscle glycogen cannot be degraded
- Clinical: (1) early exercise fatigue with: no ATP, (2) muscle cramps, (3) myoglobinuria
- Laboratory: (1) no lactic acid after exercise, (2) normal blood glucose, (3) enzyme assay confirms Dx, (4) compatible with life

ABNORMAL GLYCOGEN
- Brancher deficiencies: no branches on glycogen
- Amylo- α-1,6 glucosidase debrancher deficiency: decreased amounts of free glucose
- Glucosyl (4:4) transferase deficiency: (1) increase in α-limit dextrins (small branched oligosaccharides), (2) decrease in free glucose, (3) epinephrine challenge → increased α-limit dextrins and decrease in free glucose

FASTING HYPOGLYCEMIA
- Von Gierke’s
- Liver debrancher enzyme deficiency
- Liver phosphorylase deficiency
6. **debrancher/debrancher deficiencies (USMLE)**
   A. accumulation of abnormal glycogen
   B. brancher deficiencies: no branches on glycogen
   C. amylo-α-1,6 glucosidase debrancher deficiency: decreased amounts of free glucose
     - cannot cleave off
   D. glucosyl (4:4) transferase deficiency:
     1. increase in α-limit dextrins: small branched oligosaccharides
       - cannot cleave off the 3 glucose
     2. decrease in free glucose: need to transfer the 3 glucose residues to expose the glucose with the α-1,6 linkage
     3. epinephrine challenge leads to an increase in α-limit dextrins and a decrease in free glucose (USMLE)

7. **glycogenoses with fasting hypoglycemia**
   A. von Gierke's
   B. deficiency of liver debrancher enzymes
   C. deficiency of liver phosphorylase

**SXR disorders (USMLE):**

1. **male dominant disorder (USMLE)**
   A. affected male transmits abnormal allele to all of his daughters and none of his sons
   B. daughters are asymptomatic carriers
   C. carrier daughters transmit the abnormal allele to 50% of their sons (symptomatic) and to 50% of their daughters (asymptomatic): see additional schematics
   - normal X Y
     - symptomatic male
     - XX is asymptomatic carrier
     - female X XX XY
     - normal male
     - carrier X XX XY 50% males with disease
     - female X XX XY
     - carrier X XX XY 50% males with disease
     - female X XX XY 50% of daughters with disease XX

2. **examples (in order of decreasing frequency)**
   A. fragile X syndrome
   B. G6PD deficiency: see Hematology notes
     1. 13% of African-Americans
     2. hemolytic anemia with Heinz bodies
   C. Duchenne's muscular dystrophy: see Musculoskeletal notes
     1. deficiency of dystrophin
     2. Becker's dystrophy has a defective dystrophin (USMLE)
   D. hemophilia A/B: see Coagulation notes
   E. severe combined immunodeficiency: see Immunopathology notes
SEX-LINKED RECESSIVE

X   Y
X  XX  XY
X  XX  XY

SEX-LINKED RECESSIVE

X   Y
X  XX  XY
X  XX  XY

SEX-LINKED RECESSIVE

X   Y
X  XX  XY
X  XX  XY

SEX-LINKED DOMINANT

X   Y
X  XX  XY
X  XX  XY
F. Wiskott-Aldrich syndrome: see Immunopathology notes
G. testicular feminization: see below
H. color blindness
I. chronic granulomatous disease of childhood: see Inflammation notes
J. Bruton's agammaglobulinemia: see Immunopathology notes

3. example of SXR pedigree—

![Fragile X syndrome (USMLE):]

1. pathogenesis—
   A. SXR disease
   B. triplet repeats of 3 nucleotides:
      (1) CGG
      (2) problem with anticipation (worsens in future generations)
   C. second MC genetic cause of mental retardation
   D. MCC of mental retardation in males
   E. MC Mendelian disorder associated with mental retardation

2. S/S of fragile X syndrome—
   A. mental retardation
   B. macroorchidism: at puberty
   C. narrow face/large ears
   D. hyperactivity during childhood
   E. mild general overgrowth
   F. ~30% of female carriers are mentally retarded or have impaired learning: due to anticipation and addition of triplet repeats with future generations

3. laboratory findings—
   A. abnormal fragile X chromosome
   B. DNA analysis for carrier identification: identify CGG triplet repeat (best test to confirm)

[Fragile X syndrome (USMLE):]

Lesch Nyhan syndrome (USMLE):

1. pathogenesis—
   A. SXR disease
   B. deficiency of HGPRT: no inhibition of PRPP in purine metabolism

2. clinical—
   A. hyperuricemia
   B. mental retardation
   C. self mutilation

[SXD disorders:

1. percentages of children with the abnormal allele are the same as those in SXR disorders—
   A. dominant abnormal allele causes disease in both males and females
   B. affected woman transmits symptomatic disease to 50% of her daughters and 50% of her sons
   C. affected males transmit symptomatic disease to all of their daughters and none of their sons

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2. examples—
   A. familial hypophosphatemia:
      (1) alias vitamin D resistant rickets
      (2) defect in the proximal reabsorption of phosphate and conversion of 25(OH)D₃ to 1,25 (OH)₂D₃
   B. Alport syndrome:
      (1) hereditary glomerulonephritis associated with nerve deafness
      (2) increased incidence in Latter Day Saints (Mormons)

3. example of SXD pedigree (has not been asked yet on USMLE)—

```
  O   O   ○   ○
  O ∙ O ∙ ○ ∙ ○
  ○ ∙ ○ ∙ ○ ∙ ○
```

**Multifactorial (polygenic) inheritance:**

1. pathogenesis—
   A. multiple small mutations plus the effect of environment
   B. should be suspected when there is an increased prevalence of disease among relatives of affected individuals
   C. parents and offspring have 50% of their genes in common
   D. second-degree relatives have an average of one-fourth of their genes in common
   E. third-degree relatives have one-eighth of their genes in common
   F. genes become diluted out in more distant relatives
   G. risk of an affected individual passing the disorder on to their offspring is conditioned by the number of mutant genes involved and the male-to-female prevalence of the disease

2. examples—
   A. cleft lip or palate
   B. congenital heart disease
   C. coronary artery disease
   D. gout
   E. type II DM
   F. essential hypertension
   G. open neural defects
   H. congenital pyloric stenosis

**Mitochondrial DNA disorders:**

1. mtDNA primarily codes for enzymes involved in mitochondrial oxidative phosphorylation reactions—
   A. ova contain mitochondria: **affected women transmit symptomatic abnormal allele to all their children**
   B. sperm lose their mitochondria during fertilization: **affected males do not transmit abnormal allele to any of their children**

2. examples—
   A. **Leber's hereditary optic neuropathy (USMLE)**
   B. myoclonic epilepsy
C. lactic acid with stroke

3. example of a mtDNA pedigree (USMLE) 

Sex differentiation disorders (USMLE, know this well):

1. Y chromosome is determinant of genetic sex—
   A. absence of Y chromosome results in differentiation of germinal tissue into ovaries: wolffian duct structures undergo apoptosis
   B. presence of Y chromosome causes germinal tissue to differentiate into testes: müllerian inhibitory factor is synthesized → apoptosis of müllerian tissue in the male fetus
   C. fetal testosterone develops:
      (1) epididymis
      (2) seminal vesicles
      (3) vas deferens
   D. fetal dihydrotestosterone (DHT) develops:
      (1) prostate: underscores why DHT is responsible for prostate hyperplasia/cancer and not testosterone
      (2) external male genitalia: fusion of the labia → scrotum, extension of clitoris → penis
   E. function of 5-α-reductase: converts testosterone into DHT

2. true hermaphroditism—
   A. patient has both male/female gonads:
      (1) ovary and testis, or
      (2) ovotestis
   B. majority are 46 XX genotype

3. concept of pseudohermaphrodite—
   A. patient whose phenotype (appearance) is not in agreement with the genotype (true gonadal sex),
   B. male pseudohermaphrodite:
      (1) genotypic male (XY with testes)
      (2) phenotype appears female (female genitalia)
      (3) e.g., testicular feminization
   C. female pseudohermaphrodite:
      (1) genotypic female (XX with ovaries)
      (2) phenotypically resembles a male
      (3) e.g., virilization in adrenogenital syndrome

5-α-reductase deficiency:

1. male pseudohermaphrodite

2. absence of DHT effect on male fetus—
   A. testes located in inguinal canals
   B. absence of prostate gland; no DHT effect
   C. absence of all müllerian structures:
(1) no tubes/uterus/cervix/upper one-third of vagina,
(2) müllerian inhibitory factor is present
D. external genitalia female due to absence of DHT effect:
(1) blind vaginal pouch
(2) vagina partly müllerian in origin and partly of urogenital sinus origin

3. presence of testosterone effect—
A. epididymis
B. seminal vesicles
C. vas deferens

Testicular feminization (USMLE):
1. pathogenesis—
A. SXR disease
B. MCC of male pseudohermaphroditism
C. deficiency of androgen receptors
D. DHT and testosterone are present but cannot function without a receptor

2. clinical findings—
A. no müllerian structures: müllerian inhibitory factor is present
B. no male accessory structures:
   (1) no testosterone effect
   (2) absent epididymis/ seminal vesicles/vas deferens/prostate gland
C. external genitalia remain female: no DHT effect
D. vagina ends as a blind pouch:
   (1) upper part of vagina is absent (müllerian origin)
   (2) lower part is present (represents urogenital sinus)
E. testicles located in inguinal canal: surgically removed owing to a risk for seminoma
F. estrogen unopposed: secondary female characteristics are well developed
G. patient is reared as a female

3. laboratory findings—
A. normal testosterone/DHT
B. increased LH: LH does not respond to the negative feedback of testosterone

Reifenstein syndrome:
1. SXR disease
2. end-organ refractoriness (complete or partial) to the effect of testosterone and DHT
3. receptors are present

Adrenogenital syndrome overview (USMLE):
1. pathogenesis—
A. AR disease
B. enzyme deficiencies in adrenal steroid synthesis
C. MCC of female pseudohermaphroditism
D. less common cause of male pseudohermaphroditism

2. adrenal biochemistry—
A. refer to schematic: top half the schematic is present in ovaries and Leydig cells of males
B. enzyme deficient in zona glomerulosa: 17-hydroxylase
C. enzyme deficient in zona fasciculata/reticularis: 18-hydroxylase, which converts corticosterone into aldosterone and is activated by angiotensin II (not ACTH)
D. 17-ketosteroids (KS):
   (1) dehydroepiandrosterone (DHEA)/androstenedione
   (2) weak androgens
E. 17-hydroxycorticoids (17-OHCS): metabolites of 11-deoxycorticisol + cortisol
3. mechanism of adrenal gland hyperplasia—
   A. enzyme deficiencies all result in hypocortisolism →
   B. increase in ACTH →
   C. increase in ACTH leads to hyperplasia of adrenal cortex without an increase in cortisol owing to the enzyme block

Classic 21-OHase deficiency:
1. pathogenesis—
   A. AR disease
   B. MC enzyme deficiency
   C. note: substrates distal to the enzyme block decrease and those proximal to the block increase
   D. key concept (USMLE): always first determine the genetic sex of a child with ambiguous genitalia

2. S/S of 21 OHase deficiency—
   A. weakness/hypovolemia: childhood "Addisons"
      (1) due to reduced synthesis of 11-deoxycorticosterone (weak mineralocorticoid)
      (2) salt losers (renal loss of sodium)
   B. female pseudohermaphroditism: due to increased 17-KS effect on external genitalia,
   C. precocious puberty in males: due to increase in 17-KS
   D. diffuse skin hyperpigmentation: low cortisol increases ACTH → stimulates melanin pigmentation

3. lab findings in 21 OHase deficiency—
   A. increased serum 17-OH-progesterone: best screen for 21- and 11-OHase deficiencies
   B. increased urine pregnanetriol: urine metabolite of 17-OH-progesterone
   C. electrolyte abnormalities: deficiency of 11-deoxycorticosterone leads to hyponatremia, hyperkalemia, metabolic acidosis (similar to Addison's disease)
   D. increased 17-KS
   E. decreased 17-OHCS
   F. hypocortisolism
   G. increased ACTH
   H. prenatal testing is available for the enzyme defect

Non-classic 21-OHase deficiency in adults:
1. pathogenesis—
   A. AR disease: some books say that it is the MC genetic disease in the United States
   B. incomplete 21-OHase deficiency: main problem is with an increase in 17-KS and not salt loss
   C. S/S of non-classic 21 OHase deficiency—
      (1) hirsutism in females: increased hair in hair-bearing areas
      (2) no signs of salt loss
      (3) cystic acne in females
      (4) secondary amenorrhea
      (5) pseudoprecocious puberty in boys

2. lab findings of non-classic 21 OHase deficiency—
   A. increase in 17-OH-progesterone in blood: screening test of choice
   B. ACTH stimulation test is performed if the screening test is positive: further increase in 17-OH-progesterone (proximal to enzyme block)
CALCULATION OF PREVALENCE

- Carrier rate of CF = 1/25: ? prevalence
- Number couples at risk: 1/25 x 1/25 = 1/625
- Risk of CF: 1/625 x 1/4 = prevalence of ~1/2500

HARDY-WEINBERG FOR SIMPLETONS

- Prevalence of CF = 1/2500: ? carrier rate of CF
- Number of couples at risk = 1/2500 ÷ 1/4 = 1/625
- Carrier rate of CF = 1/√625 = 1/25
- divide prevalence by 1/2 if autosomal dominant
Classic 11-OHase deficiency:

1. **Pathogenesis**—
   A. AR disease
   B. 11-OHase enzyme deficiency

2. **S/S of classic 11 OHase deficiency**—
   A. salt retention with hypertension: due to increased 11-deoxycorticosterone
   B. female pseudohemaphroditism: due to increased 17-KS
   C. precocious puberty in males: due to increased 17-KS
   D. skin hyperpigmentation: due to increased ACTH

3. **Lab findings in classic 11 OHase deficiency**—
   A. increased 17-OH-progesterone/urine pregnantriol
   B. increased 17-KS
   C. increased 17-OHCS: due to an increase in 11-deoxycortisol proximal to the block
   D. hypocortisolism
   E. increased ACTH

4. **Metapyrone test**—
   A. used in the evaluation of hypocortisolism to determine if it is due to ACTH deficiency or Addison's disease,
   B. metapyrone blocks 11-OHase: normal findings include
      (1) decrease in cortisol causes an increase in ACTH
      (2) increase in ACTH increases 11-deoxycortisol proximal to the block
   C. metapyrone test findings in hypopituitarism: both plasma ACTH and 11 deoxycortisol are decreased
   D. metapyrone test findings in Addison's disease: plasma ACTH is increased but 11-deoxycortisol is decreased

**Calculation of the prevalence of a genetic disease given the carrier rate (USMLE):** e.g., cystic fibrosis (CF)

1. **If the carrier rate of CF is 1/25, the prevalence is calculated as follows:**
2. **Number of couples at risk**— is equal to the carrier rate in males * the carrier rate in females, or 1/25 * 1/25 = 1/625 couples are at risk
3. **Risk of having a child with CF (AR disease)**— 1/4, hence 1/625 * 1/4 = prevalence of ~1/2500
Calculation of the carrier rate of a disease given the prevalence of a genetic disease: Hardy-Weinberg equation (USMLE)—
1. reflects the distribution of a mutant gene in the population
2. gene has 2 alleles—
   A. A (normal gene) and a (abnormal gene)
   B. possible combinations are AA (homozygous), Aa (heterozygous) and aa (homozygous)
   C. gene frequencies of these three genotypes are in the proportion: $p^2$ (AA), $2pq$ (Aa) and $q^2$ (aa), where $p$ equals the frequency of gene A and q equals the alternative gene of A, which is a
   D. relation of p to q is expressed as follows: $(1-q) = p$
   E. using the CF example, if the prevalence is $1/2500$, the frequency of gene a ($q$) is $1/50$ (square root of $1/2500$), carrier rate (Aa) is: $2pq$, or $2 \times 49/50$ ($p = 50/50 - 1/50 = 49/50$) x $1/50$ ($q = 0.04 = 4\%$ of the population, or a 1/25 carrier rate
3. for simpletons, like myself who do not understand the above—
   A. if you understand how to calculate prevalence from the carrier rate, then working backwards is what the Hardy Weinberg equation is calculating
   B. prevalence of CF = $1/2500$, what is the carrier rate of CF?:
      (1) number of couples at risk = $1/2500 \div 1/4 = 1/625$
      (2) carrier rate of CF = $1/625 = 1/25$
      (3) divide prevalence by 1/2 if the disease is autosomal dominant

Deformations and malformations:
1. deformations—
   A. anatomical defects resulting from mechanical factors (extrinsic forces) that usually occur in the last two trimesters after organs have developed:
   B. e.g., oligohydramnios producing facial and limb abnormalities (called Potter’s facies)
2. malformation—
   A. disturbance (e.g., drugs, infection) that occurs in the morphogenesis of an organ(s)
   B. examples:
      (1) hypospadias faulty closure of urethral folds (USMLE)
      (2) epispadias
         a. defect in genital tubercle
         b. associated with exstrophy of bladder
         c. urethra opens on the ventral surface of the penis (USMLE)
      (3) club foot
      (4) ventricular septal defect

Mechanisms of teratogens (USMLE):
1. teratogens are most detrimental during the embryonic period—
   A. first 9 weeks of life: 4th–5th week most sensitive for teratogens
   B. open neural defects: occur when tube normally closes between the 23rd–28th day
2. growth of fetus—
   A. hyperplasia normally occurs during the first half of pregnancy:
      (1) some teratogens may interfere with cell mitosis (e.g., alcohol, rubella, cell toxins)
      (2) produces symmetric growth retardation
   B. hypertrophy primarily occurs in the second half of pregnancy: teratogens acting in this phase produce asymmetric growth retardation
3. specific effects of some teratogens—
   A. interfere with formation of mitotic spindle
   B. interfere with production of ATP
C. interfere with gene production: e.g., isotretinoin effect on Hox/hedgehog genes (important in embryonic patterning)

**Teratogen (USMLE)—cocaine**
1. maternal effects—
   A. stillbirths
   B. hypertension
   C. abruptio placenta
   D. newborns small for gestational age
   E. premature labor
2. newborn effects—
   A. hyperactivity
   B. CNS: (1) microcephaly (MC effect) (2) seizures (3) intraventricular hemorrhage
   C. interruption of blood flow leading to infarction: (1) CNS (2) bowel (3) limbs (missing digits)

**Maternal diabetes mellitus (USMLE) and the teratogenic effects in newborns:**
1. increased birthweight (macrosomia, large for gestational age)—
   A. hyperinsulinism in the fetus from poor maternal glycemic control increases muscle mass: insulin increases amino acid uptake in muscle
   B. hyperinsulinism increases fat deposition: insulin increases deposition of TG in adipose
2. open neural tube defects
3. cleft lip/palate
4. respiratory distress syndrome—fetal hyperinsulinism in response to maternal hyperglycemia inhibits fetal surfactant production by type II pneumocytes
5. transposition of the great vessels

**Teratogen—diethylstilbestrol (DES, USMLE):**
1. DES—interferes with development of müllerian structures in female fetus causing abnormalities in the following:
   A. tubes
   B. uterus
   C. cervix
   D. upper one-third of vagina
2. female siblings—
   A. vaginal adenosis: (1) MC abnormality (2) precursor of clear cell adenocarcinoma of the vagina/cervix: USMLE picture of adenocarcinoma in a woman with repeated abortions
   B. cervical incompetence: increased incidence of spontaneous abortions
   C. uterine abnormalities: problems with implantation
   D. fallopian tube abnormalities: fertility problems

**Fetal alcohol syndrome and teratogenic effects in newborns (USMLE):**
1. MC teratogen in United States—
   A. 2:1000 live births
   B. 30–45% of offspring of women who have more than 4 to 6 drinks/day
2. **S/S of the fetal alcohol syndrome**—
   A. mental retardation: MC abnormality *(USMLE)*
   B. intrauterine growth retardation
   C. maxillary hypoplasia
   D. microcephaly
   E. atrial septal defects: **least common finding** *(USMLE)*
   F. hypoglycemia at birth

* Heroin effects in newborns:
  1. small for gestational age
  2. **clinical findings**—
     A. irritability/hyperactivity
     B. high pitched cry
     C. excessive hunger/salivation/sweating/tremors
     D. fist sucking
     E. temperature instability
     F. seizures

* Teratogen—**isotretinoin** *(USMLE)*:
  1. **isotretinoin**—
     A. used in treating cystic acne
     B. must order a pregnancy test before placing a woman on the drug
     C. patient must be on birth control pills while taking the drug
  2. **newborn effects** *(3 C's)*—
     A. craniofacial abnormalities:
        1. microtia (small ears)
        2. micrognathia
        3. cleft palate
     B. cardiac defects
     C. CNS malformations:
        1. hydrocephalus
        2. microcephaly

* Teratogen—**lithium**:
  1. cardiac abnormalities
  2. Ebstein's anomaly

* Maternal phenylketonuria (USMLE) and its effects in newborns:
  1. mother must be on a phenylalanine free diet while pregnant
  2. **newborn effects** *(mother not on a phenylalanine free diet)*—
     A. 25% chance of having a child with congenital abnormalities
     B. 90% chance that these include microcephaly and severe mental retardation

* Teratogen—**phenytoin** and its effects on newborns:
  1. **fetal growth disturbances**—
     A. hypoplasia of the distal phalanges: nail hypoplasia
     B. CNS abnormalities
     C. cleft lip/palate
  2. **congenital heart disease**

* Maternal smoking *(USMLE)* during pregnancy:
  1. **pathogenesis**—
     A. vasoconstrictive effects of nicotine produce placental ischemia
     B. endothelial damage increases the risk for thrombosis in placental vessels
2. **effects on the newborn**
   A. low birth weight babies
   B. called the fetal tobacco syndrome
   C. includes smoking marijuana,

3. **maternal effect**
   A. increases premature births
   B. increases spontaneous abortions/abruptio placenta/premature rupture of membranes
   C. increases perinatal mortality
   D. increases postpartum uterine bleeding
   E. reduces fertility

 Mothers with SLE and its effects in newborns:
 1. SLE patients who have anti-Ro (anti-SS-A) IgG antibodies in their serum  
    **→ crosses placenta → attacks baby's heart**
 2. newborns may develop complete heart blocks

 Teratogen - **thalidomide (USMLE):**
 1. thalidomide-
     A. previously used in the United States to control nausea associated with pregnancy
     B. currently used in Rx of leprosy
 2. **newborn effects**
     A. limb abnormalities:
        (1) amelia (absent limbs)
        (2) phocomelia (seal-like limbs)

 Teratogen - **valproate:** open neural tube defects

 Teratogen - **warfarin:**
 1. contraindicated in pregnancy - should use heparin
 2. **newborn effects**
     A. CNS defects
     B. nasal hypoplasia

 Congenital infections:
 1. **TORCH syndrome**
     A. group of congenital or perinatal infections
     B. TORCH stands for Toxoplasmosis, Other (HBV, AIDS, parvovirus, syphilis, etc.),
        Rubella, CMV (cytomegalovirus), Herpes
 2. **increase in IgM in cord blood** - not a very sensitive screening test
 3. **vertical transmission**
     A. mother to fetus
     B. **transplacental: MC type**
     C. **perinatal:**
        (1) blood contamination during delivery: e.g., HIV, HBV
        (2) cervical infection
           a. HSV 2
           b. *Chlamydia*
        (3) breast feeding
           a. HIV
           b. HBV
           c. CMV
Congenital CMV:
1. MC in-utero viral infection—
   A. part of the TORCH complex
   B. majority are asymptomatic: 85–90%
2. transmission to fetus— primarily transplacental
3. S/S of congenital CMV—
   A. bilateral sensorineural hearing loss: MC complication
   B. psychomotor retardation
   C. periventricular calcification:
      1. noted skull x-ray
      2. complication of encephalitis
   D. neonatal cholestasis:
      1. jaundice
      2. hepatosplenomegaly
   E. small for gestational age
   r. anemia/thrombocytopenia
   t. interstitial pneumonia
   H. chorioretinitis: may lead to blindness
   I. microcephaly
4. laboratory Dx of congenital CMV—
   A. urine culture is gold standard: urine cytology reveals large, basophilic intranuclear inclusions ("owl eyes") in renal tubular cells
   B. IgM TORCH titers
5. Rx of congenital CMV—
   A. ganciclovir
   B. foscarnet

Congenital rubella (USMLE):
1. part of the TORCH complex
2. transmission to fetus—
   A. primarily transplacental: highest incidence of congenital anomalies in first 8 weeks
   B. virus interferes with protein synthesis and produces a vasculitis
3. S/S of congenital rubella—
   A. sensorineural deafness: MC complication
   B. cataracts
   C. congenital heart disease: patent ductus arteriosus MC type
   D. mental retardation
   E. hepatosplenomegaly
   F. anemia/thrombocytopenia
   G. newborns highly infective: continue to shed virus
4. mothers who are seronegative for rubella—
   A. do not immunize during pregnancy
   B. immunize after baby is delivered
5. lab Dx of congenital rubella— serological tests

Congenital toxoplasmosis:
1. part of the TORCH complex
2. transmission to fetus (USMLE)—
   A. primarily transplacental
   B. contracted by women after exposure to cat litter: pregnant women should avoid cleaning cat litter during pregnancy
C. contracted also by handling or eating undercooked meat products
D. greater risk of fetal infection later in pregnancy than earlier in pregnancy

3. **S/S of congenital toxoplasmosis**—
   A. chorioretinitis:
      (1) MC late complication
      (2) often leads to blindness
   B. CNS calcifications:
      (1) dense calcifications in white matter
      (2) curvilinear in basal ganglia
   C. hepatosplenomegaly: jaundice common
   D. mental retardation
   E. seizures: common late finding
   F. hydrocephalus

4. **lab Dx of congenital toxoplasmosis**—
   A. Sabin Feldman dye test (uses live organisms): "gold standard" test but is rarely performed
   B. serologic tests most often used

5. **Rx of congenital toxoplasmosis**— pyrimethamine + sulfadiazine

**Congenital Herpes type 2:**

1. part of the TORCH complex

2. **transmission to fetus (USMLE)—**
   A. primarily contracted by passing through the birth canal in women actively shedding the virus
   B. routine antepartum cultures are not recommended
   C. women actively shedding the HSV-2 virus are delivered by C-section
   D. greater chance of fetal infection with primary rather than recurrent Herpes: higher viral burden with primary disease

3. **S/S of congenital Herpes**—
   A. infection localized to CNS:
      (1) intracranial calcifications
      (2) encephalitis
   B. infection localized to skin/eyes/mouth
   C. disseminated infection
   D. left untreated most will develop disseminated disease: majority will die or suffer permanent neurologic sequelae

4. **lab Dx of congenital Herpes**—
   A. culture
   B. serologic tests

5. **Rx**— acyclovir

**Congenital syphilis:**

1. **transmission to fetus (USMLE)—**
   A. primarily transplacental
   B. uncommon infection during first 5 months of pregnancy: anatomical barriers prevent access to the fetal circulation
   C. greater chance of contracting fetal infection in third trimester

2. **S/S of early neonatal syphilis (first 2 yrs)—**
   A. hepatomegaly: MC sign
   B. osteochondritis: inflammation of bone
   C. mucocutaneous lesions
D. pneumonia alba: lobar pneumonia
E. persistent rhinitis: snuffles
F. severe anemia/thrombocytopenia
G. generalized lymphadenopathy

3. S/S of late neonatal syphilis (>2 yrs)—
   A. frontal bossing: MC sign
   B. saber shins
   C. rhagades: perioral linear scars
   D. Hutchinson's triad:
      (1) teeth
         a. notched upper central incisors (Hutchinson’s teeth)
         b. malformed molars (mulberry molars)
      (2) interstitial keratitis (blindness)
      (3) sensorineural hearing loss

4. lab Dx—
   A. identify T. pallidum in tissue
   B. serologic tests:
      (1) four-fold increase in RPR/VDRL
      (2) cerebral spinal fluid VDRL
      (3) FTA-ABS

5. Rx— penicillin

Congenital varicella-zoster virus:
1. chorioretinitis: potential for blindness
2. disseminated disease
3. limb hypoplasia
4. cortical atrophy in the brain
5. vesicular skin lesions

Sudden infant death syndrome (SIDS):
1. definition—sudden death of an infant under one year of age that remains unexplained after a complete postmortem exam
2. pathogenesis—
   A. still unknown (USMLE)
   B. apnea hypothesis: respiratory center abnormality and/or obstruction to air flow
   C. autopsy findings primarily exhibit signs of hypoxia:
      (1) thickened pulmonary arteries
      (2) petechiae on the pleura/epicardium
      (3) mild inflammation in lungs
   D. baby sleeping supine has reduced deaths

3. clinical findings—
   A. peak incidence 2–3 mths after birth: usually occurs at night
   B. history of a minor URI, prior to death
   C. maternal risk factors:
      (1) low socioeconomic status
      (2) smoking parents
      (3) drug abuse
   D. infant risk factors:
      (1) prematurity
      (2) previous SIDS victims in the family
4. **USMLE scenario**
   A. the decline in deaths due to SIDS is mostly attributed to:
      (1) **having the baby sleep supine**
      (2) babies rebreathe their own CO₂ if they are placed in the prone position
      (3) those with immature central chemoreceptors do not respond to the respiratory acidosis by moving their heads and die
   B. retinal hemorrhages in infant who died:
      (1) child abuse (shaking syndrome)
      (2) not SIDS

**Stillbirths:**
1. definition—delivery of a dead child
2. causes—
   A. most often the result of antepartum hemorrhage; e.g., premature separation of the placenta
   B. infection:
      (1) premature rupture of membranes
      (2) chorioamnionitis from group B streptococcus
   C. abnormal karyotypes: 5–10%
   D. cord strangulation
3. risk factors—
   A. multiple gestations
   B. intravenous drug abuse
   C. preeclampsia
   D. increasing maternal age
   E. maternal smoking

**Spontaneous abortion:**
1. definition—pregnancy that terminates before the fetus is able to remain alive outside the uterus
2. causes—
   A. ~50% have a fetal karyotypic abnormality: **usually a trisomy 16**
   B. maternal factors:
      (1) infections
         a. *Streptococcus agalactiae*
         b. *Listeria monocytogenes*
      (2) antiphospholipid syndrome
      (3) parovirus infection
      (4) DES exposure
   C. placental abnormalities

**Disorders of prematurity and the neonatal period:**
1. newborn classification based on weight and gestational age—
   A. appropriate for gestational age (AGA)
   B. small for gestational age (SGA); highest mortality
   C. large for gestational age (LGA); usually due to maternal DM
2. majority of deaths in childhood occur during the neonatal period (USMLE)—
   A. first 4 weeks of life
   B. MCCs are respiratory distress syndrome (RDS) and congenital anomalies
3. problems with preterm infants (born before 37 weeks)—
   A. surfactant deficiency:
1. preterm lungs lack surfactant (USMLE)
2. predisposes to RDS
3. mothers are given glucocorticoids prior to delivery to increase surfactant synthesis
B. problems with maintaining body temperature
C. conjugating systems in liver are immature: danger of kernicterus
D. kidneys cannot handle excess solute
E. increased incidence of CNS intraventricular hemorrhage
F. persistence of patent ductus arteriosus: due to hypoxemia

4. Apgar score—
A. taken at 1 and 5 minutes
B. evaluates the following:
   1. heart rate (should be >100)
   2. respiratory effort (should be crying)
   3. muscle tone (should be active motion)
   4. reflex irritability to catheter in nose (should be cough/sneeze)
   5. color (should be pink)
C. score of 0 to 2 is given to each of the 5 components:
   1. low scores correlate with increased mortality
   2. scores >7 have almost no mortality

Age dependent and age related disorders:
1. theories of aging—
   A. stochastic:
      1. cumulative injury to cells due to free radical injury
      2. cross-linking of proteins
      3. cumulative DNA damage from FRs
      4. accumulation of errors in protein synthesis adversely affects cellular function
   B. programmed: apoptosis genes are programmed to kill cells at a set time

2. age-dependent—
   A. inevitable with age
   B. see below

3. age-related—
   A. greater incidence with age: not inevitable with age
   B. see below

General age dependent changes:
1. increased body fat—
   A. increases volume of distribution of fat-soluble drugs
   B. decreases the number of insulin receptors: glucose intolerance

2. decreased lean body mass and total body weight— reduces the volume of distribution of water-soluble drugs

Age-dependent findings in the lungs (USMLE):
1. obstructive type of pattern in pulmonary function tests (PFTs)— so-called “senile emphysema”:
   A. decreased elasticity (reduced recoil on expiration)
   B. decreased forced expiratory volume in 1 second (FEV₁sec)
   C. decreased forced vital capacity (FVC)
   D. increased total lung capacity (TLC)
   E. increased residual volume (RV)

2. mild hypoxemia
Age-dependent changes in the aorta (USMLE):
1. loss of elasticity
2. decreased baroreceptor sensitivity—
   A. increased risk for orthostatic hypotension
   B. impaired response to hypovolemia
3. decreased β-adrenergic responsiveness—
   A. decreased cardiac output and heart rate in response to stress
   B. at rest, the cardiac output is unchanged

Age-dependent type of arthritis:
1. osteoarthritis in weight bearing joints—
2. MCC of pain in the elderly
3. MCC of disability from rheumatologic disease

Age-dependent CNS changes:
1. cerebral atrophy—mild forgetfulness,
2. impaired sleep patterns—
   A. insomnia
   B. early waking
3. decreased dopaminergic synthesis—Parkinsonian-like gait

Age-dependent eye disorders:
1. cataracts—
   A. visual impairment increases the risk for falls
   B. falls are the MCC of fractures in patients >65 yrs of age
2. arcus senilis—ring of cholesterol around the cornea
3. presbyopia—inability to focus on near objects

Age-dependent ear disorders (USMLE):
1. presbycusis—
   A. sensorineural hearing loss; particularly at high frequency
   B. problems with discriminating speech
2. otosclerosis—fusion of the ear ossicles producing conductive hearing loss

Age-dependent changes in immune system (USMLE):
1. decreased T cell function
2. increase in false positive serum antinuclear antibodies (ANAs) and rheumatoid factor
3. decrease in skin reactions to antigens (called anergy)—
   A. PPD
   B. common antigens in testing for cellular immunity

Age-dependent skin changes (USMLE):
1. loss of skin elasticity—increased cross-bridging of collagen
2. increase in body fat
3. increase in vessel instability—
   A. senile purpura over the dorsum of the hands and lower legs
   B. develop in areas subject to normal trauma (USMLE picture)
4. decreased sweating—
   A. eccrine glands fibrosed
   B. danger of heat stroke
Age-dependent GI changes:
1. decreased gastric acidity—
   A. increase in serum gastrin
   B. predisposes to Helicobacter pylori infection
2. decreased colonic motility—
   A. constipation
   B. predisposes to diverticulosis
3. decreased activity of the hepatic microsomal enzyme system—
   A. delayed metabolism of some drugs
   B. danger of drug toxicities

Age-dependent reproductive tract disorders in men (USMLE):
1. prostate hyperplasia—
   A. increased urine residual volume with subsequent increase in urinary tract infections (UTIs)
   B. danger of septic shock
2. prostate cancer—only cancer that is age dependent
3. decreased testosterone—impotence

Age-dependent reproductive tract disorders in women:
1. breast and vulvar atrophy
2. decreased estrogen
3. increased gonadotropins—
   A. increased FSH and LH
   B. due to a decrease in estrogen and progesterone, respectively

Age-dependent endocrine changes:
1. increased glucose intolerance (USMLE)—due to increase in body fat and subsequent reduction in insulin receptor synthesis
2. decreased plasma renin activity and aldosterone—unknown mechanism
3. increased antidiuretic hormone (ADH)—tendency to develop hyponatremia
4. increased atrial natriuretic peptide—tendency to develop hyponatremia
5. decreased absorption of vitamin D—
   A. tendency for developing osteomalacia (decreased bone mineralization)
   B. risk for fracture
   C. increasing vitamin D supplements prevents both osteomalacia and osteoporosis

Age-dependent renal changes (USMLE):
1. decreased GFR—
   A. reduction in the creatinine clearance
   B. risk of drug toxicity due to slow clearance of drugs
2. decreased ability to concentrate and dilute urine—problems may occur with excess water load and salt load
3. increased incidence of bacteriuria

Age-dependent changes affecting pharmacokinetics: adverse pharmacokinetic changes, including
1. increased α-1 glycoprotein
2. increased body fat
3. decreased renal function
4. decreased hepatic blood flow
5. decreased lean body mass
Age-related changes in cardiovascular system:
1. **atherosclerosis (USMLE)**— increased incidence of coronary artery disease, peripheral vascular disease, and strokes
2. **temporal arteritis**
3. **aortic stenosis**— MC valvular abnormality in the elderly
4. **diastolic dysfunction**—
   A. decreased compliance of the heart during diastole;
   B. back-up of blood into the lungs and heart failure
5. **aortic sclerosis**—
   A. hardening and fibrosis of the aortic cusps that is not hemodynamically significant
   B. murmur simulates aortic stenosis
6. **systolic hypertension**— due to loss of aortic elasticity

Age-related disorders in the musculoskeletal system:
1. **osteoarthritis (USMLE)**— particularly the vertebral column in females and femoral head in males
2. Paget’s disease of bone
3. **rheumatoid arthritis**— Sjogren’s syndrome more common as well

Age-related disorders in respiratory system:
1. **pneumonia (USMLE)**—
   A. usually *Streptococcus pneumoniae*: underscores importance of Pneumovax vaccination in elderly
   B. diminished cough effectiveness and mucociliary clearing
2. **primary lung cancer**— particularly in smokers

Age-related disorders in CNS (USMLE):
1. Alzheimer’s disease
2. Parkinson’s disease
3. **strokes**— atherosclerotic type is MC type of stroke
4. **subdural hematomas**— falls cause tearing of bridging veins in subdural space leading to a venous clot

Age-related disorders in the eyes (USMLE):
1. macular degeneration—
   A. MCC of blindness in elderly
   B. effects 30% of the elderly
2. limitation in upward gaze

Age-related disorders in immune system:
1. monoclonal gammopathies of undetermined significance— MCC of monoclonal gammopathy
2. multiple myeloma— MC primary malignancy of bone

Age-related skin disorders (USMLE):
1. UVB light-induced cancers—
   A. **basal cell carcinoma (USMLE picture)**: MC skin cancer
   B. squamous cell carcinoma
   C. **malignant melanoma (USMLE picture)**
2. **actinic (solar) keratosis (USMLE picture)**—
   A. UVB light-related
   B. precursor for squamous cell carcinoma
3. **pressure sores**— pressure on capillaries is the most important factor
Age-related reproductive disorders:
1. women—cancers of:
   A. breast
   B. endometrium
   C. ovary
2. men—malignant lymphoma of the testicle

Age-related renal disorders:
1. renovascular hypertension secondary to atherosclerosis
2. renal adenocarcinoma—particularly in smokers
3. urinary incontinence

Age-related endocrine disorder: type II diabetes mellitus

Questions used in the board review:

A 51 year old woman delivers a full-term baby that has repeated vomiting of bile stained material. A flat plate of the abdomen reveals air in the stomach and proximal duodenum and no air in the remainder of the bowel. The maternal serum α-fetoprotein level is low. The baby has 46 chromosomes. The mechanism of the child's disease is most closely associated with...
A. a Mendelian disorder
B. a Robertsonian translocation
C. nondisjunction in meiosis
D. a point mutation of a nucleotide
E. a microdeletion disorder

B

If an African American woman with sickle cell disease has children with a man lacking the abnormal β-chain, you would expect...
A. 25% of their children to have sickle cell trait
B. 50% of their children to have sickle cell trait
C. 25% of their children to have sickle cell disease
D. 50% of their children to have sickle cell disease
E. all of their children to have sickle cell trait

E

A 17-year-old adolescent presents with primary amenorrhea. Physical exam reveals normal secondary female sex characteristics. Discrete masses are noted in both inguinal canals. A speculum exam of the vagina indicates a blind pouch. You would expect this patient to also have...
A. a prostate gland
B. seminal vesicles
C. an androgen receptor deficiency
D. one Barr body on a buccal smear
E. ovaries in the inguinal canal

C
While examining a 13-year-old boy during a routine physical examination, you note bilaterally enlarged, non-tender testicles that do not transilluminate, a high arched palate, and a mid-systolic ejection click followed by a short murmur. You call the school counselor and find that the child has a moderately severe attention deficit syndrome. Which of the following studies would you recommend on this boy that would best explain all of the abnormalities noted on the examination?

A. Echocardiogram
B. Buccal smear
C. Serum gonadotropins
D. Identification of triplet repeat
E. Chromosome study on his father

Prader-Willi and Angelman's syndrome have different clinical features, however they both share a defect at the same location on the same chromosome. This is an example of...

A. variable expressivity
B. a Robertsonian translocation
C. genetic heterogeneity
D. genomic imprinting
E. a balanced translocation

If the carrier rate for the sickle cell abnormality is 1 in 12, the prevalence of sickle cell disease is approximately 1 in...

A. 144
B. 288
C. 576
D. 720
E. 1440

Which one of the following transplacental infections is transmitted to the newborn after the fifth month of gestation?

A. Cytomegalovirus
B. Toxoplasmosis
C. Syphilis
D. Herpes genitalis
E. Rubella

A pregnant woman during her first trimester developed fever, a maculopapular rash, arthritis, and painful postauricular lymphadenopathy. Which of the following complications could potentially occur in her newborn child?

A. Periventricular calcification
B. Saddle nose deformity
C. Sensorineural hearing loss
D. Limb hypoplasia
E. Craniofacial abnormalities
Environmental pathology

Top 5 causes of death in the United States in descending order (USMLE):
1. heart disease
2. cancer
3. stroke
4. chronic obstructive pulmonary disease (COPD)
5. motor vehicle accidents

Top 5 risk factors leading to increased morbidity/mortality in the United States in descending order (USMLE):
1. cigarette smoking
2. dietary factors and activity patterns—
   A. high saturated fat
   B. low fiber diet
   C. lack of exercise
3. alcohol abuse
4. microbial agents
5. toxic agents

Gunshot wounds:
1. types—
   A. contact wounds: contain soot and gunpowder in the wound (called fouling)
   B. intermediate wounds:
      (1) powder tattooing (stippling) of skin around the entrance site
      (2) no fouling
   C. distant wounds: no powder tattooing
2. exit wounds are larger and more irregular than entrance wounds

Motor vehicle accidents (MVAs):
1. MCC accidental death between 1–24 ys of age—
   A. commonly alcohol-related; particularly in teenagers
   B. seat belts and air bags have reduced morbidity/mortality
2. MVA is MC cause of death (COD) in 15–25 age bracket—note: in a Black male in this age bracket, homicide is the MC COD

Drowning:
1. third MC COD in children from 1–14 years of age
2. near drowning—survival following asphyxiation secondary to submersion
3. wet drowning—
   A. 90% of cases
   B. initial laryngospasm on contact with water→relaxation/aspiration of water
4. dry drowning—intense laryngospasm without significant relaxation
5. fresh/salt water drowning—
   A. whether fresh or salt water drowning, surfactant is destroyed in lungs→
   B. atelectasis with intrapulmonary shunting→
   C. diffuse alveolar damage and initiates spasm in the bronchioles
   D. immediate COD in drowning is cardiac arrhythmia

Burns:
1. first degree burns—
   A. painful partial thickness burns: e.g., sunburn
(2) extremely high temperatures after induction of anesthesia by halothane and succinylcholine (muscle relaxant),

D. Rx of malignant hyperthermia:
  (1) **dantrolene**
  (2) screen family members with muscle biopsy and caffeine/halothane contraction test on muscle

6. **USMLE scenario**
   A. body temperature and redness of skin for a patient walking briskly on a hot day:
      (1) no increase in body temperature
      (2) vasodilatation of vessels in skin producing redness
      (3) choice D in schematic
   B. similar question for a marathon runner on a hot day:
      (1) increase in body temperature (probably heat exhaustion),
      (2) vasodilatation of vessels in skin producing redness
      (3) choice C in schematic

![Vasodilatation diagram]

**Cold injuries:**

1. frostbite—
   A. localized tissue injury secondary to direct (ice crystallization in cells) and indirect damage (vasodilatation/thrombosis)
   B. tissue painless

2. generalized hypothermia—
   A. core body temperature <35°C
   B. whole body exposed to freezing temperatures for a prolonged period of time:
      (1) uncoupling of oxidative phosphorylation
      (2) venous pooling that may progress into circulatory failure and death
   C. Rx: warm patient in lukewarm water + warm blankets

**Electrical injury:**

1. **Ohm's Law**—
   A. current (I, amps) = voltage (E) / resistance (R, ohms)
   B. I (amps) = E (volts) / R (ohms)

2. current is most important factor in electrocution— alternating current (AC) > direct current (DC) risk for electrocution,

3. resistance—
   A. dry skin has the highest tissue resistance to current; particularly the hands and feet
   B. wet skin lowers the resistance to current; since voltage is a constant, lowering resistance increases current

4. current moving from the left arm to the right leg is most dangerous (USMLE):
   (1) involves the heart → ventricular fibrillation
   (2) blood is an excellent conductor of current

4. **COD**— cardiorespiratory arrest with ventricular fibrillation and respiratory paralysis
(3) oxygen

D. prevention:
   (1) acclimatize before ascending
   (2) acetazolamide
      a. carbonic anhydrase inhibitor
      b. produces metabolic acidosis → compensation for the expected respiratory alkalosis

3. high altitude pulmonary edema—
   A. non-cardiogenic: not related to heart failure
   B. Rx of high altitude pulmonary edema:
      (1) immediate descent
      (2) oxygen

Changes after death: rigor mortis due to decrease in ATP in muscle (USMLE)

Drugs of abuse (DOA):
1. types of DOA—
   A. sedatives:
      (1) barbiturates
      (2) alcohol
   B. stimulants: cocaine
   C. hallucinogens: lysergic acid diethylamide
   D. there is some overlap among the drugs in these groups

2. MC DOAs in adolescents—
   A. marijuana
   B. alcohol

3. patient criteria for compulsive drug use—
   A. psychologic dependence: craving/motivation for procuring drug
   B. physiologic dependence: withdrawal symptoms occur when D/C the drug
   C. tolerance: drug dose must be increased to produce the same desired effects
   D. MC in 18–25 yr old age group: three times more common in males than females

4. CNS effects of long-term drug abuse—
   A. damage to neurotransmitter receptor sites
   B. cerebral atrophy may occur with certain drugs: e.g., alcohol

5. water soluble DOA—
   A. examples:
      (1) alcohol
      (2) opioids
      (3) stimulants
   B. cleared more rapidly by the kidneys:
      (1) often cleared within 24-h
      (2) detection more difficult

6. lipophilic DOA—
   A. examples:
      (1) **THC in marijuana**
      (2) barbiturates
   B. take longer to clear out through the kidneys:
      (1) days to months
      (3) rendered water soluble by liver cytochrome system
      (4) easier to detect than water soluble DOAs
2. **opiate/sedative syndrome**—
   
   A. examples:
      (1) heroin
      (2) benzodiazepines
      (3) barbiturates
   
   B. S/S of opiate/sedative toxicity:
      (1) respiratory depression → respiratory acidosis
      (2) stupor/coma
      (3) seizures
      (4) miotic pupils (pinpoint pupils)
      (5) absent deep tendon reflexes (DTRs)
      (6) hypotension

3. **anticholinergic syndrome**—
   
   A. examples:
      (1) antidepressants
      (2) antihistamines
      (3) antiparkinson-type medications
      (4) atropine
      (5) muscle relaxants
   
   B. S/S of anticholinergic toxic syndromes:
      (1) mydriasis (dilated pupils)
      (2) fever elevation often into hyperthermic ranges
      (3) dry skin
      (4) dementia
      (5) tachycardia
      (6) myoclonic jerks/seizures

4. **pschodelic/ hallucinogenic syndrome**—
   
   A. PCP
   
   B. LSD

5. **antidotes used in unconscious patients**—
   
   A. dextrose: R/O possible hypoglycemia from insulin overdose
   
   B. naloxone: possible opiate overdose
   
   C. intravenous thiamine:
      (1) possible alcohol effect
      (2) glucose may precipitate Wernicke's encephalopathy

6. **intravenous drug abuse (IVDA)**—
   
   A. MC localized infection: skin abscesses due to *Staphylococcus aureus*
   
   B. systemic infections:
      (1) **HBV (MC systemic infection): high viral burden**
      (2) HIV (22% of all cases of HIV)
      (3) infective endocarditis
         a. 	MC tricuspid and aortic valve
         b. 	*S. aureus* MCC
(4) brain abscesses
(5) osteomyelitis
(6) tetanus (complication of “skin popping”)

Opiate DOAs:

1. examples—
   A. heroin: diacetylmorphine
   B. morphine
   C. meperidine
   D. methadone
   E. codeine

2. general comments—
   A. opiates are depressant drugs
   B. heroin (morphine is a derivative of heroin) and codeine derive from the poppy plant
   C. withdrawal symptoms/ tolerance are associated with these drugs

3. heroin—
   A. derived from poppy plant
   B. administration:
      (1) IV/SC
      (2) snorting/smoking
      (3) usually “cut” with some agent (e.g., quinine, talc)
      (4) granulomatous reactions occur in skin/lungs from the cutting agents
   C. S/S of heroin overdose:
      (1) respiratory depression
      (2) miotic pupils
      (3) non-cardiogenic pulmonary edema (USMLE): frothing from the mouth is common
      (4) focal segmental glomerulosclerosis (hypertension + nephrotic syndrome)
   D. Rx for heroin overdose:
      (1) naloxone (USMLE)
      (2) naloxone is a morphine derivative with a high affinity for opioid binding sites of the mu receptor type

4. meperidine—MC DOA in health professionals

5. 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP, USMLE)—
   A. by-product of attempted synthesis of meperidine
   B. produces irreversible Parkinson’s: cytotoxic to neurons in nigrostriatal dopaminergic pathways

6. withdrawal symptoms of opioid abuse—
   A. adrenergic symptoms:
      (1) anxiety/sweating
      (2) prevented by clonidine
   B. fever
   C. rhinorrhea
   D. N/V
   E. cramping in the stomach

7. methadone—
   A. legal synthetic opioid taken orally
   B. mainly used to detoxify opiate abusers
   C. long-acting drug:
      (1) saturates CNS opiate receptors
      (2) prevents sudden euphoric action associated with heroin
(3) causes physical dependence/tolerance
(4) naloxone must be used for a longer time in drug overdose

Benzodiazepine toxicity:
1. mechanism of action (MOA)—
   A. enhance the frequency of opening up of \textit{GABA}_A receptor-chloride ion channels \textcolor{blue}{(USMLE)}\textit{→ increases chloride ion conductance}
   B. GABA (γ-aminobutyric acid) is an inhibitory neurotransmitter
   C. benzodiazepines depress mental/respiratory function: lesser degree than barbiturates
   D. withdrawal symptoms/tolerance occur: effect enhanced with alcohol
2. clinical uses—
   A. tranquilizers
   B. sedatives
   C. muscle relaxants
   D. anticonvulsants
   E. anesthetics
   F. drug of choice for alcohol withdrawal syndrome
3. S/S of toxicity—
   A. drowsiness
   B. dysarthria
   C. ataxia
4. Rx of toxicity \textcolor{blue}{(USMLE)}—
   A. flumazenil
   B. antagonist of benzodiazepine
   C. does not block barbiturates or other depressants
   D. does not work effectively if mixed overdoses with antidepressants are present

Barbiturate toxicity:
1. MOA—
   A. enhance the duration of opening up of the \textit{GABA}_A receptor-chloride ion channels \textcolor{blue}{(USMLE)}\textit{→ increases chloride ion conductance}
   B. depress neuronal activity in reticular activating system\textit{→ inhibits the inhibitory effects of GABA and glycine (an amino acid inhibitory neurotransmitter)}
   C. withdrawal/tolerance occurs
2. clinical uses— similar to benzodiazepines
3. S/S of barbiturate overdose—
   A. respiratory/mental status depression
   B. coma
   C. loss of DTRs
   D. bullae over pressure points: erythema multiforme
   E. hypothermia
   F. hypotension
4. Rx of barbiturate overdose—
   A. maintain airway/blood pressure
   B. gastric lavage with activated charcoal
   C. increase urine excretion of drug in the urine with forced alkaline diuresis using sodium bicarbonate

Cocaine:
1. MC COD from DOA in United States
2. MOA—
   A. blocks uptake of neurotransmitters dopamine/NOR by presynaptic axon \textcolor{blue}{(USMLE)}
B. sympathomimetic drug
C. predisposes to:
   (1) sudden death
   (2) acute myocardial infarction (AMI)/stroke
   (3) pulmonary edema
   (4) ventricular arrhythmias
   (5) myocarditis
D. withdrawal/tolerance occur

3. S/S of cocaine overdose—
   A. hypertension/sinus tachycardia
   B. psychosis/seizure activity
   C. perforated/ulcerated nasal septum
   D. mydriasis

4. Rx of cocaine overdose—
   A. benzodiazepines to control seizure activity
   B. lidocaine for ventricular arrhythmias
   C. labetalol for adrenergic symptoms

Amphetamines:
1. MOA—
   A. release catecholamines from presynaptic terminals (USMLE)
   B. examples of amphetamines:
      (1) dextroamphetamine (Rx obesity)
      (2) methylphenidate
         a. Rx ADHD
         b. Rx narcolepsy
      (3) methamphetamine (“ice” is street form of the drug)
   C. withdrawal/tolerance occur

2. S/S of amphetamine overdose—
   A. cardiovascular abnormalities:
      (1) arrhythmias/ tachycardia
      (2) hypertension
      (3) AMI
   B. extreme hyperexcitability
   C. hallucinations: drug that most simulates schizophrenia (USMLE)
   D. rhabdomyolysis with myoglobinuria
   E. mydriasis
   F. hyperthermia

3. Rx of amphetamine overdose—
   A. activated charcoal
   B. benzodiazepines for seizures/agitation
   C. haloperidol for hallucinations
   D. propranolol or lidocaine for arrhythmias

Marijuana:
1. MC illegal DOA used in United States
2. MOA—
   A. contains the psychoactive stimulant Δ9-tetrahydrocannabinol (THC):
      (1) THC binds to receptors in substantia nigra, globus pallidus, hippocampus, cerebellum
      (2) derives from leaves/flowering tops of hemp plants (Cannabis sativa)
3. **clinical uses (USMLE)**
   A. cancer: decrease N/V in cancer patients
   B. lower intraocular pressure in glaucoma
   C. analgesia

4. **S/S of marijuana use**
   A. tachycardia
   B. **reddening of conjunctiva (USMLE)**
   C. orthostatic hypotension
   D. euphoria
   E. uncontrollable laughter
   F. **delayed reaction time (USMLE)**
   G. inability to judge speed/distance
   H. gynecomastia
   I. COPD

5. **USMLE scenario**
   A. engineer driving a train involved in a crash with an oncoming train was found to have THC metabolites in his urine
   B. ? why did this occur → delayed reaction time

**LSD (lysergic acid diethylamide):**

1. **MOA**
   A. ergot alkaloid that binds to D₂ dopamine receptors in the brain; also blocks 5-HT₂ serotonin receptor in peripheral tissue
   B. not associated with withdrawal symptoms: tolerance has been observed
   C. predisposes to chromosomal breakage leading to congenital defects

2. **S/S of LSD toxicity**
   A. hallucinations
   B. diaphoresis
   C. mydriasis
   D. hypertension
   E. flashbacks

**PCP (phencyclidine):**

1. **angel dust**

2. **MOA**
   A. reacts with opioid-like sigma receptors and subtypes of glutamate receptors (antagonist)
   B. most dangerous hallucinogenic drug
   C. initially introduced as a dissociative anesthetic: separates bodily functions from the mind without a loss of consciousness
   D. no withdrawal/tolerance occurs

3. **S/S of PCP toxicity**
   A. agitation/violent behavior
   B. coma with the eyes open
   C. impervious to pain
   D. auditory and visual hallucinations
   E. hypertension
F. hyperacusis
G. myotonic jerks
H. horizontal/vertical nystagmus
I. hyperthermia

4. Rx of PCP toxicity—
   A. benzodiazepine for agitation
   B. propranolol for adrenergic symptoms
   C. diphenhydramine for myoclonic activity

Alcohol (ethyl alcohol, ethanol):
1. sites of alcohol reabsorption—
   A. small intestine: 75%
   B. stomach:
      (1) 25%
      (2) partially metabolized by alcohol dehydrogenase

2. liver metabolism—
   A. summary:
      \[ \text{alcohol dehydrogenase} \quad \text{aldehyde dehydrogenase} (\text{blocked by disulfiram}) \]
      \[ \text{alcohol} \rightarrow \text{acetaldehyde} + \text{NADH} \rightarrow \text{acetate} + \text{NADH} \rightarrow \text{acetyl CoA} \]
   B. metabolized ~8 mL/, which clears ~15 mg/dL/h

3. pharmacologic action—
   A. CNS depressant in descending order—
      (1) cerebral cortex
      (2) limbic system
      (3) cerebellum
      (4) lower brain stem
   B. potentiates inhibitory neurotransmitters like γ-aminobenzoic acid

4. aldehyde dehydrogenase deficiency—
   A. affects ~40% of Asians
   B. build-up of acetaldehyde and GI upset: similar to action of disulfiram

5. S/S of alcohol toxicity—
   A. 50 mg/dL:
      (1) euphoria
      (2) gregarious
   B. 100 mg/dL:
      (1) legally drunk in most states (USMLE)
      (2) slurred speech/uncoordinated
   C. 125–150 mg/dL:
      (1) combativeness
      (2) unrestrained behavior
   D. 200–250 mg/dL → lethargic
   E. 300–350 mg/dL → stupor or coma
   F. >500 mg/dL → death

6. delirium tremens—
   A. following occur 3–5 d after complete withdrawal:
      (1) tremulousness
(2) disorientation
(3) visual hallucinations
(4) agitation
(5) β-adrenergic signs
(6) incontinence

B. Rx with IV diazepam and thiamine

Diseases where alcohol is the leading cause:
1. thiamine deficiency—
   A. Wernicke’s syndrome
   B. Korsakoff’s psychosis
   C. congestive cardiomyopathy
2. macrocytic anemia— folate deficiency
3. acquired sideroblastic anemia— microcytic anemia with ringed sideroblasts
4. Mallory Weiss syndrome— tear of the distal esophagus/proximal stomach from retching
5. Boerhaave’s syndrome— rupture of the distal esophagus/proximal stomach from retching
6. cirrhosis
7. esophageal varices— effect of portal vein hypertension due to alcoholic cirrhosis
8. fatty change in the liver
9. chronic pancreatitis
10. acute pancreatitis

Alcohol as a cancer risk:
1. squamous carcinoma (synergistic with smoking)—
   A. oropharynx
   B. esophagus
   C. larynx
2. adenocarcinoma—
   A. pancreas
   B. liver

Alcohol effects on CNS/PNS:
1. Wernicke’s syndrome/Korsakoff’s psychosis
2. cerebellar degeneration— Hu and Yo antibodies noted in spinal fluid
3. dementia
4. DTs—
5. distal peripheral neuropathy
6. optic atrophy
7. central pontine myelinolysis— demyelination syndrome due to rapid IV Rx of hyponatremia

Alcohol effects on hematologic system:
1. folate deficiency
2. thrombocytopenia—
   A. direct toxic effect on megakaryocytes
   B. hypersplenism
3. neutropenia— hypersplenism
4. sideroblastic anemia
5. iron deficiency— due to bleeding from:
   A. esophagitis
   B. gastritis
   C. esophageal varices
6. prolongs prothrombin time (PT)— coagulation factor deficiencies from liver disease
Alcohol effects on the GI system:
1. esophageal varices
2. esophagitis
3. GERD
4. acute hemorrhagic gastritis
5. Mallory-Weiss/Boerhaave's syndrome
6. fatty liver
7. alcoholic hepatitis
8. cirrhosis
9. hemosiderosis—
   A. acquired iron overload
   B. iron primarily deposits in liver
10. gallstones
11. acute/chronic pancreatitis

Alcohol effects on the cardiovascular system:
1. congestive cardiomyopathy—
   A. direct toxic effect on myocardial tissue
   B. thiamine deficiency
2. cardiac arrhythmias—paroxysmal tachycardia
3. hyperlipidemia—type IV and V hypertriglyceridemia

Alcohol effects on the genitourinary system:
1. impotence—
   A. decreases erectile capacity
   B. reduces testosterone levels by a direct toxic effect on Leydig cells
   C. inhibits gonadotropin release
   D. increases sex-hormone binding protein: increases binding of free testosterone
2. secondary amenorrhea—decreases gonadotropins

Alcohol effects on the respiratory system:
1. lung abscesses—aspiration of infected oropharyngeal secretions
2. Klebsiella pneumoniae pneumonia—
   A. fat gram-negative rods in mucoid sputum
   B. tendency for cavitation in upper lobes
3. TB

Alcohol effects on immune system:
1. increased susceptibility to infection
2. impaired healing

Alcohol effects on the musculoskeletal system:
1. myopathy—
   A. increased serum CK
   B. rhabdomyolysis
2. increased incidence of gout—increased lactate and β-OHB anions compete for excretion with uric acid in the kidneys

Lab findings in alcohol abuse: see General Principles of Laboratory Medicine

Smoking:
1. MCC of premature death in the United States—
   A. accounts for ~20% of all deaths
   B. MC single preventable cause of cancer (USMLE)
C. smoking has declined in the United States
D. incidence of smoking is increasing in women and decreasing in men

2. test used to document nicotine intake (USMLE)-
   A. plasma or urine level of cotinine
   B. cotinine is only derived from the metabolism of nicotine

3. MOA of nicotine-
   A. absorbed rapidly into the pulmonary circulation
   B. moves into the brain where it attaches to nicotinic cholinergic receptors to produce its
      gratifying effects/complication of smoking
   C. highly addictive agent

Cancers where smoking is the leading cause:

1. lung cancer—
   A. squamous
   B. small cell
   C. adenocarcinoma to a lesser extent
   D. MCC of death due to cancer in both men and women

2. oral squamous cancer
3. pancreatic adenocarcinoma
4. esophagus— squamous
5. larynx— squamous
6. transitional cell carcinoma of bladder
7. renal adenocarcinoma
8. inactivation of the p-53 suppressor gene by a point mutation on chromosome 17 is the
   MC genetic defect in smoking-induced cancer

Cancers where smoking has been implicated but is not the MC risk factor:

1. cervical cancer—
   A. squamous
   B. carcinogens found in cervical secretions

2. stomach adenocarcinoma
3. breast adenocarcinoma— primarily in women who are slow acetylators of N-acetyltransferase
   2 enzymes
4. prostate adenocarcinoma
5. colon adenocarcinoma
6. leukemia— increased risk of both lymphoid and myeloid leukemias
7. alcohol is a cocarcinogen with smoking that further enhances the risk of oropharyngeal,
   esophageal, laryngeal cancers
8. smoking + asbestos exposure markedly enhances the incidence of primary lung cancer—
   A. no association of smoking with mesothelioma
   B. whether the patient is a smoker or not, lung cancer is the most common cancer associated
      with asbestos exposure

Smoking effects on the cardiovascular/CNS systems:

1. increases risk for AMI— increased risk for recurrent AMI as well
2. increases risk for sudden cardiac death
3. increases risk for peripheral vascular disease
4. increases risk for strokes
5. contributing factors—
   A. enhanced atherosclerosis: chemicals in smoke
   B. nicotine effect on blood pressure and heart rate
   C. atherogenic lipid profile
Smoking effects on the respiratory system:
1. COPD—
   A. ~80% of all cases
   B. chronic bronchitis
   C. emphysema
2. recurrent infections—
   A. pneumonia
   B. URIs
3. exacerbates bronchial asthma
4. cancer— see above

Smoking effects on the GI system:
1. GERD
2. delays the rate of ulcer healing
3. increased risk for oral, upper and lower GI cancer— see above
4. USMLE scenario: smoker with history of peptic ulcer disease, ? advice: stop smoking

Effects of smokeless tobacco (snuff, chewing tobacco):
1. nicotine addiction
2. oral leukoplasia/cancer—
   A. inside the lip
   B. under the tongue or cheek
3. verrucous squamous cancer
4. nasal cancer— snuff users
5. aggravation of cardiovascular disease— nicotine effect

Smoking effects on bone and menopause—
1. increases the risk for osteoporosis in men and women
2. biochemical reaction in women—
   A. estradiol (most potent estrogen) is normally metabolized in the liver into estrone→
   B. estrone is metabolized into methoxyestrone (no hormonal activity) or estriol (strong estrogen activity)→
   C. smokers have greater conversion of estrone into the inactive metabolite →
   D. low estriol levels→
   E. low estrogen increases the risk for osteoporosis and premature menopause

Passive smoking effect on children:
1. pathogenesis—
   A. ~75% of total combustion product in a cigarette is exhaled
   B. risk of passive smoke extends to children as well as adults
2. increases the incidence of SIDS
3. increases risk for lung cancer— 1–2 times increased cancer risk
4. exacerbates asthma
5. increases risk for otitis media
6. increases risk for recurrent upper and lower respiratory infections

Miscellaneous smoking effects:
1. increases risk for developing proteinuria in diabetes mellitus
2. directly responsible for ~25% of residential fires
3. vitamin C deficiency
Beneficial effects smoking cessation (USMLE):

1. longevity—smokers who quit before 50 yrs of age have half the risk of dying over the next 15 yrs than a smoker has.
2. lung cancer—
   A. in 10 yrs, there is a 50% reduction in lung cancer when compared to a smoker
   B. after 15 yrs, there is only a 16% risk for lung cancer when compared to a smoker
3. AMI—AMI risk approaches that of a nonsmoker after 1 yr of abstinence
4. pregnancy—pregnant women who stop smoking in the first trimester reduce the risk of a low birthweight baby to that of a nonsmoker
5. forced expiratory volume in 1 second (FEV₁/sec)—
   A. it is not improved by cessation of smoking
   B. rate of decline is similar to that of a non-smoker

Acetaminophen toxicity:

1. MOA—
   A. weak cyclooxygenase inhibitor: lacks anti-inflammatory activity
   B. inhibitor of CNS prostaglandin: antipyretic activity
   C. mechanism of analgesia unclear
2. dose related hepatotoxicity—
   A. fatal liver failure within 3–5 days
   B. MC drug-induced cause of fulminant hepatic failure
3. free radical metabolite also contributes to renal papillary necrosis

Toxic effects of alkylating agents (nitrogen mustards, chlorambucil, busulfan, cyclophosphamide, mitomycin C):

1. bone marrow suppression
2. induce second malignancies—non-Hodgkin’s lymphoma MC type of cancer
3. cyclophosphamide—
   A. transitional cell carcinoma of bladder
   B. hemorrhagic cystitis
   C. interstitial fibrosis in lungs
4. busulfan—interstitial fibrosis in the lungs

Chloramphenicol:

1. MOA—inhibits protein synthesis (50S)
2. adults—reversible (idiopathic) aplastic anemia with cytoplasmic vacuoles in erythroid/granulocyte precursors
3. newborns—
   A. dose-related toxicity in newborns:
   B. inadequate conjugation of the drug in the liver increases drug levels→
   C. "gray baby syndrome"→hypothermia, bradycardia, diarrhea, cyanosis (gray skin) and hypotension

Estrogen:

1. functions—
   A. proliferative phase of menstrual cycle
   B. lipid effects:
      (1) lowers LDL/VLDL
      (2) increases HDL: protects against coronary artery disease
   C. prevent osteoporosis: inhibits osteoclast activating factor (IL-1) secreted by osteoblasts
2. unopposed excess in estrogen—
   A. natural estrogens are less thrombogenic than synthetic estrogens
B. synthetic estrogens increase synthesis of coagulation factors:
   (1) fibrinogen/V/VIII
   (2) predisposes to venous thrombosis/stroke/AMI/pulmonary embolism/hepatic vein thrombosis
   (3) even greater risk if patient is a smoker
C. increases liver synthesis of transcortin and thyroid binding globulin (USMLE):
   (1) increases total cortisol/thyroxine levels
   (2) no increase in free hormone
D. increases liver synthesis of sex hormone binding globulin:
   (1) lowers free testosterone
   (2) clinical significance (impotence) in hyperestrinism in males with cirrhosis
E. synthetic estrogens decrease antithrombin III: predisposes to venous thrombosis/stroke/AMI/pulmonary embolism/hepatic vein thrombosis
F. cancer risk:
   (1) endometrial
   (2) breast
G. gynecomastia in men
H. liver/gallbladder disorders:
   (1) intrahepatic cholestasis
   (2) cholelithiasis

Oral contraceptives:
1. pill effects—
   A. inhibit LH surge, which prevents ovulation
   B. increase malar eminence pigmentation:
      (1) "pregnancy mask"
      (2) called chloasma (USMLE)
   C. ethinyl estradiol (synthetic estrogen) increases liver synthesis of many proteins
   D. 19-nortestosterone (progestational agent) effects:
      (1) water retention/weight gain
      (2) reduction in estrogen receptor synthesis (atrophy of endometrial glands)
      (3) increase LDL
      (4) decrease HDL

2. complications—
   A. thrombogenic: see estrogen discussion
   B. stimulate tryptophan metabolism: lowers serotonin → depression
   C. increases liver synthesis of angiotensinogen: MCC of hypertension in young women
   D. liver disorders:
      (1) intrahepatic cholestasis
      (2) hepatic adenoma: tendency to rupture (USMLE)
      (3) hepatocellular carcinoma
      (4) increase gallstone formation
   E. cancer risks:
      (1) cervical
      (2) breast controversial
      (3) hepatocellular carcinoma

3. protective/preventive effects of pills—
   A. fibrocystic change in the breast
   B. endometrial cancer
   C. ovarian cancer: less ovulation reduces risk for cancer
   D. pelvic inflammatory disease: Neisseria gonorrhoeae not Chlamydia trachomatis
E. uterine leiomyomas
F. endometriosis
G. acne
H. rheumatoid arthritis

**Drugs and interstitial pulmonary fibrosis:** drugs include (know all of these for USMLE)
1. amiodarone
2. bleomycin
3. busulfan
4. cyclophosphamide
5. nitrofurantoin
6. nitrosourea
7. methysergide: also retroperitoneal fibrosis and Raynaud phenomenon
8. methotrexate
9. procarbazine

**Iron toxicity:**
1. **clinical setting**— accidental overdose of ferrous sulfate in children
2. **S/S of iron toxicity**—
   A. hemorrhagic gastritis
   B. hepatic necrosis with liver failure
   C. shock/metabolic acidosis
   D. x-rays reveal undigested radiopaque pills in GI tract
3. **Rx (USMLE) of iron toxicity**—
   A. iron-binding agents
   B. oral phosphate or bicarbonate salts (precipitate unabsorbed iron)
   C. parenteral deferoxamine

**Methotrexate:**
1. **MOA**— inhibits dihydrofolate reductase (USMLE)
2. **clinical uses**—
   A. cancer:
      1. acute lymphoblastic leukemia (ALL)
      2. acute myelogenous leukemia (AML)
      3. malignant lymphoma
      4. choriocarcinoma
      5. breast cancer
   B. rheumatoid arthritis
   C. psoriasis
   D. abortions
3. **complications**—
   A. macrocytic anemia due to folate deficiency
   B. myelosuppression,
   C. hepatic fibrosis

**Penicillin:**
1. **MOA**—
   A. inhibit bacterial wall synthesis
   B. bind to receptors in cell wall
   C. inhibit transpeptidase
   D. activate autolytic enzymes
   E. example of noncompetitive inhibitor
2. complications—
   A. hypersensitivity vasculitis: polyarteritis nodosa
   B. warm autoimmune hemolytic anemia: type II hypersensitivity
   C. acute interstitial nephritis with renal failure: type IV hypersensitivity
   D. anaphylaxis/skin rash: type I hypersensitivity (USMLE)

Aspirin:
1. MOA—
   A. irreversibly acetylates cyclooxygenase
   B. cyclooxygenase has two isoforms (USMLE):
      (1) COX I
         a. present in non-inflammatory cells
         b. involved in normal prostaglandin functions
      (2) COX II: present in inflammatory cells
   C. salicylates and other NSAIDs inhibit both COX I and II: COX I > COX II

2. toxicity—
   A. accidental overdose common in children and arthritics
   B. high concentration in oil of wintergreen (USMLE)
   C. directly stimulate respiratory center (USMLE): primary respiratory alkalosis
   D. produces increased anion gap metabolic acidosis (USMLE):
      (1) uncouples oxidative phosphorylation (produces lactic acidosis, danger of hyperthermia)
      (2) salicylic acid
      (3) children quickly pass through respiratory alkalosis phase and present with profound metabolic acidosis
   E. adults usually present with a mixed disorder: primary respiratory alkalosis + primary metabolic acidosis (pH is normal)
   F. miscellaneous complications:
      (1) renal papillary necrosis: blocks vasodilator effect of renal prostaglandin
      (2) triad asthma (USMLE)
         a. aspirin sensitivity
         b. asthma
         c. nasal polyps
      (3) acute gastritis
      (4) peptic ulcers (decreases prostaglandins)
      (5) fulminant hepatitis
      (6) bleeding
         a. platelet dysfunction
         b. gastritis
      (7) vertigo and tinnitus
      (8) hyperpyrexia
      (9) convulsions/coma
      (10) Reye syndrome
         a. child with flu/chickenpox takes aspirin
         b. encephalopathy
         c. fatty liver

3. Rx of salicylate intoxication—
   A. gastric lavage
   B. alkalinate urine: increase excretion

4. USMLE scenarios—
   A. child who ingests 30 adult aspirins will most likely develop:
(1) increased anion gap metabolic acidosis
(2) children, unlike adults, do not commonly develop a mixed metabolic acidosis and respiratory alkalosis

B. patient on a loop diuretic develops fever; what could they take for the fever?:
   (1) acetaminophen not aspirin or other types of NSAIDs
   (2) aspirin/other NSAIDs will block renal synthesis of prostaglandins and leave angiotensin II's vasoconstrictive effects unopposed

Occupation exposure relationships:
1. automobile mechanic—carbon monoxide
2. pesticide industry—
   A. organophosphates
   B. arsenic
3. meat packing—polyvinyl chloride with risk of hepatic angiosarcoma
4. insulation/demolition/roofing material—
   A. asbestos:
      (1) lung cancer
      (2) mesothelioma
      (3) fibrous pleural plaques \(\text{(MC overall complication of asbestos)}\)
   B. formaldehyde
5. dry cleaning—carbon tetrachloride
6. rubber/chemical industry—
   A. benzene:
      (1) aplastic anemia
      (2) leukemia
   B. aniline dyes: bladder cancer
7. battery, smelter, plumber/foundry—lead poisoning
8. painter—
   A. methylene chloride: converted into carbon monoxide
   B. solvents
   C. lead
9. petroleum—
   A. benzene
   B. polycyclic hydrocarbons: lung cancer
10. sewer worker—hydrogen sulfide gas: sulfhemoglobinemia

Isopropyl alcohol (rubbing alcohol) poisoning:
1. metabolism—
   A. metabolic end-product in the liver is acetone: no metabolic acidosis unlike other alcohols
   B. increases serum osmolal gap: difference between calculated and measured serum osmolality >10
2. clinical—
   A. deep coma
   B. hyporeflexia

Methyl alcohol (Wood's alcohol): see Fluids and Hemodynamics
Ethylene glycol (antifreeze): see Fluids and Hemodynamics
Benzene:
1. aplastic anemia
2. acute myelogenous leukemia
Carbon monoxide (CO):
1. MCC of death due to poisoning in the United States—
   A. common accidental injury or method for suicide
   B. odorless
2. sources of CO—
   A. automobile exhaust
   B. domestic/natural gas
   C. smoke in fires
   D. cigarette smoke: 8–10%
   E. methylene chloride
   F. wood stoves with blocked vent (USMLE)
   G. space heaters (USMLE)
3. effect on O₂ content— decreases SaO₂
4. complications—
   A. CNS: necrosis of globus pallidus/substantia nigra (Parkinson's disease)
   B. heart: accelerates atherosclerosis
5. S/S of CO toxicity—
   A. cherry red color of skin/blood: not a reliable sign
   B. headache:
      (1) first sign (USMLE)
      (2) ~30% concentration
   C. CO >60% generally results in death
6. lab findings—
   A. normal PaO₂
   B. decreased SaO₂ (oxygen saturation):
      (1) only noted if directly measured: usual ABGs calculate SaO₂ from the PaO₂, hence SaO₂ is normal (false negative)
      (2) pulse oximeter will show a normal SaO₂
7. Rx of CO poisoning— inhalation of 100% O₂
8. USMLE scenario— people in a room with a space heater have a headache:
   A. CO poisoning
   B. Rx with 100% oxygen

Chlorinated hydrocarbons:
1. source— insecticides like DDT
2. clinical— toxic neuronal injury:
   A. hyperexcitability
   B. convulsions
   C. delirium
   D. coma

Corrosives:
1. alkalis—
   A. 85% of poisonings
   B. sodium hydroxide: Drano
   C. penetrate tissue owing to liquefactive necrosis
   D. severe corrosive esophagitis:
      (1) subsequent stricture formation
      (2) tendency for esophageal cancer

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2. acids—
   A. 15%
   B. coagulation necrosis: less penetration
3. Rx of corrosive poisonings—endoscopy to assess damage

Cyanide:
1. MOA—
   A. systemic asphyxiant
   B. blocks cytochrome oxidase in oxidative phosphorylation system
2. sources—combustion of polyurethane products during residential fires
3. clinical—
   A. bitter almond smell to breath
   B. hypoxic cell injury: brain, kidneys, liver, heart, etc.
4. Rx of cyanide poisoning—
   A. nitrates: amyl and sodium nitrite → create methemoglobin → methemoglobin competes with cytochrome oxidase for cyanide
   B. thiosulfate: combines with cyanide from cyanmethemoglobin → nontoxic thiocyanate

Lead poisoning:
1. MOA—
   A. binds to disulfide groups and denatures enzymes
   B. denatures ribonuclease: prevents breakdown of ribosomes → coarse basophilic stippling of peripheral blood RBCs
   C. denatures ferrochelatase:
      (1) prevents iron + protoporphyrin → heme
      (2) increase in RBC protoporphyrin levels
      (3) decrease in heme → microcytic anemia with ringed sideroblasts
   D. denatures ALA dehydrase:
      (1) prevents δaminolevulinic acid (ALA) → porphobilinogen
      (2) increase in δALA in urine
2. sources (USMLE)—
   A. children: PICA for lead-based paints
   B. battery factory: inhalation of dust or fumes
   C. mining
   D. lead glazed pottery
   E. moonshine whiskey: old lead radiators
   F. welding
3. clinical findings in Pb poisoning—
   A. CNS:
      (1) main target in children
      (2) cerebral edema/convulsions
      (3) demyelination/necrosis,
      (4) behavioral/motor/cognitive dysfunction
      (5) headache/memory loss (adults)
   B. peripheral nervous system:
      (1) peripheral neuropathy (adults)
      (2) e.g., wrist drop (radial nerve palsy)
      (3) claw hand (ulnar nerve palsy)
      (4) slapping gait (common peroneal nerve palsy)
   C. musculoskeletal:
      (1) deposits in epiphyses (only heavy metal with this finding)
D. hematologic:
   (1) microcytic anemia (sideroblastic type)
   (2) coarse basophilic stippling

E. GI:
   (1) lead colic (children/adults)
   (2) diarrhea
   (3) Pb visible on x-rays of abdomen
   (4) Pb line in gums (adults) with poor dentition (lead attaches to sulfides along the gingiva)

F. renal:
   (1) nephrotoxic acute tubular necrosis (coagulation necrosis of proteins in the proximal tubule)
   (2) Fanconi syndrome (proximal renal tubular acidosis with aminoaciduria, glucosuria, uricosuria)
   (3) acid-fast inclusions in renal tubular cells
   (4) chronic interstitial nephritis (increases uric acid reabsorption → gout, renal failure)

4. lab Dx of Pb poisoning—
   A. increased blood lead levels: best screen and confirmatory test
   B. increased RBC zinc protoporphyrin: old screening test
   C. increased urine 6-aminolevulinic acid

5. Rx of Pb poisoning—
   A. dimercaprol: British anti-Lewisite (BAL)
   B. EDTA

6. USMLE scenarios— employees that work in a car assembly plant (or pottery painter, or making moonshine) present with headache, nausea, vomiting, muscle weakness, and abdominal cramps

Mercury poisoning:

1. MOA—
   A. toxic in inorganic (elemental) form:
      (1) dental amalgams
      (2) insecticides
      (3) wood preservatives
      (4) batteries
      (5) used to be used in hat making industry ("mad hatter disease")
   B. toxic in organic form:
      (1) fungicides
      (2) contaminated fish

2. clinical in acute Hg intoxication—
   A. inhalation of inorganic mercury

   B. GI disease similar to lead:
      (1) N/V
      (2) abdominal pain
      (3) diarrhea
      (4) visible on x-rays

   C. renal disease: nephrotoxic ATN
   D. CNS disease: mental retardation
   E. Rx of Hg poisoning: dimercaprol
3. chronic Hg poisoning—
   A. inorganic or organic forms
   B. deposits in gums/teeth
   C. GI problems
   D. neurological problems
   E. Rx of chronic Hg poisoning: penicillamine + dimercaprol

4. organic poisoning—
   A. contaminated fish in Japan
   B. Minamata disease:
      (1) cerebral/cerebellar neuron loss
      (2) constricted visual fields

Arsenic:
1. trivalent salts and arsine gas are toxic forms
2. sources—
   A. pesticides
   B. animal dips
   C. Fowler's solution
3. acute arsenic poisoning—
   A. garlic odor to breath
   B. severe diarrhea: "rice water" stools similar to cholera
   C. Rx of acute arsenic poisoning: dimercaprol
4. chronic arsenic poisoning—
   A. skin:
      (1) arsenic melanosis (gray skin with dark macules)
      (2) squamous cell carcinoma
      (3) nails have transverse bands (Mees nails)
      (4) concentrates in keratin/hair/nails
   B. CNS/PNS findings:
      (1) headache
      (2) convulsions/coma (MC COD)
      (3) polyneuropathy
   C. renal: nephrotoxic acute tubular necrosis
   D. hematologic:
      (1) hemolytic anemia
      (2) marrow suppression
   E. cancer risk:
      (1) squamous cell carcinoma of skin
      (2) lung cancer
      (3) liver angiosarcoma
   F. Rx of chronic arsenic poisoning: dimercaprol

4. arsine gas poisoning— massive hemolysis

Mushroom poisoning (Amanita):
1. MOA— toxin inhibits RNA polymerase
2. clinical—
   A. abdominal pain/vomiting
   B. bloody diarrhea
   C. jaundice: extensive fatty change
Organophosphate poisoning:
1. MOA—
   A. irreversible block of acetylcholine esterase (noncompetitive inhibitor, USMLE): accumulation of acetylcholine at synapses/myoneural junctions
   B. easily absorbed through the skin, respiratory, and GI tract
2. source—pesticides
3. clinical—
   A. initial autonomic system overactivity:
      (1) excessive lacrimation/salivation
      (2) fecal incontinence
      (3) constricted pupils
   B. nicotinic effects later in toxicity:
      (1) muscle weakness/paralysis
      (2) muscle fasciculations
4. lab findings—low serum and RBC cholinesterase (pseudocholinesterase)
5. Rx—
   A. atropine (USMLE): Rx of choice
   B. pralidoxime (2-PAM)

Petroleum products: gasoline/kerosene
1. euphoria (drunk acting) when inhaled (or ingested)
2. addicting
3. toxic doses—
   A. convulsions
   B. tinnitus
4. lungs—
   A. non-cardiogenic pulmonary edema
   B. predisposes to pneumonia

Strychnine:
1. MOA—
   A. CNS stimulant
   B. blocks postsynaptic inhibition
2. clinical (similar to tetanus)—
   A. tetanic convulsions,
   B. opisthotonus
   C. risus sardonicus
   D. death

Black widow spider envenomation:
1. MOA of toxin—
   A. neurotoxin
   B. hour glass on undersurface of spider
2. clinical settings—
   A. picking up wood from a wood pile
   B. moving boxes in a cellar
   C. sitting on a toilet in an out-house
3. clinical—
   A. momentary sharp pain at the envenomation site—
   B. localized cramping pain—
   C. intense upper thigh/abdominal contractions/rigidity (no rebound tenderness)
4. **Rx of black widow bite**
   A. antivenin
   B. calcium gluconate for muscle spasms
   C. tetanus prophylaxis

**Brown recluse spider (violin spider) envenomation:**
1. MOA of toxin—necrotoxin
2. **clinical**—
   A. less painful than black widow
   B. begins with a slightly tender red papular lesion→hemorrhagic blister surrounded by purpura→large ulcer
   C. renal failure
   D. hemolytic anemia
3. **Rx of brown recluse bites**
   A. drugs:
      1. corticosteroids
      2. colchicine
      3. dapsone
   B. surgical excision

**Poisonous snake envenomations:**
1. **types**—
   A. pit vipers:
      1. rattlesnakes (MC bite)
      2. water moccasins
      3. copperheads
   B. true cobras:
      1. coral snake (neurotoxin→paralysis and death)
      2. coral snake has following color banding—"red and yellow kill a fellow"
      3. harmless scarlet king snake—"red and black friend of jack"
2. **pit viper envenomations**—
   A. local swelling/necrosis
   B. hematologic problems: DIC
3. **Rx of pit viper envenomations**—
   A. keep the patient from moving around
   B. bring the patient to the hospital as soon as possible
   C. avoid application of tight tourniquets, ice, or cutting and suctioning at the envenomation site: tourniquet should block lymphatic venous blood, not arterial
   D. antivenin is available: danger of serum sickness
Smoking: #1 contributory factor responsible for cancer in the United States: cancer is the second MC COD in the United States.

Primary prevention modalities in cancer:
1. **lifestyle modification**—
   A. stop smoking
   B. increase fiber/decrease dietary saturated fat
   C. reduce alcohol intake
   D. reduce weight

2. **aspirin**—decreases the incidence of the following cancers:
   A. esophageal
   B. stomach
   C. colorectal

3. **isotretinoin (retinoic acid)**—
   A. decreases leukoplakia in the lungs and GI tract
   B. Rx of acute progranulocytic leukemia (USMLE)

4. **tamoxifen**—
   A. reduces risk for a second primary malignancy in the remaining breast in a woman with previous breast cancer
   B. may reduce the incidence of a primary malignancy in women who have a strong family Hx of breast cancer

Nomenclature:
1. **benign tumors**—
   A. key distinction between benign and malignant tumors is the capacity of malignant tumors to **inva**de and **metastasize**: exceptions include
      (1) basal cell carcinoma (BCC) of skin
      (2) glioblastoma multiforme
   B. **suffix “oma” does not always indicate a benign tumor:**
      (1) melanoma
      (2) lymphoma

2. **carcinomas**—
   A. malignant tumors derived from epithelial tissue
   B. squamous cell carcinoma:
      (1) oral pharynx
      (2) mid-esophagus
      (3) larynx
      (4) lung
      (5) cervix
      (6) skin
   C. adenocarcinoma (glandular epithelium):
      (1) distal esophagus
      (2) stomach
      (3) colon
      (4) pancreas
      (5) breast
   D. transitional cell carcinoma (transitional epithelium in urinary system): bladder/renal pelvis
3. APUD tumors—
   A. APUD: amine precursor uptake and decarboxylation
   B. neuroendocrine tumors: contain dense-core neurosecretory granules on electron microscopy,
   C. S100 antigen positive (USMLE),
   D. primarily develop from neural crest/neural ectoderm:
      (1) small-cell carcinoma of lung
      (2) carcinoid tumors
      (3) melanoma
      (4) neuroblastoma

4. sarcomas—
   A. malignant tumors derived from mesenchymal tissue
   B. embryonal rhabdomyosarcoma:
      (1) skeletal muscle sarcoma
      (2) MC sarcoma in children
   C. malignant fibrous histiocytoma:
      (1) MC sarcoma in adults
      (2) liposarcoma close second
   D. gross appearance:
      (1) large
      (2) bulky
      (3) vascular
      (4) necrotic
      (5) prefer hematogenous dissemination

5. mixed tumors—
   A. two different morphologic patterns derived from the same germ cell layer
   B. e.g., mixed tumor (pleomorphic adenoma) of salivary gland (parotid MC site)

6. leukemia—
   A. cancer derived from the bone marrow stem cells
   B. chronic lymphocytic leukemia (CLL) is MC adult leukemia and overall leukemia
   C. acute lymphoblastic leukemia (ALL) is MC childhood leukemia and cancer

7. malignant lymphoma—
   A. cancer derived from the lymph nodes
   B. MC type is non-Hodgkin's lymphoma: B cell follicular lymphoma
   C. stomach is the MC extranodal site for a primary malignant lymphoma

8. teratomas—
   A. derive from all three germ cell layers: e.g., teratoma of the ovary/testis/anterior mediastinum/pineal gland
   B. commonly have teeth and bone:
      (1) visible on x-ray
      (2) MC type of germ cell tumors: totipotential tumors that may differentiate in any direction

9. trophoblastic tumors—
   A. contain syncytiotrophoblast and cytotrophoblast:
      (1) gestationally-derived MC type
      (2) male site is testicles: non-gestational
   B. syncytiotrophoblast secretes β-hCG (USMLE)

10. hamartomas—
    A. nonneoplastic lesions associated with an overgrowth of tissue that is normally present in the organ
B. examples:
   (1) bronchial hamartoma
   (2) Peutz-Jeghers polyp
   (3) hyperplastic polyp

11. choristomas (heterotopic rests)–
   A. nonneoplastic, normal tissue in a foreign location
   B. pancreatic tissue in the wall of the stomach
   C. gastric tissue/pancreatic tissue in Meckel's diverticulum

Properties of malignant cells:

1. cell cycle characteristics–
   A. majority have a longer cell cycle than the parent tissue:
      (1) G1 phase is longer
      (2) more malignant cells remain in the cell cycle
      (3) increased accumulation of cells
   B. inactivation of Rb suppressor gene and p53 suppressor gene important in malignancy
   C. **requires 30 doubling times for a tumor to be clinically evident (USMLE):** equivalent to:
      (1) $10^9$ cells
      (2) 1 gram of tissue
      (3) volume of 1 mL

2. DNA lab findings–
   A. aneuploidy: uneven multiple of 23 chromosomes
   B. S phase fraction:
      (1) measure of the number of malignant cells in the proliferating pool
      (2) $>5\%$ indicates aggressive tumor

3. nuclear features–
   A. increased nuclear/cytoplasmic ratio
   B. atypical mitotic spindles

4. miscellaneous–
   A. anaerobic metabolism
   B. lack cohesiveness
   C. not contact inhibited in culture: pile up
   D. transplantable
   E. immortal in culture

5. capacity to invade/metastasize (USMLE)–
   A. receptors for integrin molecules laminin and fibronectin: helps malignant cells adhere to extracellular matrix
   B. contain **type IV collagenases:**
      (1) dissolve basement membranes
      (2) **zinc is the metalloenzyme in collagenase (USMLE)**
   C. contain proteases
   D. secrete transforming growth factor (TGF)-α and -β: promotes angiogenesis and collagen deposition
   E. **tissues resistant to invasion (USMLE):**
      (1) mature cartilage
      (2) elastic tissue in arteries

6. types of metastasis–
   A. lymphatics:
      (1) MC type of metastasis
      (2) usually carcinomas
(3) eventually lymphatics empty into blood vessels and spread is hematogenous

B. **hematogenous**:
   (1) directly into blood vessels
   (2) usually sarcomas
   (3) lung (MC site) and bone are common sites for metastasis

C. **seeding**:
   (1) malignant cells exfoliate and implant/invade tissue

D. sites for seeding:
   (1) peritoneal cavity (MCC site, ovarian, GI, pancreatic cancers)
   (2) pleural cavity (primary/metastatic lung cancer)
   (3) subarachnoid space (glioblastoma multiforme)

**Bone metastasis:**
1. **vertebral column**—
   A. MC site for metastasis: proximal femur second MC site
   B. *Batson vertebral venous plexus*:
      (1) extends along vertebral column from cranial plexus to pelvis
      (2) tributaries penetrate vertebra/surround spinal cord
      (3) plexus connects with the vena cava

2. **pain**—
   A. MC symptom of bone metastasis
   B. **best relieved by local radiation therapy (USMLE)**
   C. bisphosphonates may relieve pain by inhibiting bone resorption
   D. ERA positive tumors of the breast: use tamoxifen as adjunct
   E. prostate cancers to bone: use anti-androgen drugs as adjunct

3. **radiographic techniques**— radionuclide bone scan: best overall test

4. **osteoblastic metastases**—
   A. **radiodense** loci are noted on plain films
   B. examples:
      (1) prostate cancer MC type
      (2) breast
   C. **increase in serum alkaline phosphatase**

5. **osteolytic metastases**—
   A. produce **lucencies** in bone on plain films
   B. MC type is associated with **lytic factors released by metastatic tumor in bone** activate osteoclasts:
      (1) vitamin D-like steriods
      (2) prostaglandin E₂
      (3) cytokines
      (4) osteoclast-activating factor (IL-1)
   C. **PTH-like peptide** released from tumor without need for bone metastasis:
      (1) primary squamous cell carcinoma in lung
      (2) renal adenocarcinoma
   D. pathologic fractures commonly occur
   E. **potential for hypercalcemia**

**Examples where metastasis is more common than primary cancer in an organ:**
1. **lymph nodes**—
   A. **MC organ metastasized to**: first site for metastasis is subcapsular sinus (USMLE)
   B. MC primary sites: breast/lung cancers
   C. MC primary cancer: non-Hodgkin's lymphoma
2. lung—
   A. MC primary site: breast
   B. MC primary cancer: adenocarcinoma
3. brain—
   A. MC primary site: lung
   B. MC primary cancer:
      (1) glioblastoma multiforme in adults
      (2) medulloblastoma in children
4. liver—
   A. MC primary site: lung (table in Sabiston Surgery text)
   B. MC primary cancer: hepatocellular carcinoma secondary to HBV postnecrotic cirrhosis
5. bone—
   A. MC primary site: breast
   B. MC primary cancer:
      (1) multiple myeloma
      (2) osteogenic sarcoma second MC primary cancer of bone
6. adrenal glands—
   A. MC primary site: lungs
   B. MC primary cancer: adenocarcinoma
7. note—
   A. breast cancer is the most common cancer in lungs and bone
   B. lung cancer is the MC cancer in liver and brain

Metastatic sites for common cancers:
1. Virchow's left supraclavicular node— metastatic stomach adenocarcinoma
2. metastatic site for breast cancer—
   A. lung
   B. bone
3. metastatic site for colorectal cancer— liver
4. metastatic site for renal adenocarcinoma— lungs
5. metastatic site for lung cancer— adrenal/liver
6. metastatic sites for melanoma— liver/lung
7. metastatic site for prostate cancer— bone
8. metastatic site for testicular cancer— paraaortic lymph nodes: not inguinal nodes

8. Important immunohistologic stains in cancer:
1. leukocyte malignancies— CD45
2. neuroendocrine tumor— S100 antigen
3. malignant melanoma—
   A. S100 antigen
   B. HB45
4. carcinomas—
   A. cytokeratin intermediate filaments
   B. CEA
   C. epithelial membrane antigen
5. sarcomas— desmin: specific for muscle-derived sarcomas

Important electron microscopy findings in cancer:
1. tonofilaments— epithelial tumor
2. Weibel Palade bodies—
   A. contain von Willebrand's factor
   B. present in angiosarcomas

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3. neurosecretory granules—
   A. black granules in cytosol
   B. APUD tumors: see above
4. melanosomes—malignant melanoma
5. thick and thin myofilaments—rhabdomyosarcomas
6. Birbeck granules—
   A. look like a tennis racket on electron microscopy
   B. histiocytic tumors: e.g., histiocytosis X

Oncogenesis:
1. sequence—think of a fraternity or sorority
   A. initiation: irreversible mutations involving protooncogenes and/or suppressor genes
   B. promotion:
      (1) growth enhancement to pass on the mutations to other cells
      (2) e.g., estrogen
   C. progression: development of tumor heterogeneity for metastasis/drug resistance
2. protooncogenes—
   A. precursors of oncogenes (genes that produce cancer)
   B. regulatory genes that code for proteins involved in growth/repair processes
   C. protooncogenes for synthesis of growth factors: sis oncogene
   D. protooncogenes for synthesis of growth factor receptors:
      (1) erbB/neu (HER-2)
      (2) ret
   E. protooncogenes for signal transduction (membrane-related guanine triphosphate (GTP)-
      binding proteins): ras
   F. protooncogenes for signal transduction (non-receptor tyrosine kinase): abl oncogene
   G. protooncogenes that synthesize nuclear transcription regulators:
      (1) myc
      (2) N-myc
3. tumor suppressor genes (anti oncogenes)—guardians of unregulated cell growth: see below
4. mechanisms of initiation (activation) of protooncogenes or inactivation of suppressor
   genes—mechanisms:
   A. point mutations (MC type)
   B. translocations
   C. overexpression
   D. amplification
5. factors responsible for mutational events leading to cancer—
   A. chemicals: MC agent
   B. viruses
   C. radiation
   D. physical agents: e.g., burn scars

Examples of initiation of protooncogenes:
1. overexpression of erbB2 (USMLE)—20–30% of invasive ductal cancers: predicts poor
   survival
2. t9;22 translocation of abl proto-oncogene—
   A. formation of bcr-abl fusion gene on chromosome 22
   B. called Philadelphia chromosome in chronic myelogenous leukemia
3. point mutation of ret—multiple endocrine neoplasia (MEN) AD syndromes
4. point mutation of ras (USMLE)—
   A. ~30% of human cancer
B. examples:
   (1) lung
   (2) colon
   (3) pancreas
   (4) leukemia (particularly acute myelogenous)

5. **t(8;14)** translocation of **myc**—
   A. **Burkitt's lymphoma**
   B. Epstein-Barr virus (EBV) causes polyclonal stimulation of B cells
   C. increases the chances for the translocation

6. amplification of **N-myc**—neuroblastoma

7. **t(14;18)** translocation—
   A. B cell immunoglobulin heavy chain is translocated in the proximity of the bcl-2 gene on chromosome 18→
   B. overexpression of bcl-2 gene product→
   C. inactivates apoptosis gene involved in programmed cell death→
   D. B cell follicular lymphoma: MC malignant lymphoma

Examples of inactivation of suppressor genes:

1. **majority of suppressor genes are inactivated by point mutation** (USMLE)—e.g., p53 suppressor gene

2. **Rb suppressor gene on chromosome 13** (USMLE)—
   A. codes for Rb protein:
      (1) prevents cells from entering S phase of cell cycle
      (2) see Cell Injury notes
   B. inactivation associated with:
      (1) retinoblastoma
      (2) osteogenic sarcoma
      (3) breast cancer
   C. retinoblastoma:
      (1) sporadic type requires 2 inactivations
      (2) AD type requires only 1 inactivation (1 already inactivated at birth)

3. **inactivation of p53 suppressor gene on chromosome 17**—
   A. normally produces a protein product that inhibits activated cyclin-dependent kinase (cdk)
      in the cell cycle: see Cell Injury notes
   B. ~25–50% of all human cancers
   C. examples:
      (1) colon
      (2) breast
      (3) lung
      (4) central nervous system
      (5) AD Li-Fraumeni multicancer syndrome: increased incidence of breast cancer,
          sarcomas, brain tumors, leukemia
   D. **oncogenesis in human papilloma virus (HPV)** (USMLE): gene products E6 and E7 in
      HPV infections inhibit p53 suppressor gene leading to cancer

4. **inactivation of the APC suppressor gene on chromosome 5**—
   A. APC: adenomatous polyposis coli
   B. associated with AD familial polyposis syndrome and AD Gardner's syndrome
   C. other cancers: lung, esophagus, stomach, pancreas

5. **inactivation of the NF1 (chromosome 17) and NF2 (chromosome 22) suppressor genes**—
   A. NF = neurofibromatosis
   B. see Genetics notes
6. **inactivation of BRCA-1 (chromosome 17) and BRCA-2 (chromosome 13) (USMLE)**
   A. normally involved in DNA repair
   B. BRCA-1 inactivation associated with breast/ovarian/colon/prostate cancers
   C. inactivation of BRCA-2 associated with male/female breast cancer

7. **inactivation of WT-1 (chromosome 11)**
   A. normally involved in nuclear transcription
   B. associated with AD Wilm's tumor

**Chemical carcinogens:**
1. **account for 80–90% of cancers**—particularly the carcinogens in cigarette smoke
2. **mechanism of action (MOA)**
   A. indirect acting chemical carcinogens:
      (1) most chemicals are inactive in their native states
      (2) activated by enzymes in the cytochrome P-450 or other enzyme system (bacterial enzymes or enzymes induced by alcohol)
      (3) electron deficient (attracted to nuclear proteins rich in electrons, e.g., DNA)
   B. direct acting chemical carcinogens: e.g., alkylating agents
3. **transitional carcinoma of bladder**
   A. polycyclic hydrocarbons in cigarette smoke: MCC
   B. aniline dyes
   C. cyclophosphamide
   D. benzo(a)pyrene
   E. phenacetin
4. **angiosarcoma of liver**
   A. vinyl chloride: MCC
   B. arsenic
   C. Thorotrast
5. **lung cancer**
   A. polycyclic hydrocarbons: MCC
   B. uranium: radon gas in mines
   C. asbestos: additive carcinogenic effect if combined with smoking
   D. chromium
   E. arsenic
   F. nickel
   G. cadmium
6. **hepatocellular carcinoma**
   A. aflatoxins: especially in association with HBV cirrhosis
   B. oral contraceptives
   C. Thorotrast
   D. alcohol
7. **leukemia**
   A. benzene
   B. alkylating agents: also predispose to malignant lymphoma,
   C. polycyclic hydrocarbons
8. **squamous cell carcinoma of oral pharynx**
   A. polycyclic hydrocarbons in cigarette smoke MCC
   B. smokeless tobacco
9. **squamous cell carcinoma of esophagus**
   A. polycyclic hydrocarbons MCC
   B. nitrosamines
   C. alcohol

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10. squamous cell carcinoma of larynx—polycyclic hydrocarbons MCC
11. pancreatic adenocarcinoma—
   A. polycyclic hydrocarbons MCC
   B. alcohol: setting of chronic pancreatitis
12. prostate adenocarcinoma—cadmium
13. clear cell adenocarcinoma of the vagina/cervix—diethylstilbestrol
14. squamous cell carcinoma of skin—
   A. immunosuppressive agents: squamous carcinoma is MC cancer associated with immunosuppressive agents
   B. tar/soot/oils: chimney sweeper cancer
15. cervical squamous cell carcinoma—
   A. polycyclic hydrocarbons
   B. oral contraceptives

Viral carcinogens:
1. cell types—usually nonpermissive cells prevent an oncogenic RNA or DNA virus from completing its replication cycle causing death of the cell
2. leukemia/lymphoma—
   A. EBV:
      (1) Burkitt’s lymphoma
      (2) primary CNS lymphoma (cocarcinogen with HIV)
      (3) polyclonal lymphoma
   B. HTLV-1: adult T cell leukemia
   C. HTLV-2: hairy cell leukemia
   D. HIV: primary CNS lymphoma
3. nasopharyngeal carcinoma—EBV
4. hepatocellular carcinoma—
   A. HBV:
      (1) MCC
      (2) association with aflatoxins and oral contraceptives as well
   B. HCV
5. Kaposi’s sarcoma—
   A. MC cancer in AIDS → MC location is SKIN
   B. herpesvirus 8
6. squamous cell carcinoma of cervix and anus (homosexuals)—HPV type 16, 18, 31

Radiation:
1. MOA—also review Environmental pathology notes
   A. ionizing particles (e.g., α- and β-particles, γ-rays, x-rays) hydrolyze water into free OH radicals: mutagenic to DNA
   B. UVB light: formation of thymidine dimers (distort the DNA molecule)
2. radiation-induced cancers—
   A. leukemia:
      (1) MC radiation-induced cancer
      (2) increased in radiologists (USMLE)
      (3) increased in atomic bomb victims
   B. papillary carcinoma thyroid
   C. lung cancer: radon gas from uranium
   D. breast cancer
   E. liver angiosarcoma: Thorotrast
   F. osteogenic sarcoma
3. UVB-light induced cancers—
A. basal cell carcinoma (BCC): MC type
B. squamous cell carcinoma
C. malignant melanoma
D. xeroderma pigmentosum (USMLE):
   (1) AR disease
   (2) deficiency of DNA repair enzymes (cannot splice out damage to DNA)

Bacteria linked to cancer:
1. *Helicobacter pylori*
2. gastric adenocarcinoma
3. low-grade mucosa-associated primary malignant lymphomas of the stomach

Scar-related cancers:
1. lungs—
   A. peripheral located scars
   B. usually adenocarcinoma
2. burn scars— squamous cell carcinoma
3. chronically draining sinus tracts (USMLE)— squamous cell carcinoma

Grade and stage of cancer:
1. grade—
   A. based primarily on the histologic appearance of the tumor
   B. degree of differentiation:
      (1) low grade (well-differentiated)
      (2) high grade (poorly differentiated, anaplastic)
   C. nuclear features:
      (1) chromatin pattern
      (2) mitotic activity
   D. invasiveness
2. stage—
   A. most important prognostic factor
   B. TNM system: system progresses from least important to most important prognostic factor (e.g., metastasis to liver is worse than to regional lymph nodes)
      (1) T = size/microscopic appearance of tumor
      (2) N = lymph node status
      (3) M = hematogenous dissemination to other sites (poorest prognosis if extranodal metastasis)

Host defense against tumors:
1. mechanisms—
   A. humoral:
      (1) antibodies
      (2) complement
   B. type IV cellular immunity:
      (1) most efficient mechanism
      (2) e.g., cytotoxic T cells
   C. NK cells:
      (1) direct killing
      (2) indirect through type II hypersensitivity
      (3) lymphokine activated NK cells (NK cells activated with IL-2)
   D. macrophages: activated by γ-interferon

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E. non-specific enhancement of immune system:
   (1) use of BCG vaccination (infuse into bladder in transitional cell carcinoma)
   (2) vaccinate with Corynebacteria species
F. tumor vaccines prepared from host tumor tissue,
G. tumor-specific antigens (TSAs):
   (1) produced by tumors
   (2) host develops antibodies against TSAs
   (3) virus-induced cancers produce the most antigenic TSAs
   (4) chemical-induced cancers produce the least antigenic TSAs

**Cachexia:**
1. tumor necrosis factor-α
2. secreted from host macrophages/cancer cells
3. irreversible catabolic reaction on host

**Hematologic associations with cancer:**
1. anemia of chronic disease – MC anemia
2. iron deficiency – e.g., right-sided colorectal cancer
3. macrocytic anemia – secondary to folate deficiency from rapid tumor growth:
   A. leukemia
   B. lymphomas
4. autoimmun hemolytic anemia –
   A. CLL
   B. HTLV-1 T cell lymphomas/leukemia
5. microangiopathic hemolytic anemia –
   A. schistocytes in peripheral blood
   B. RBCs damaged by tumor emboli in vessels
6. myelophtisic anemia (USMLE) – anemia related to metastasis to the bone marrow
7. marrow suppression – due to radiation and/or chemotherapy
8. leukoerythroblastic peripheral smear – metastasis to the bone marrow pushes immature hematopoietic elements (e.g., nucleated RBCs, myeloblasts) into the peripheral blood
9. hypercoagulable state –
   A. increase in coagulation factor synthesis:
      (1) fibrinogen
      (2) V
      (3) VIII
   B. release of tissue thromboplastin: activates the extrinsic coagulation system
   C. thrombocytosis: cancer accounts ~30% of all cases of thrombocytosis
   D. decreased liver synthesis of antithrombin III and protein C
10. DIC – common in disseminated cancers: e.g., leukemia

**Fever in cancer patients:**
1. usually infections –
   A. gram negative sepsis:
      (1) E. coli
      (2) P. aeruginosa
   B. infection is MC COD in cancer
2. malignancies associated with fever not related to infection –
   A. Hodgkin's disease: Pel Ebstein fever
   B. renal adenocarcinoma
   C. osteogenic sarcoma
Paraneoplastic syndromes:

1. **definition**—
   A. remote effects of a tumor unrelated to metastasis
   B. ~10–15% of tumors
   C. may predate onset of metastasis in the tumor

2. **hypercalcemia (USMLE)**—
   A. MC paraneoplastic syndrome
   B. malignancy accounts for ~40% of all cases of hypercalcemia
   C. MC type is metastasis to bone and release of osteoclast activating factors:
   D. secretion of a PTH-like peptide:
      (1) metastasis not necessary
      (2) cancers include primary squamous cancer of the lung, renal adenocarcinoma, breast cancer
   E. lab findings:
      (1) hypercalcemia
      (2) low serum PTH

3. **Eaton-Lambert syndrome**— myasthenia gravis-like syndrome associated with small cell carcinoma of the lung

4. **Sweet syndrome**— fever, neutrophilic leukocytosis, red papular rash associated with acute leukemia

5. **skin lesions associated with gastric adenocarcinoma (USMLE)**— note: 2 pigmented skin lesions are potential markers of the same cancer
   A. Leser-Trelat sign: multiple outcroppings of pigmented seborrheic keratoses (these skin lesions are not neoplastic)
   B. acanthosis nigricans: black, verrucoid-appearing lesion usually located in the axilla

6. **pulmonary osteoarthropathy (USMLE)**—
   A. clubbing of the nails with an underlying periosteal reaction of bone
   B. associated with primary lung cancer

7. **superficial migratory thrombophlebitis (Trouseau’s sign, USMLE)**— associated with pancreatic adenocarcinoma

8. **dermatomyositis**— increased incidence of primary lung and breast cancer,

9. **membranous glomerulonephritis**—
   A. produces nephrotic syndrome
   B. cancers:
      (1) colorectal
      (2) Hodgkin’s disease

10. **sterile marantic vegetations on cardiac valves**— mucous secreting pancreatic/colorectal cancers,

11. **hyponatremia (ADH) or ectopic Cushing’s syndrome (ACTH)**— ectopic secretion from small carcinoma of the lung

12. **hypercalcemia (PTH-like peptide) or secondary polycythemia (EPO)**— renal adenocarcinoma

13. **hypoglycemia (insulin-like factor) or secondary polycythemia (EPO)**— hepatocellular carcinoma

14. **hypocalcemia (calcitonin) or hypercortisolism (ACTH)**—
   A. medullary carcinoma of the thyroid:
   B. calcitonin is also the tumor marker
   C. calcitonin is converted into amyloid in the tumor
   D. MEN IIa/IIb association

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15. **gynecomastia (β-hCG)**—
   A. gestationally or non-gestationally derived trophoblastic tumors
   B. examples:
      1. hydatidiform moles (benign)
      2. choriocarcinoma (malignant)

16. **flushing, diarrhea (serotonin)**—
   A. carcinoid syndrome: primary site for carcinoid tumor is usually terminal ileum *(USMLE)*
   B. medullary carcinoma of thyroid

17. **increase in α-fetoprotein (AFP)**—
   A. hepatocellular carcinoma
   B. endodermal (yolk sac) sinus tumors: MC germ cell tumor of ovary/testis in children

18. **increase in α1-antitrypsin**—hepatocellular carcinoma

19. **tumor markers for testicular cancers**—
   A. AFP: yolk sac tumor
   B. β-hCG: choriocarcinoma

20. **tumor markers for multiple myeloma**—
   A. Bence Jones’s protein:
      1. light chains in the urine
      2. best detected with urine electrophoresis
   B. β₂-microglobulin: increased levels indicate a poor prognosis

21. **tumor marker for surface-derived ovarian cancers**—CA 125

22. **tumor markers for small cell carcinoma of the lung**—
   A. carcinoembryonic antigen (CEA)
   B. bombesin

23. **tumor marker for prostate cancer**—
   A. prostate specific antigen (PSA):
      1. more sensitive than specific (also elevated in prostate hyperplasia)
      2. not increased after a rectal exam (antigen not an enzyme)
   B. prostatic acid phosphatase is no longer used as a marker: it is increased after rectal exam

24. **tumor markers for breast cancer**—
   A. CA 15-3
   B. CEA

25. **tumor marker for colorectal cancer**—
   A. CEA
   B. primarily used to detect recurrences rather than as a primary screen for colorectal cancer

26. **tumor markers for pancreatic carcinoma**—
   A. CA 19-9
   B. CEA

27. **enzyme elevated in malignant lymphomas**—
   A. lactate dehydrogenase (LDH)
   B. particularly the LDH₃ isoenzyme fraction
   C. also increased in dysgerminomas

**Cancers in children:**

1. **ALL**—MC overall cancer
2. **CNS tumors**—
   A. medulloblastoma of cerebellum
   B. note: cerebellar astrocytomas are more common, but they are benign
3. Burkitt's lymphoma—
   A. MC site is abdomen
   B. paraaortic nodes
   C. terminal ileum
4. neuroblastoma—
   A. hypertension
   B. unilateral mass in abdomen
5. Wilm's tumor—
   A. hypertension
   B. unilateral mass in abdomen
   C. AD type has aniridia and hemihypertrophy
6. Ewing's sarcoma— "onion skinning" around affected bone

Cancers in decreasing order of incidence in men:
1. prostate
2. lung
3. colorectal

Cancers in decreasing order of incidence in women:
1. breast: incidence has stabilized over the past few years
2. lung
3. colorectal

Cancer mortalities in decreasing order in men:
1. lung
2. prostate
3. colorectal

Cancer mortalities in decreasing order in women:
1. lung
2. breast
3. colorectal— colorectal cancer is the second most common cancer and cancer killer in men and women

Cancers that are decreasing in incidence in the United States:
1. cervix (USMLE)— due to Pap screens detecting cervical dysplasia and carcinoma in-situ
2. stomach—
   A. those involved with intestinal metaplasia and Helicobacter pylori
   B. there is no decrease in incidence in the signet ring type producing linitis plastica
3. endometrial— Pap smears are not sensitive in detecting hyperplasia, the precursor of endometrial cancer

Cancers that are increasing in incidence in the United States and in other countries:
1. breast— due to early detection by mammography
2. prostate— due to detection by PSA and digital rectal exam
3. lung—
   A. particularly in women
   B. incidence is decreasing in men
4. multiple myeloma
5. malignant lymphoma
6. pancreatic carcinoma
7. malignant melanoma
8. cancers in African-Americans—
   A. cancer in general is more common in African-Americans than whites

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B. exceptions are malignant melanoma and testicular cancer which are less common in African-Americans than whites

9. cancer that is increasing at the fastest rate worldwide—
   A. malignant melanoma
   B. Australia has the greatest increase
   C. lymphatic mapping using dyes and radiolabeled isotopes are used to identify sentinel nodes draining the tumor

10. MC cancer in Southeast China— nasopharyngeal carcinoma secondary to EBV
11. MC cancer in Northern China— esophageal cancer
12. MC cancer in Japan—
   A. stomach adenocarcinoma: due to smoked products
   B. HTLV-1 associated adult T cell leukemia/lymphoma is also increased

13. MC cancer in Southeast Asia—
   A. hepatocellular carcinoma
   B. due to HBV + aflatoxins (molds) in food

14. MC malignant lymphoma in Africa—
   A. Burkitt’s lymphoma
   B. due to EBV
   C. located in the jaw

15. MC cancer prevented by immunization—
   A. hepatocellular carcinoma
   B. due to HBV vaccination
   C. also prevents HBV and HDV

16. MC cancer in the Southeast Asia causally-related to α-thalassemia—
   A. choriocarcinoma
   B. Hb Bart’s disease (deletion of all 4 α-globin genes) is associated with spontaneous abortions, which in turn predispose to choriocarcinoma

17. cancers associated with parasitic diseases—
   A. cholangiocarcinoma: due to Clonorchis sinensis
   B. squamous cancer of the bladder: due to Schistosoma hematobium

Gynecologic cancers:
1. decreasing incidence of gynecologic cancers—
   A. endometrial
   B. ovarian
   C. cervical

2. decreasing mortality of gynecologic cancers—
   A. ovarian
   B. cervical
   C. endometrial

3. age brackets for gynecologic cancers (USMLE)—
   A. cervical: 45 y old
   B. endometrial: 55 y old
   C. ovarian: 65 y old

4. notes—
   A. endometrial carcinoma is MC gynecologic cancer and has the best prognosis
   B. palpable ovary in a postmenopausal woman is ovarian cancer until proven otherwise

Genetic disorders as risk factors for neoplasia:
1. chromosome syndromes and cancer—
   A. Down syndrome: acute leukemia
2. **AR syndromes associated with cancer**—
   A. chromosome instability syndromes:
      (1) ataxia telangiectasia (malignant lymphoma)
      (2) Bloom’s syndrome (acute leukemia)
      (3) Fanconi syndrome (**USMLE, DNA repair defects, acute leukemia**)  
   B. Turcot’s syndrome: polyposis + brain tumors: only AR polyposis syndrome,
   C. xeroderma pigmentosum

3. **SXRs associated with cancer**—
   A. Wiskott-Aldrich syndrome with:
      (1) B/T cell immunodeficiency
      (2) eczema
      (3) thrombocytopenia
      (4) increased risk for malignant lymphoma
   B. sex-linked lymphoproliferative syndrome due to EBV: increased risk for malignant lymphoma

4. **AD cancer/tumor syndromes**—
   A. Li-Fraumeni multicancer syndrome: breast, sarcomas, brain tumors, leukemia
   B. MEN-I syndrome:
      (1) pituitary tumors
      (2) parathyroid adenomas
      (3) pancreatic tumors
         a. usually Zollinger-Ellison syndrome
         b. followed by insulinoma
   C. MEN-IIa:
      (1) medullary carcinoma of thyroid
      (2) parathyroid adenoma/hyperplasia
      (3) pheochromocytoma
   D. MEN-IIb:
      (1) medullary carcinoma of thyroid
      (2) mucosal neuromas in the lips/tongue
      (3) pheochromocytoma
   E. familial polyposis
   F. Peutz-Jeghers syndrome: increased incidence of sex cord tumors with annular tubules: benign tumor
   G. tuberous sclerosis:
      (1) rhabdomyoma in heart in children
      (2) CNS glial tumors
      (3) skin: adenoma sebaceum
      (4) hamartomas (CNS astrocyte proliferations, angiomyolipoma in kidneys)
   H. neurofibromatosis
   I. Wilm’s tumor
   J. Osler-Weber-Rendu (hereditary telangiectasia): angiomas of skin and mucous membranes in GI tract
   K. retinoblastoma
   L. von Hippel-Lindau disease:
      (1) cerebellar hemangioblastoma
      (2) bilateral renal adenocarcinoma
      (3) pheochromocytoma
D. Plummer Vinson syndrome: due to iron deficiency
E. nitrosamines

3. distal esophagus (adenocarcinoma)—Barrett’s esophagus: MC cancer of esophagus

4. stomach (adenocarcinoma)—
   A. intestinal metaplasia in chronic atrophic gastritis of antrum/pylorus: associated with Helicobacter pylori
   B. smoking
   C. atrophic gastritis of body/fundus: pernicious anemia
   D. adenomatous polyps
   E. nitrosamines
   F. vitamin C deficiency

5. stomach (malignant lymphoma)—Helicobacter pylori

6. small intestine (malignant lymphoma)—
   A. celiac disease: T cell lymphoma
   B. IgA heavy chain disease
   C. Crohn’s disease

7. colon (adenocarcinoma)—
   A. age >50 y old
   B. low fiber/high fat diet
   C. familial polyposis syndromes
   D. ulcerative colitis: greater risk than Crohn’s disease
   E. villous adenoma
   F. adenomatous polyps >2 cm
   G. BRCA-1
   H. radiation
   I. smoking

8. anus (squamous carcinoma)—HPV: unprotected anal intercourse

9. hepatocellular carcinoma—
   A. postnecrotic cirrhosis due to HBV: especially with aflatoxins
   B. other types of cirrhosis:
      (1) HCV-related
      (2) hemochromatosis
      (3) alcohol
      (4) α1-antitrypsin deficiency
   C. Thorotrast
   D. oral contraceptives

10. cholangiocarcinoma—
    A. primary sclerosing pericholangitis
    B. Clonorchis sinensis

11. hepatic angiosarcoma—
    A. vinyl chloride
    B. arsenic
    C. Thorotrast

12. gallbladder (adenocarcinoma)—
    A. cholelithiasis
    B. porcelain gallbladder

13. pancreas (adenocarcinoma)—
    A. smoking
    B. chronic pancreatitis: alcohol-related
    C. diabetes mellitus
Risk factors for cancers of urinary tract/male reproductive:
1. kidney (adenocarcinoma)—
   A. smoking
   B. von Hippel-Lindau
2. renal pelvis/ureter/bladder (transitional cell carcinoma)—
   A. smoking
   B. aniline dyes
   C. phenacetin
   D. cyclophosphamide
   E. benzidine
3. bladder (squamous carcinoma)— *Schistosoma hematoium*
4. prostate (adenocarcinoma)—
   A. age: age-dependent cancer
   B. smoking
   C. cadmium
5. testicle (germ cell tumors)—
   A. seminoma MC germ cell tumor
   B. cryptorchid testis
   C. testicular feminization
   D. DES exposure
6. penis (squamous cancer)—
   A. erythroplasia of Queyrat
   B. Bowen's disease
   C. balanitis xerotica obliterans
   D. uncircumcised

Risk factors for cancers of female reproductive tract/breast:
1. vulva (squamous carcinoma)—
   A. HPV types 16/18
   B. Bowen's disease
   C. immunosuppression
2. vagina (squamous cancer)— HPV types 16, 18
3. vagina (clear cell adenocarcinoma)— DES exposure
4. cervix (squamous carcinoma)—
   A. HPV types 16/18
   B. drug immunosuppression
   C. smoking
   D. oral contraceptives
5. endometrium (adenocarcinoma)—
   A. unopposed estrogen from:
      (1) obesity
      (2) early menarche/late menopause
      (3) nulliparity
      (4) estrogen Rx without progesterone
      (5) granulosa cell tumor of ovary
      (6) polycystic ovarian syndrome
   B. history of breast cancer
6. uterine mixed tumors— pelvic irradiation
7. ovarian tumors—
   A. dysgerminoma: Turner's syndrome
B. Peutz Jeghers syndrome
C. smoking
D. BRCA-1
8. breast (adenocarcinoma)–
   A. age >50
   B. unopposed estrogen: particularly atypical ductal hyperplasia
   C. history of endometrial cancer
   D. high fat/low fiber diet
   E. family history: particularly first generation relatives
   F. radiation
   G. BRCA-1/BRCA-2 gene
   H. Klinefelter’s
   I. Li-Fraumeni multicancer syndrome

Risk factors for endocrine cancers–
1. papillary adenocarcinoma of thyroid–
   A. radiation exposure
   B. adult male/child with solitary thyroid nodule
2. medullary carcinoma of thyroid–
   A. AD MEN Ila/Ilb
   B. particularly AD type with C cell hyperplasia
3. malignant lymphoma of thyroid– Hashimoto’s thyroiditis

Risk factors for musculoskeletal cancers:
1. osteogenic sarcoma–
   A. irradiation
   B. Paget’s disease
   C. AD syndrome involving Rb suppressor gene on chromosome 13
2. chondrosarcoma– enchondromatosis: Ollier’s disease

Risk factors for CNS/special senses cancers:
1. glial tumors–
   A. Turcot syndrome
   B. tuberous sclerosis
   C. neurofibromatosis
   D. Li-Fraumeni multicancer syndrome
2. CNS lymphoma–
   A. HIV/EBV
   B. increased incidence of primary CNS lymphoma is directly related to increased incidence of AIDS
3. retinoblastoma

Risk factors for hematopoietic cancers:
1. acute leukemia–
   A. irradiation
   B. alkylating agents
   C. Down syndrome
   D. chromosome instability syndromes
   E. Li-Fraumeni multicancer syndrome
   F. benzene
   G. myelodysplastic syndrome
   H. myeloproliferative diseases: e.g., polycythemia rubra vera
2. chronic myelogenous leukemia—irradiation
3. hairy cell leukemia—HTLV II,
4. T cell leukemia/lymphoma—HTLV I
5. Burkitt's lymphoma (B cell lymphoma)—EBV

Types of chemotherapy agents:
1. cytotoxic drugs—alkylating agents
2. hormones—
   A. DES in prostate cancer
   B. progesterone in endometrial cancer
3. cytokines—recombinant α-interferon in Rx of Kaposi’s sarcoma
4. antihormones—
   A. tamoxifen an anti-estrogen used in the Rx of ERA positive breast cancers
   B. 5-α reductase inhibitors block dihydrotestosterone effect in prostate cancer
5. biologic—BCG in bladder cancer
6. plant products—paclitaxel from the Pacific yew tree in Rx of ovarian cancer

Benefits of chemotherapy:
1. adjuvant Rx along with surgery/radiation
2. potential cure—e.g., gestationally derived choriocarcinoma
3. palliation
4. preoperative modality to shrink tumor

Terms applied to chemotherapy:
1. induction—try to induce complete remission
2. consolidation—try to kill any remaining cancer cells in patients that enter remission
3. maintenance—try to prolong remissions
4. adjuvant—
   A. similar in concept to consolidation therapy
   B. most important modality to destroy micrometastases

Causes of failure of advanced cancers to respond to chemotherapy:
1. tumor heterogeneity—cell subpopulations are resistant to chemotherapy
2. large numbers of neoplastic cells are not in the cell cycle—malignant cells are in the Go resting phase

Cell cycle specific chemotherapy agents:
1. definition—involve a specific phase of the cell cycle
2. anti-metabolites
3. bleomycin
4. plant alkaloids—
   A. vinca alkaloids
   B. paclitaxel

Cell cycle-nonspecific chemotherapy agents:
1. definition—agents are active throughout the cell cycle
   A. drugs inhibiting DNA synthesis: alkylate or intercalate
   B. drugs inhibiting mitosis
2. alkylating agents
3. antibiotics
4. cisplatin
5. nitrosourea
6. L-asparaginase

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Antimetabolites:

1. mechanism of action (MOA)—
   A. compete with normal metabolites for the regulatory site of a key enzyme
   B. substitute for a metabolite normally incorporated into DNA or RNA
   C. work best in the S phase (DNA replication) of the cell cycle; useful in tumors with rapid cell proliferation

2. methotrexate—
   A. antimetabolite that inhibits dihydrofolate reductase in folic acid metabolism
   B. complications: see Environmental Pathology notes

3. 6-mercaptopurine (6-MP)—
   A. antimetabolite (purine analog) that blocks purine synthesis
   B. complications:
      (1) if associated with allopurinol, reduce the dose (allopurinol is an xanthine oxidase inhibitor and 6-MP is a purine)
      (2) marrow suppression

4. 5-fluorouracil (5-FU)—
   A. antimetabolite (pyrimidine analog) that blocks the formation of thymidylic acid by inhibiting thymidylate synthetase: effective throughout the cell cycle
   B. complications:
      (1) BM suppression
      (2) mucositis

5. cytarabine (ara C)—
   A. antimetabolite (pyrimidine antagonist) that blocks DNA and RNA: effective in the S phase
   B. complications:
      (1) myelosuppression
      (2) cerebellar ataxia
      (3) hepatitis/pancreatitis

6. 2-chlorodeoxyadenosine—
   A. antimetabolite (purine analog) that resists degradation by adenosine deaminase: primary Rx for hairy cell leukemia
   B. complication: myelosuppression

7. hydroxyurea—
   A. anti-metabolite that inhibits ribonucleotide reductase, which converts ribonucleotides to deoxyribonucleotides:
      (1) crosses the blood brain barrier
      (2) main Rx for chronic myelogenous leukemia
      (3) increases HbF synthesis
   B. complications:
      (1) GI toxicity
      (2) leukopenia

Antitumor antibiotics:

1. MOA—
   A. interfere with DNA metabolism by breaking up DNA
   B. majority are derived from Streptomyces species

2. bleomycin—
   A. antibiotic that breaks DNA by an oxidative process involving free radicals
   B. inhibits DNA ligase involved in DNA repair
   C. most effective in the G2 phase (synthesis of tubulin for the mitotic spindle)
D. complications:
   (1) pulmonary fibrosis
   (2) edema of the hands
   (3) no BM suppression
3. dactinomycin (actinomycin D)—
   A. antibiotic that interferes with DNA synthesis by intercalating between DNA base pairs leading to the formation of FRs that break the DNA strand
   B. most effective in S phase
   C. inhibits topoisomerases, which are enzymes that repair single or double DNA breaks
   D. complications: severe myelosuppression
4. daunomycin—
   A. antibiotic similar to dactinomycin: see above
   B. complications:
      (1) dose-dependent cardiotoxicity
      (2) marrow suppression
      (3) red urine: due to the drug
5. doxorubicin—
   A. antibiotic similar to dactinomycin: see above
   B. complications: same as those listed for daunomycin
6. mitomycin—
   A. antibiotic similar to dactinomycin: see above
   B. complications:
      (1) thrombocytopenia/leukopenia
      (2) hemolytic-uremic syndrome: microangiopathic hemolytic anemia and renal failure
      (3) interstitial pneumonitis
7. etoposide—
   A. antibiotic (plant alkaloid) that inhibits topoisomerases
   B. complications: BM depression
8. paclitaxel—
   A. antibiotic (plant alkaloid) that interferes with disassembly microtubules in the M phase of the cycle: binds to tubulin and stabilizes it so that it cannot disassemble
   B. complications:
      (1) neutropenia/thrombocytopenia
      (2) fluid retention
      (3) hypersensitivity reactions (flushing, angioedema, urticaria)
      (4) peripheral neuropathy
9. vincristine/vinblastine—
   A. antibiotics (plant alkaloids) that disrupt the assembly of microtubules in the mitotic spindle
      (1) bind to tubulin and prevent polymerization of tubulin dimers used to assemble microtubules
      (1) inhibit the M phase of the cycle
      (2) derive from the periwinkle plant
   B. complications:
      (1) peripheral neuropathy (muscle weakness, areflexia)
      (2) bone marrow suppression
      (3) SIADH
      (4) Raynaud's phenomenon

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Alkylating agents:

1. MOA—
   A. impair cell function by alkylating DNA, RNA, and other proteins
   B. alkylation primarily leads to breakage of DNA strands and cross-linking, which inhibits strand replication

2. mechlorethamine (nitrogen mustard)—
   A. alkylating agent that produces bone marrow (BM) suppression
   B. part of the MOPP regimen in treating Hodgkin's lymphoma

3. cyclophosphamide—
   A. alkylating agent: nitrogen mustard that is changed by the cytochrome system into phosphoamide which interacts with DNA
   B. complications:
      (1) hemorrhagic cystitis (blocked with mesna)
      (2) transitional cell carcinoma of the bladder
      (3) BM suppression
      (4) SiADH

4. nitrosoureas (BCNU, CCNU)—
   A. alkylating agents:
      (1) inhibit both DNA and RNA replication
      (2) effective in the S phase
      (3) excellent concentration in brain
   B. complications:
      (1) BM suppression with aplastic anemia
      (2) pulmonary fibrosis

5. busulfan—
   A. alkylating agent
   B. complications:
      (1) marrow suppression
      (2) skin pigmentation similar to Addison’s disease
      (3) pulmonary fibrosis
      (4) adrenal insufficiency
      (5) sterility

6. chlorambucil—
   A. alkylating agent
   B. complications:
      (1) second malignancies (non-Hodgkin's lymphoma)
      (2) myelosuppression

7. melphalan—
   A. alkylating agent
   B. complications:
      (1) marrow suppression
      (2) interstitial pneumonitis
      (3) non-Hodgkin's lymphoma (NHL)

8. streptozocin—
   A. alkylating agent:
      (1) Rx of islet cell tumors
      (2) carcinoid syndrome
   B. complications:
      (1) nephrotoxicity (proximal RTA)
      (2) hypoglycemia

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9. cisplatin—
   A. alkylating agent
   B. complications:
      (1) nephrotoxicity
      (2) magnesium wasting (hypomagnesemia)
      (3) acoustic nerve dysfunction: ototoxicity
      (4) peripheral neuropathy

10. thiotepa—
    A. alkylating agent
    B. complication: marrow suppression

Miscellaneous chemotherapy agents:
1. L-asparaginase—
   A. MOA:
      (1) hydrolyzes blood asparagine (tumor cells lack nutrient for protein synthesis)
      (2) only enzyme antitumor agent
   B. complications:
      (1) hypersensitivity reactions and anaphylaxis
      (2) hepatitis
      (3) encephalopathy
      (4) hyperglycemia
      (5) no BM suppression

2. procarbazine—
   A. MOA:
      (1) inhibits DNA and RNA
      (2) monamine oxidase inhibitor that after oxidation by hepatic enzymes acts as an alkylating agent
   B. complications:
      (1) teratogenic
      (2) peripheral neuropathy
      (3) sterility
      (4) contraindicated when taking foods with tyramine (cheese, wine), owing to it being a MAO inhibitor

3. interleukin-2—
   A. MOA:
      (1) increases T cell proliferation
      (2) increases lymphokine-activated natural killer cells
      (3) Rx of malignant melanoma
   B. complications: vascular leak syndrome

4. α-interferon—
   A. MOA:
      (1) inhibits cell proliferation
      (2) increases lytic potential of NK cells
      (3) increases the expression of class I antigens (increases cytotoxicity of CD8 cytotoxic T cells)
      (4) Rx of AIDS-related Kaposi’s sarcoma
   B. complications:
      (1) fever
      (2) headaches
      (3) myalgia
      (4) cardiovascular disturbances
5. **tamoxifen**
   A. **MOA:**
      (1) *weak estrogen that acts as an estrogen antagonist* that binds to estrogen receptors *(USMLE)*
      (2) disrupts estrogens effect on RNA synthesis
      (3) adjuvant therapy in ERA positive breast cancer: weak estrogenic activity prevents osteoporosis and CAD
   B. **complications:**
      (1) endometrial hyperplasia/carcinoma
      (2) venous thrombosis
      (3) hot flushes

6. **diethylstilbestrol**
   A. **MOA:**
      (1) estrogen compound that competes with androgens for intracellular receptor sites
      (2) blocks the growth promoting effect of estrogens
      (3) in pregnant women, it blocks müllerian differentiation in fetus
      (4) used in Rx of prostate cancer
   B. **complications:**
      (1) gynecomastia
      (2) venous thrombosis
      (3) **clear cell adenocarcinoma of the vagina/cervix** in female siblings

7. **leuprolide**
   A. **MOA:**
      (1) analog of GnRH that when administered in a sustained fashion inhibits the release of LH and FSH: decreases testosterone and DHT
      (2) Rx of prostate cancer
   B. **complication:** hypogonadism

**Questions used during the board review:**

į In which of the following sites is the MOST COMMON primary cancer an adenocarcinoma?
   SELECT 2
   A. Esophagus
   B. Bladder
   C. Larynx
   D. Cervix
   E. Lung

į Which of the following genes regulates kinases in the cell division cycle, hence assuming an important role in the development of human cancer?
   A. c-ras proto-oncogene
   B. erb B proto-oncogene
   C. Rb-1 suppressor gene
   D. c-myc proto-oncogene
   E. p-53 suppressor gene
A primary cancer is more common than metastasis in which of the following sites?
A. Lymph node
B. Colon
C. Brain
D. Bone
E. Lung

A 55 year old woman with breast cancer has an infiltrating ductal carcinoma that is 2 cm in size, ERA and PRA positive, metastatic to 5 out of 20 axillary lymph nodes, and metastatic to both the vertebral column and liver. Which of the following MOST influences the ultimate prognosis in this patient?
A. Her age
B. ERA/PRA status
C. Size of the tumor
D. Axillary node involvement
E. Bone and liver involvement

(extranodal metastasis is worse than nodal metastasis)

Which of the following is the second most common cancer and cancer killer in men and women?
A. Malignant melanoma
B. Lung cancer
C. Colorectal cancer
D. Malignant lymphoma
E. Stomach cancer

A tumor that could potentially produce Cushing's syndrome and hyponatremia is most likely located in the...
A. kidney
B. placenta
C. liver
D. thyroid
E. lung

Both AFP and β-hCG are most likely to be elevated in which primary tumor site?
A. Lung
B. Testicle
C. Liver
D. Colon
E. Ovary

Which of the following cancers is prevented by immunization with a commonly used vaccine?
A. Pancreatic carcinoma
B. Stomach carcinoma
C. Transitional cell carcinoma
D. Hepatocellular carcinoma
E. Cervical carcinoma