Study Guide 6

This guide covers chapters 11 and 12. Chapter 11 finishes the chemistry domain: where each pathway runs, which enzyme commits it, what controls it and what a missing enzyme or vitamin does to a patient. Chapter 12 opens pathology with the general rules (adapt, die, inflame, heal, clot, mutate, turn malignant) that explain every named disease in chapter 13. Both chapters reward reasoning from mechanism, so for each fact ask what breaks and what the patient shows. Work one chapter at a time, study the diagram, cover the steps of each worked case, then finish with the ten board-style items. The cram sheet at the end puts both chapters on one page.

WHAT THIS GUIDE COVERS

- Chapter 11 · ΔG and ATP, NAD+, FAD and NADPH, glycolysis and its control, PDH and its cofactors, the citric acid cycle, the electron transport chain, inhibitors and uncouplers, gluconeogenesis, glycogen metabolism and storage diseases, the pentose phosphate pathway and G6PD, fructose and galactose disorders, beta oxidation, ketones, fatty acid and cholesterol synthesis, the urea cycle, amino acid products and inborn errors, hormone classes, steroidogenesis and CAH, second messengers, vitamins and minerals.
- Chapter 12 · adaptations, reversible and irreversible injury, necrosis and apoptosis, calcification, acute and chronic inflammation, mediators, repair and healing, edema, thrombosis, embolism, infarction and shock, neoplasm nomenclature, benign versus malignant, oncogenes and tumor suppressors, carcinogens, metastasis to bone, grading and staging, Mendelian and chromosomal disorders, Marfan and Ehlers Danlos syndromes, teratogens, hypersensitivity, autoimmunity, immunodeficiency, amyloid, smoking, alcohol and nutrition.

CHAPTER 11

Metabolism, Bioenergetics, Hormones, Vitamins and Minerals

Read it in full: **Chapter 11 in the review book**. Practice it: **the practice exams** (Exam 6 covers this chapter) and **the flashcards**.

What to know

A negative **ΔG** means a reaction can proceed; enzymes change only the rate. ATP hydrolysis releases about 7.3 kcal/mol (standard) and couples unfavorable reactions. Electrons from fuels are carried by **NAD+** (niacin) and **FAD** (riboflavin) to the electron transport chain; **NADPH** is the reducing currency of synthesis, glutathione and the respiratory burst. Creatine phosphate buffers ATP in the first seconds of hard exercise.

Glycolysis runs in the cytosol of every cell: one glucose gives 2 pyruvate, net 2 ATP and 2 NADH. Its control points are hexokinase or glucokinase, **PFK-1 (rate limiting**; activated by AMP and fructose-2,6-bisphosphate, inhibited by ATP and citrate) and pyruvate kinase. Hexokinase has a low Km and is product inhibited; glucokinase (liver, beta cell) has a high Km and is the beta cell's glucose sensor. Insulin raises fructose-2,6-bisphosphate (glycolysis on); glucagon lowers it. Without oxygen or mitochondria, LDH makes lactate to regenerate NAD+ (Cori cycle). Red cells make 2,3-BPG; pyruvate kinase deficiency causes hemolysis. Fluoride inhibits enolase.

Pyruvate dehydrogenase is the irreversible mitochondrial bridge to acetyl-CoA, so acetyl-CoA can never become glucose. Its five cofactors are thiamine (B1), lipoic acid, CoA (B5), FAD (B2) and NAD+ (B3): Tender Loving Care For Nancy. Giving glucose before thiamine to a malnourished drinker can precipitate Wernicke encephalopathy. Arsenite binds lipoic acid. PDH deficiency gives lactic acidosis and is treated with fat and the purely ketogenic amino acids leucine and lysine.

The **citric acid cycle** (matrix) yields per turn 3 NADH, 1 FADH2, 1 GTP and 2 CO2; it turns twice per glucose. Isocitrate dehydrogenase is rate limiting. Succinate dehydrogenase is also Complex II. In the **electron transport chain** Complexes I, III and IV pump protons and ATP synthase (Complex V) uses the gradient. Yields: about 2.5 ATP per NADH and 1.5 per FADH2, 30 to 32 ATP per glucose. Inhibitors (rotenone at I, antimycin A at III, **cyanide and CO at IV**, oligomycin at ATP synthase) stop oxygen use; **uncouplers** (2,4-DNP, high-dose aspirin, thermogenin) raise oxygen use and heat but lower ATP.

Gluconeogenesis (mainly liver) bypasses three glycolytic steps with pyruvate carboxylase (biotin, activated by acetyl-CoA), PEPCK, fructose-1,6-bisphosphatase (rate limiting) and glucose-6-

phosphatase (liver and kidney only, so muscle cannot release glucose). It needs ATP and acetyl-CoA from beta oxidation, which is why fatty acid oxidation defects cause **hypoketotic hypoglycemia**. Ethanol raises NADH and blocks gluconeogenesis, so a fasting binge can cause severe hypoglycemia.

Glycogen synthase and glycogen phosphorylase (needs B6) are rate limiting. One PKA phosphorylation (glucagon, epinephrine) turns phosphorylase on and synthase off; insulin's phosphatase reverses both; muscle phosphorylase also responds to calcium and AMP. Storage diseases: liver enzyme missing gives fasting hypoglycemia and a big liver; muscle enzyme missing gives exercise intolerance. **Von Gierke** (glucose-6-phosphatase): severe hypoglycemia, lactic acidosis, high urate and triglycerides. **Pompe** (lysosomal acid maltase): cardiomegaly. Cori (debranching). **McArdle** (muscle phosphorylase): early cramps, myoglobinuria, second wind, no lactate rise.

The pentose phosphate pathway makes NADPH (**G6PD**, rate limiting) and ribose; transketolase needs thiamine. G6PD deficiency (X-linked) gives oxidant hemolysis with Heinz bodies and bite cells (fava beans, sulfonamides, primaquine). Fructose: aldolase B deficiency (hereditary fructose intolerance) causes hypoglycemia and liver failure after fruit; fructokinase deficiency is benign. Galactose: classic galactosemia (uridyltransferase) causes failure to thrive, cataracts and E. coli sepsis. Aldose reductase makes sorbitol, which damages lens, nerve and kidney in diabetes.

CPT-I is rate limiting for beta oxidation and is inhibited by **malonyl-CoA**, so a cell cannot make and burn fat at once. Palmitate yields 8 acetyl-CoA, 7 NADH and 7 FADH2, about 106 ATP net. Odd-chain fatty acids end in propionyl-CoA, which needs biotin and B12 to become succinyl-CoA. MCAD deficiency gives hypoketotic hypoglycemia in a fasting infant. Ketones (HMG-CoA synthase) are made by the liver, which lacks thiophorase and cannot use them; red cells never can. The urine dipstick misses beta-hydroxybutyrate. Acetyl-CoA carboxylase (biotin) is rate limiting for fat synthesis; HMG-CoA reductase (statins) for cholesterol, and statins also lower CoQ10.

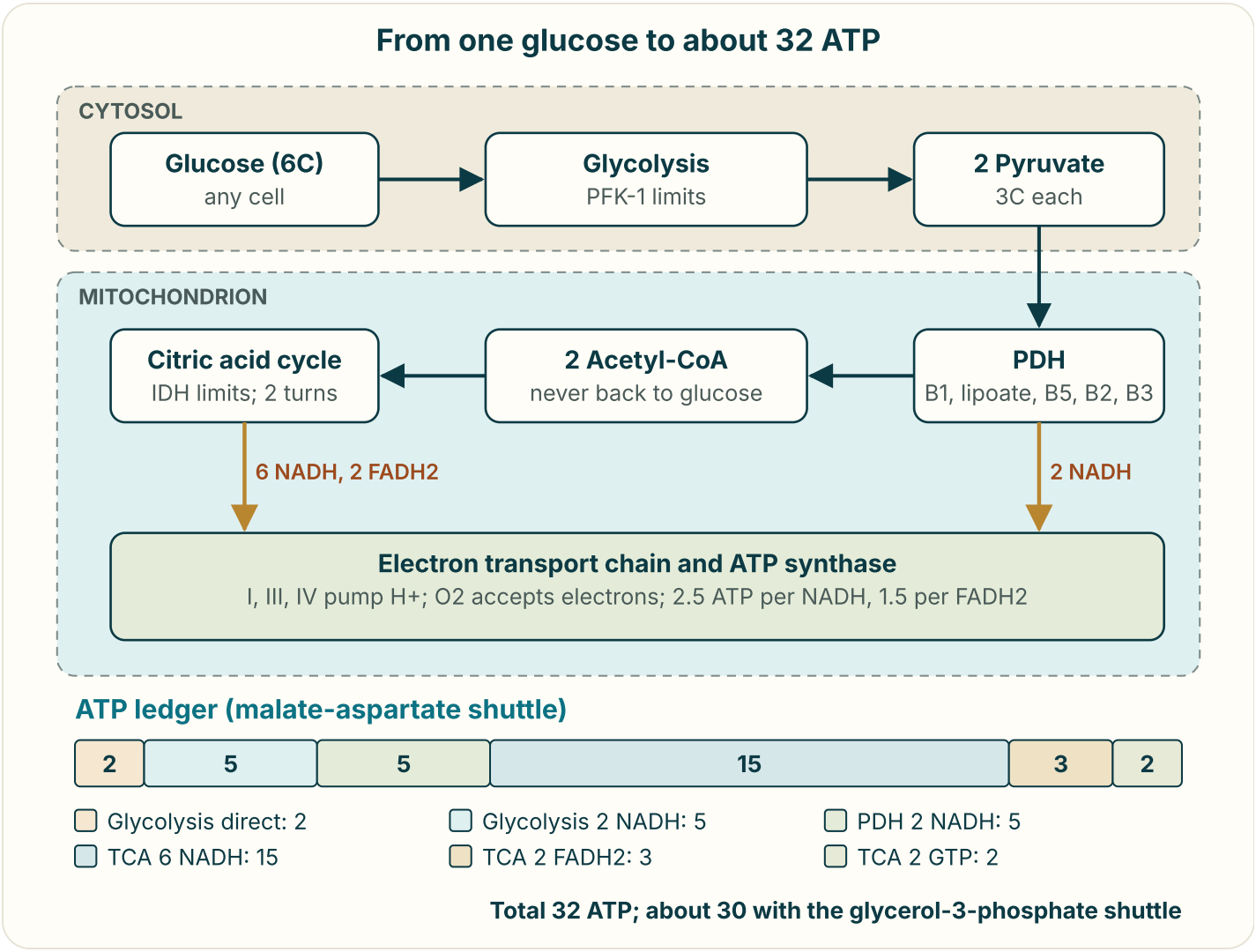
Transamination (ALT, AST) needs **B6**. The urea cycle runs in the liver: **CPS-I** (mitochondrial, rate limiting, needs N-acetylglutamate), then OTC, then cytosolic steps; urea's second nitrogen comes from aspartate. Hyperammonemia gives vomiting, asterixis and coma. **OTC deficiency** is most common, X-linked, with orotic aciduria. Amino acid products: tyrosine to catecholamines (BH4,

B6, vitamin C), tryptophan to serotonin and niacin, glycine plus succinyl-CoA to heme (ALA synthase, B6), arginine to nitric oxide. Inborn errors: **PKU** (musty odor), **alkaptonuria** (dark urine, ochronosis, early spine and large-joint arthropathy with disc calcification), maple syrup urine disease (B1), homocystinuria (lens down and in, thrombosis), cystinuria (hexagonal stones).

Hormone biochemistry: peptides are stored and travel free; steroids come from cholesterol through StAR and desmolase and travel bound; proinsulin gives insulin and C-peptide in equal amounts; POMC gives ACTH, MSH and beta-endorphin. **21-hydroxylase deficiency** (over 90% of CAH) gives salt wasting, hyperkalemia and virilization; 11β-hydroxylase deficiency virilizes with hypertension. Second messengers: Gs cAMP (FSH, LH, ACTH, TSH, PTH, glucagon, beta receptors), Gq IP3 and DAG (GOAT HAG), cGMP (ANP, BNP, NO), tyrosine kinase (insulin, IGF-1), JAK-STAT (GH, prolactin, EPO), nuclear (steroids, T3, calcitriol). Cholera toxin locks Gs on; pertussis toxin blocks Gi.

Fat-soluble vitamins (A, D, E, K) need fat absorption and can be toxic. A: night blindness; excess gives pseudotumor cerebri and is teratogenic. D: rickets and osteomalacia. E: hemolysis and spinocerebellar degeneration. K: carboxylation of II, VII, IX, X, C, S and osteocalcin. Water-soluble: **B1** beriberi and Wernicke Korsakoff; B2 cheilosis; **B3** pellagra (dermatitis, diarrhea, dementia); **B6** neuropathy, seizures, sideroblastic anemia (isoniazid); B7 raw egg whites; **folate** megaloblastic anemia and neural tube defects; **B12** megaloblastic anemia plus subacute combined degeneration, with raised methylmalonic acid; **C** scurvy.

Minerals: iron is absorbed as Fe2+ in the duodenum; hepcidin blocks ferroportin. Iron deficiency: low ferritin, high TIBC. Anemia of chronic disease: high ferritin, low TIBC. **Hemochromatosis**: high iron, ferritin and saturation, with arthropathy of the 2nd and 3rd MCPs. Copper: lysyl oxidase; Menkes deficiency; Wilson excess (Kayser-Fleischer rings). Zinc: wound healing, taste; excess zinc causes copper deficiency. Magnesium is needed for PTH release, so low magnesium gives refractory hypocalcemia. Alkalosis lowers ionized calcium. B12 deficiency (metformin, acid suppression, vegan diet, gastric surgery) can mimic lumbar stenosis with numb feet and a positive Romberg.



Most ATP comes from the mitochondrion. Glycolysis nets only 2 ATP; the electron carriers sent to the chain supply the rest.

LOCK THESE IN

- Glycolysis: cytosol, PFK-1 rate limiting, net 2 ATP. PDH cofactors: B1, lipoate, B5, B2, B3.
- TCA: isocitrate dehydrogenase rate limiting; 3 NADH, 1 FADH2, 1 GTP per turn. About 30 to 32 ATP per glucose.
- Inhibitors stop O2 use (cyanide, CO at IV); uncouplers raise O2 use and heat, lower ATP.
- Glucose-6-phosphatase only in liver and kidney; von Gierke = its deficiency. McArdle = muscle phosphorylase.
- Malonyl-CoA inhibits CPT-I; liver makes ketones but cannot use them; HMG-CoA reductase is the statin target.
- CPS-I needs N-acetylglutamate; OTC deficiency is X-linked with orotic aciduria. Transamination needs B6.
- 21-hydroxylase deficiency: salt wasting plus virilization. GOAT HAG use Gq.
- B12 deficiency adds neurologic damage and high methylmalonic acid; folate does not.

Rate-limiting enzymes and their regulators

Pathway	Enzyme	Key regulation
Glycolysis	PFK-1	+ AMP, F-2,6-BP; - ATP, citrate
Gluconeogenesis	Fructose-1,6-bisphosphatase	- F-2,6-BP, AMP; + citrate
TCA cycle	Isocitrate dehydrogenase	+ ADP, Ca2+; - ATP, NADH
Glycogen synthesis / breakdown	Glycogen synthase / phosphorylase	Insulin on / glucagon, epinephrine on
Pentose phosphate	G6PD	+ NADP+
Fatty acid synthesis	Acetyl-CoA carboxylase	+ insulin, citrate; - glucagon
Beta oxidation	CPT-I	- malonyl-CoA
Ketogenesis	HMG-CoA synthase	Fasting, low insulin
Cholesterol synthesis	HMG-CoA reductase	+ insulin; - cholesterol, statins
Urea cycle	CPS-I	+ N-acetylglutamate
Heme synthesis	ALA synthase	B6; - heme

Vitamins at a glance

Vitamin	Coenzyme or role	Deficiency
B1 thiamine	TPP: PDH, α-KG DH, transketolase	Beriberi, Wernicke Korsakoff
B3 niacin	NAD+, NADP+	Pellagra: dermatitis, diarrhea, dementia
B6 pyridoxine	PLP: transamination, ALA synthase	Neuropathy, seizures, sideroblastic anemia
B9 folate	THF: one-carbon, thymidine	Megaloblastic anemia, neural tube defects
B12 cobalamin	Methionine synthase, methylmalonyl-CoA mutase	Megaloblastic anemia, subacute combined degeneration
C ascorbate	Collagen hydroxylation	Scurvy
A retinol	Rhodopsin, epithelial differentiation	Night blindness; excess teratogenic
D calciferol	Calcium and phosphate absorption	Rickets, osteomalacia
E tocopherol	Membrane antioxidant	Hemolysis, spinocerebellar degeneration
K	γ-carboxylation of II, VII, IX, X	Bleeding, long PT

Worked cases

WORKED CASE 1 · COUNTING ATP FROM ONE GLUCOSE

Total the aerobic yield of one glucose using about 2.5 ATP per NADH and 1.5 per FADH2.

STEP 1 · GLYCOLYSIS

Net 2 ATP and 2 NADH. With the malate-aspartate shuttle the NADH give 2 × 2.5 = 5 ATP.

STEP 2 · PDH

2 pyruvate give 2 NADH: 2 × 2.5 = 5 ATP.

STEP 3 · CITRIC ACID CYCLE, TWO TURNS

6 NADH = 15 ATP, 2 FADH2 = 3 ATP, 2 GTP = 2 ATP.

STEP 4 · ADD IT UP

2 + 5 + 5 + 15 + 3 + 2 = 32 ATP.

SHUTTLE CHECK

With the glycerol-3-phosphate shuttle (muscle, brain), cytosolic NADH yields 1.5 each, so 2 × 1.5 = 3 instead of 5, giving 30 ATP.

WORKED CASE 2 · CRAMPS EARLY IN THE WORKOUT

Kai, 19, gets severe cramps in the first minutes of hard exercise, passes dark urine afterward, and feels better if he rests briefly and starts again.

STEP 1 · SORT LIVER VERSUS MUSCLE

No fasting hypoglycemia or big liver; symptoms come with exertion, so a muscle enzyme is missing.

STEP 2 · NAME THE ENZYME

Muscle glycogen phosphorylase: muscle cannot break down its glycogen for the first burst of work.

STEP 3 · EXPLAIN THE SECOND WIND

After a pause, blood glucose and fatty acids reach the muscle and take over.

STEP 4 · NAME THE DISEASE AND TEST CLUE

McArdle disease (type V). No rise in blood lactate on the forearm exercise test.

STEP 5 · ACT

Dark urine means myoglobinuria: check CK and kidney function before any vigorous rehab, and refer.

WORKED CASE 3 · FASTER BREATHING, MORE HEAT, LESS ATP

A patient takes a large overdose of a weight-loss product containing 2,4-dinitrophenol and develops fever and rapid breathing.

STEP 1 · NAME THE CLASS

2,4-DNP is an uncoupler: it carries protons back across the inner membrane without passing through ATP synthase.

STEP 2 · PREDICT OXYGEN USE

The gradient keeps collapsing, so the chain runs fast and oxygen use rises.

STEP 3 · PREDICT ATP AND HEAT

ATP synthesis falls and the energy is released as heat: hyperthermia.

CONTRAST

Cyanide (Complex IV) and oligomycin (ATP synthase) stop oxygen use; only uncouplers raise it while lowering ATP.

TRAPS PEOPLE FALL INTO

- **Acetyl-CoA and glucose.** PDH is irreversible, so acetyl-CoA and even-chain fatty acids can never make glucose.
- **Thiamine before glucose.** In a malnourished drinker, give thiamine first or glucose can precipitate Wernicke encephalopathy.
- **Muscle glycogen.** Muscle lacks glucose-6-phosphatase and cannot release glucose into the blood.
- **Ketones in the liver.** The liver makes ketones but lacks thiophorase, so it cannot use them.
- **OTC versus CPS-I.** Both raise ammonia; only OTC deficiency raises urinary orotic acid.
- **Folate masking B12.** Folate can correct the anemia of B12 deficiency while nerve damage progresses.

Chapter 11 self-test · ten board-style items

1. Which enzyme catalyzes the rate-limiting step of glycolysis?

A. Hexokinase
B. Pyruvate kinase
C. Glyceraldehyde-3-P dehydrogenase
D. Phosphofructokinase-1

D. Phosphofructokinase-1 PFK-1 commits fructose-6-phosphate and is controlled by AMP, fructose-2,6-bisphosphate, ATP and citrate.

2. A malnourished drinker becomes confused and ataxic with ophthalmoplegia after IV glucose. Which enzyme function failed?

A. Glucose-6-phosphatase lacking B6
B. Lactate dehydrogenase lacking niacin
C. Pyruvate dehydrogenase lacking thiamine
D. Pyruvate carboxylase lacking biotin

C. Pyruvate dehydrogenase lacking thiamine Glucose drives flux into PDH, which needs thiamine pyrophosphate. Wernicke encephalopathy follows.

3. A poison raises oxygen consumption and body temperature while ATP synthesis falls. What type of agent is it?

A. An ATP synthase block
B. An uncoupling agent
C. A Complex IV block
D. A Complex I block

B. An uncoupling agent Uncouplers dissipate the proton gradient, so the chain speeds up while the energy becomes heat.

4. An infant has severe fasting hypoglycemia, a large liver and kidneys, lactic acidosis and high uric acid. Which enzyme is deficient?

A. Glucose-6-phosphatase
B. Branching enzyme
C. Lysosomal acid maltase
D. Muscle glycogen phosphorylase

A. Glucose-6-phosphatase Von Gierke disease traps glucose-6-phosphate, which spills into lactate, triglyceride and urate pathways.

5. A man develops dark urine, jaundice and anemia with bite cells after taking a sulfonamide. Which enzyme is deficient?

A. Pyruvate kinase in the red cell
B. Glucose-6-phosphate dehydrogenase
C. Galactokinase in the liver cell
D. Aldolase B in the liver cell

B. Glucose-6-phosphate dehydrogenase G6PD makes the NADPH that keeps glutathione reduced; oxidant drugs then cause hemolysis.

6. Which molecule prevents a liver cell from oxidizing fatty acids while it is making them?

A. Carnitine
B. Acetoacetate
C. Malonyl-CoA
D. Citrate

C. Malonyl-CoA Malonyl-CoA, the first product of fatty acid synthesis, inhibits CPT-I.

7. A boy with vomiting and lethargy has a high ammonia and a raised urinary orotic acid, but his blood count is normal. Which enzyme is most likely deficient?

A. Ornithine transcarbamylase
B. Carbamoyl phosphate synthetase I
C. Argininosuccinate lyase
D. Arginase

A. Ornithine transcarbamylase OTC deficiency is X-linked; carbamoyl phosphate spills into pyrimidine synthesis and raises orotic acid.

8. A man of 50 has urine that darkens on standing, blue-black ear cartilage and early disc calcification. Which condition fits?

A. Phenylketonuria
B. Homocystinuria
C. Cystinuria
D. Alkaptonuria

D. Alkaptonuria Homogentisate oxidase deficiency deposits pigment in connective tissue (ochronosis) and causes early spinal arthropathy.

9. A newborn girl has ambiguous genitalia, low sodium and high potassium. Which enzyme is most likely deficient?

A. Aromatase
B. 21-hydroxylase
C. 11β-hydroxylase
D. 17α-hydroxylase

B. 21-hydroxylase Without 21-hydroxylase, cortisol and aldosterone fall and precursors are shunted to androgens.

10. Megaloblastic anemia with raised homocysteine and raised methylmalonic acid points to deficiency of

A. vitamin B6
B. folate
C. vitamin C
D. vitamin B12

D. vitamin B12 Only B12 is needed by methylmalonyl-CoA mutase, so methylmalonic acid rises in B12 but not folate deficiency.

CHAPTER 12

General Pathology: Cell Injury, Inflammation, Neoplasia, Genetics and Immunopathology

Read it in full: **Chapter 12 in the review book**. Practice it: **the practice exams** (Exam 6 covers this chapter) and **the flashcards**.

What to know

Cells adapt by **hypertrophy** (size; the only option for permanent cells such as cardiac and skeletal muscle), **hyperplasia** (number), **atrophy** and **metaplasia** (one mature type replaced by another,

as in Barrett esophagus or a smoker's bronchus). **Dysplasia** is disordered growth and can precede cancer. Myositis ossificans is mesenchymal metaplasia in a bruised muscle. Hypoxia is the commonest cause of injury; ischemia is worse because it also stops substrate delivery.

Mechanisms of injury: ATP loss (pump fails, cell swells), mitochondrial damage (cytochrome c release), calcium influx, free radicals and membrane damage. **Cell swelling** is the earliest reversible sign; inability to restore mitochondria and profound membrane damage mark the point of no return. Nuclear signs of death are pyknosis, karyorrhexis and karyolysis. Leaked enzymes (troponin, CK, ALT) prove irreversible membrane damage.

Necrosis is uncontrolled death of groups of cells with inflammation. **Coagulative**: infarcts of solid organs except the brain. **Liquefactive**: brain infarcts and abscesses. **Caseous**: tuberculosis. **Fat**: pancreatitis (saponification). **Fibrinoid**: vasculitis. Gangrene is coagulative necrosis of a limb, wet with infection. **Apoptosis** is ATP-dependent, caspase-driven death of single cells with shrinkage, intact membranes and no inflammation; BCL-2 blocks it, BAX and p53 promote it.

Dystrophic calcification occurs in damaged tissue with normal calcium (atheroma, calcific tendinitis of the supraspinatus, disc calcification, myositis ossificans, psammoma bodies). **Metastatic calcification** occurs in normal tissue when calcium or phosphate is high (hyperparathyroidism, kidney failure, vitamin D toxicity). Lipofuscin is wear-and-tear pigment; hemosiderin follows hemorrhage.

Acute inflammation is vascular (vasodilation, increased venular permeability, protein-rich **exudate**) then cellular: rolling on selectins, firm adhesion of integrins to ICAM-1, transmigration by PECAM-1, chemotaxis (C5a, LTB4, IL-8) and phagocytosis with the respiratory burst. Histamine is released first. Bradykinin causes pain and permeability (ACE inhibitor angioedema). IL-1, IL-6 and TNF drive fever and the acute phase response (CRP, fibrinogen raising ESR). Chronic granulomatous disease (NADPH oxidase) fails against catalase-positive organisms.

Chronic inflammation brings macrophages, lymphocytes and plasma cells. A **granuloma** is epithelioid macrophages with giant cells, driven by Th1 IFN-γ and TNF (anti-TNF drugs can reactivate TB). Caseating: TB and fungi; noncaseating: sarcoidosis, Crohn disease. Repair runs granulation tissue (VEGF, days 3 to 5), then **type III collagen**, remodeled to **type I**; strength is

about 10% at one week and only 70 to 80% by three months. Infection is the main enemy of healing; vitamin C, zinc and protein are needed. Ligament healing follows the same timeline, which supports graded loading.

Edema: transudates come from pressure problems with intact vessels; exudates from leaky vessels. **Virchow triad** (endothelial injury, stasis, hypercoagulability) explains thrombosis; factor V Leiden is the commonest inherited cause. Lines of Zahn mark a clot formed in flowing blood. Most pulmonary emboli come from deep leg veins above the knee; fat emboli follow long-bone fractures in 1 to 3 days. Emboli: FAT BAT. White infarcts occur in solid end-artery organs; red infarcts in lung, liver and torsion. Neurons die after 3 to 5 minutes of ischemia. Neurogenic shock after cord injury gives hypotension with bradycardia.

Carcinomas arise from epithelium, sarcomas from mesenchyme; lymphoma, melanoma, mesothelioma and seminoma are malignant despite the -oma. **Metastasis** is the single most reliable sign of malignancy; carcinoma in situ has not crossed the basement membrane. Oncogenes need one hit (RAS, HER2, MYC, BCR-ABL); tumor suppressors need two (**p53**, **RB**, APC, BRCA). Carcinogens: aflatoxin (liver), asbestos (mesothelioma), vinyl chloride (hepatic angiosarcoma), aniline dyes (bladder), UV (thymine dimers), HPV 16 and 18, EBV, hepatitis B and C. **Stage outweighs grade** for prognosis.

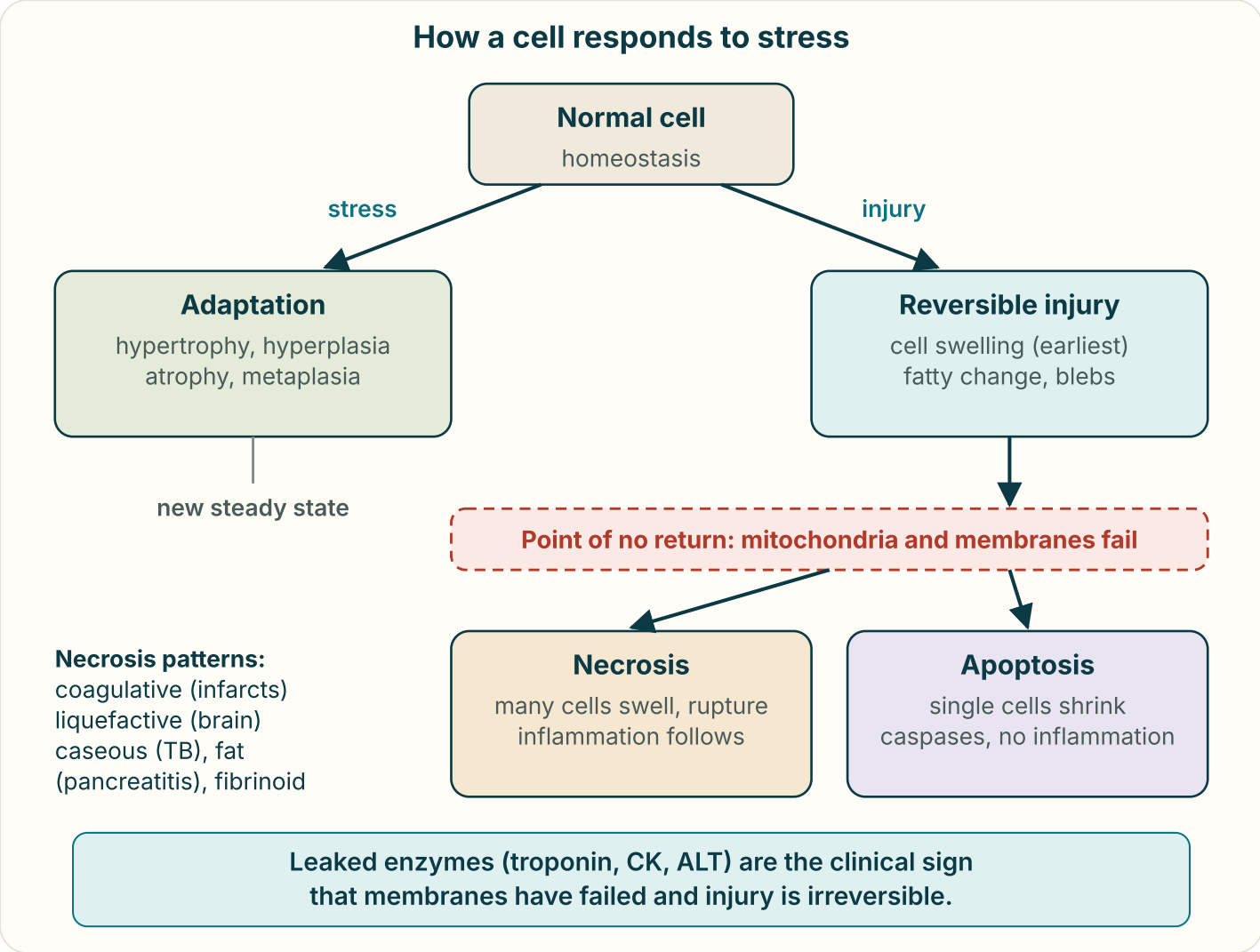
Metastases are the commonest malignant bone tumors in adults and favor the **vertebral bodies**, reached through the valveless Batson plexus. They destroy the pedicle early (winking owl sign) and usually **spare the disc**, unlike infection. Prostate, thyroid, breast, lung and kidney (Please Take Both Lungs and Kidneys): **prostate is blastic**, kidney and thyroid lytic and expansile, lung lytic, breast mostly lytic or mixed. Myeloma is punched-out lytic with a cold bone scan. Red flags: age over 50, cancer history (strongest), weight loss, night pain, failure to improve in a month.

Autosomal dominant disorders hit structural proteins and appear every generation (Marfan, achondroplasia, osteogenesis imperfecta, familial hypercholesterolemia, NF1, Huntington). Recessive disorders hit enzymes and skip generations (cystic fibrosis, sickle cell, PKU, lysosomal storage). X-linked recessive disorders affect sons of carrier mothers, never father to son (Duchenne, hemophilia, G6PD). Mitochondrial disorders pass from the mother to all children.

Anticipation (repeats), imprinting (Prader-Willi paternal, Angelman maternal) and pleiotropy are tested by name.

Down syndrome (trisomy 21) brings atlantoaxial instability from transverse ligament laxity: an ADI over 3 mm in adults or 5 mm in children contraindicates high-velocity cervical adjusting. Klinefelter (47,XXY) and Turner (45,X) are the core sex-chromosome disorders. **Marfan** (fibrillin-1): tall, long limbs, lens up and out, aortic root dilation and dissection. **Ehlers-Danlos** (collagen): hypermobility, fragile skin; the vascular type (type III collagen) ruptures arteries. Prefer stabilization exercise to repeated thrusts on lax joints. Teratogens act most in weeks 3 to 8; folic acid prevents neural tube defects.

Hypersensitivity (ACID): type I IgE on mast cells (minutes; anaphylaxis, asthma); type II antibody against fixed antigens (hemolysis, Goodpasture, Graves, myasthenia); type III immune complexes with low complement (SLE, poststreptococcal GN, serum sickness); type IV T cells, 48 to 72 hours (PPD, contact dermatitis, MS). HLA-B27 marks the spondyloarthropathies, DR4 rheumatoid arthritis. B cell defects give pyogenic infections, T cell defects viral and fungal ones, C5 to C9 defects Neisseria. Amyloid stains with Congo red (apple-green birefringence); β2-microglobulin amyloid in dialysis causes carpal tunnel syndrome. Kwashiorkor has edema; marasmus does not. BMI 30 or more is obesity.



Adapt, injure, then die. Swelling is reversible; once mitochondria and membranes fail the cell dies by necrosis or apoptosis.

LOCK THESE IN

- Permanent cells adapt only by hypertrophy; metaplasia can progress to dysplasia and cancer.
- Swelling is reversible; mitochondrial failure and membrane rupture are not.
- Coagulative necrosis in infarcts except brain (liquefactive); caseous in TB; apoptosis without inflammation.
- Dystrophic calcification: dead tissue, normal calcium. Metastatic: normal tissue, high calcium or phosphate.
- Repair: granulation tissue, type III collagen, then type I; strength never fully returns.
- Virchow triad; most PE from deep leg veins; FAT BAT emboli.
- Bone metastases favor vertebral bodies, destroy pedicles, spare discs; prostate blastic.
- ACID hypersensitivity; Down syndrome ADI limits: over 3 mm adult, over 5 mm child.

Patterns of cell death

Type	Features	Setting
Coagulative	Architecture kept, ghost cells	Infarcts of heart, kidney, spleen
Liquefactive	Enzymatic digestion to liquid	Brain infarct, abscess
Caseous	Cheese-like debris in a granuloma	Tuberculosis, systemic fungi
Fat	Saponification with calcium	Acute pancreatitis, breast trauma
Fibrinoid	Immune complexes and fibrin in vessel walls	Vasculitis, malignant hypertension
Gangrenous	Coagulative (dry) or infected (wet)	Diabetic and ischemic feet
Apoptosis	Shrinkage, caspases, intact membrane, no inflammation	Embryogenesis, viral hepatitis

Tumors that seed bone

Primary	Usual appearance	Note
Prostate	Blastic (ivory vertebra)	High PSA and ALP
Breast	Mostly lytic or mixed	Commonest source in women
Lung	Lytic	Hypercalcemia possible
Kidney	Lytic, expansile, vascular	May be the first sign
Thyroid (follicular)	Lytic, expansile	Hematogenous spread
Multiple myeloma	Punched-out lytic, cold bone scan	CRAB, M spike

Worked cases

WORKED CASE 1 · NIGHT PAIN IN AN OLDER PATIENT

Frank, 68, treated for prostate cancer five years ago, has thoracolumbar pain that is worse at night and has lost weight. An AP film shows one pedicle missing at L2 and a dense vertebral body at L3; the discs are preserved.

STEP 1 · COUNT THE RED FLAGS

Age over 50, prior cancer (the strongest predictor), night pain and weight loss.

STEP 2 · READ THE PEDICLE

A missing pedicle (winking owl sign) suggests metastasis, which enters the posterior body and pedicle early.

STEP 3 · READ THE DENSITY

A dense vertebra in an older man fits blastic prostate metastasis (ivory vertebra).

STEP 4 · READ THE DISC

Preserved discs argue against infection, which crosses the disc.

STEP 5 · ACT

Do not adjust the involved segments. Refer for imaging and oncology care; Batson plexus explains the spinal route.

WORKED CASE 2 · TRANSUDATE OR EXUDATE

Two patients have leg swelling. One has heart failure; the other has a hot, red, tender calf with fever after a skin wound.

STEP 1 · APPLY STARLING FORCES

In heart failure, capillary hydrostatic pressure rises with intact vessels: a low-protein transudate.

STEP 2 · APPLY INFLAMMATION

In cellulitis, histamine, bradykinin and leukotrienes open endothelial gaps: a protein-rich exudate with cells.

STEP 3 · NAME THE MEASURE

Exudate has high protein and specific gravity above 1.020; transudate is low on both.

REMEMBER THE THIRD CAUSE

A swollen, tender calf after surgery or immobilization may be DVT (Virchow triad): no massage, same-day duplex referral.

WORKED CASE 3 · A TALL PATIENT WITH LONG FINGERS

Ezra, 24, is 6 ft 6 in with long fingers, a pectus excavatum and scoliosis. His arm span exceeds his height. He wants his thoracic spine adjusted.

STEP 1 · NAME THE PATTERN

Tall stature, arachnodactyly, chest wall deformity and scoliosis suggest Marfan syndrome (fibrillin-1, autosomal dominant).

STEP 2 · FIND THE DANGER

Cystic medial degeneration of the aorta leads to root dilation and dissection.

STEP 3 · SCREEN

Ask about lens dislocation (up and out) and family history; refer for echocardiography.

STEP 4 · ACT

Avoid forceful thrusts until cleared. Sudden tearing chest or interscapular pain is dissection until proven otherwise: call emergency services.

TRAPS PEOPLE FALL INTO

- **Brain infarcts.** They are liquefactive, not coagulative.
- **Calcification and calcium.** Dystrophic calcification happens with normal serum calcium.
- **Grade versus stage.** Stage, the anatomic spread, is the stronger predictor of prognosis.
- **Disc and tumor.** Metastases usually spare the disc; crossing the disc points to infection.
- **X-linked spread.** An affected father never passes an X-linked disorder to his sons; all his daughters are carriers.
- **Type IV hypersensitivity.** It involves T cells and no antibody, and it takes 48 to 72 hours.

Chapter 12 self-test · ten board-style items

1. Which change is the earliest light-microscopic sign of reversible cell injury?

A. Rupture of the plasma membrane
B. Karyorrhexis
C. Pyknosis of the nucleus
D. Cellular swelling

D. Cellular swelling ATP loss fails the sodium pump, water enters and the cell swells. Nuclear changes mark irreversible injury.

2. A myocardial infarct shows preserved cell outlines with no nuclei. Which necrosis is this?

A. Caseous
B. Coagulative
C. Fibrinoid
D. Liquefactive

B. Coagulative Protein denaturation preserves architecture for days in infarcts of solid organs other than the brain.

3. Calcium deposits in the supraspinatus tendon of a patient with normal serum calcium are

A. a form of apoptosis
B. a sign of hyperparathyroidism
C. dystrophic calcification
D. metastatic calcification

C. dystrophic calcification Damaged tissue calcifies with normal serum calcium; metastatic calcification needs high calcium or phosphate.

4. Which molecules mediate the firm adhesion of neutrophils to endothelium?

A. Integrins binding ICAM-1
B. Selectins binding sialyl Lewis X
C. PECAM-1 between cells
D. C5a binding its receptor

A. Integrins binding ICAM-1 Selectins slow (roll) the cell; integrins on the leukocyte bind ICAM-1 and VCAM-1 for firm adhesion.

5. A wound one week after suturing has roughly what share of normal tensile strength?

A. Full strength
B. About 80 percent
C. About 10 percent
D. About 50 percent

C. About 10 percent Strength is about 10% at one week and plateaus at 70 to 80% by about three months.

6. Which part of Virchow triad dominates arterial thrombosis?

A. Venous stasis
B. Endothelial injury
C. Low plasma oncotic pressure
D. Inherited hypercoagulability

B. Endothelial injury Arterial and cardiac thrombi form mainly on injured endothelium such as ruptured plaque.

7. Which statement best separates a malignant from a benign tumor?

A. It has a capsule
B. Its cells look well differentiated
C. It grows quickly
D. It can metastasize

D. It can metastasize Metastasis is the single most reliable sign of malignancy; growth rate and differentiation overlap.

8. Which metastasis is classically osteoblastic?

A. Prostate carcinoma
B. Renal cell carcinoma
C. Lung carcinoma
D. Thyroid carcinoma

A. Prostate carcinoma Prostate metastases lay down dense new bone (ivory vertebra); kidney and thyroid are lytic and expansile.

9. A disorder skips generations, affects both sexes and appears in children of two unaffected carriers. Which pattern?

A. Autosomal dominant
B. X-linked recessive
C. Autosomal recessive
D. Mitochondrial

C. Autosomal recessive Two carrier parents give a 25% risk per child; recessive disorders usually involve enzymes.

10. A positive tuberculin skin test read at 48 to 72 hours is which hypersensitivity type?

A. Type IV
B. Type III
C. Type II
D. Type I

A. Type IV Delayed, T cell mediated reactions take 48 to 72 hours and involve no antibody.

Cram sheet

Both chapters on one page. Cover the right columns and rebuild each row from memory. If a row will not come back, go back to that chapter.

Metabolism and vitamins

Topic	Rule	Board hook
Glycolysis	PFK-1; net 2 ATP	Fluoride blocks enolase
PDH	B1, lipoate, B5, B2, B3	Thiamine before glucose
TCA and ETC	IDH limits; 30 to 32 ATP	Cyanide stops O2 use; uncouplers raise it
Gluconeogenesis	F-1,6-BPase limits; G6Pase liver and kidney	FAO defects: hypoketotic hypoglycemia
Glycogen	PKA: phosphorylase on, synthase off	Von Gierke, Pompe, Cori, McArdle
PPP	G6PD makes NADPH	Heinz bodies, bite cells
Fat	CPT-I blocked by malonyl-CoA	Liver cannot use ketones
Nitrogen	CPS-I with NAG; OTC X-linked	Orotic acid in OTC
Inborn errors	PKU, alkaptonuria, MSUD, homocystinuria	Ochronosis and disc calcification
Hormones	21-hydroxylase CAH; GOAT HAG Gq	Cholera Gs on, pertussis Gi off
Vitamins	B12 neuro plus MMA; folate none	Wernicke: B1
Minerals	Ferritin low in iron deficiency, high in chronic disease	Hemochromatosis 2nd, 3rd MCP

General pathology

Topic	Rule	Board hook
Adaptation	Hypertrophy, hyperplasia, atrophy, metaplasia	Barrett esophagus
Death	Coagulative, liquefactive, caseous, fat, fibrinoid	Apoptosis: caspases, no inflammation
Calcification	Dystrophic normal Ca; metastatic high Ca	Calcific tendinitis is dystrophic
Inflammation	Selectins, integrins, PECAM, chemotaxis	CGD: catalase positive bugs
Repair	Type III then type I collagen	10% strength at one week
Hemodynamics	Virchow triad; FAT BAT	Fat emboli 1 to 3 days after fracture
Neoplasia	Oncogene one hit; suppressor two	Stage over grade
Bone metastasis	Vertebral body, pedicle, disc spared	Prostate blastic
Genetics	AD structural, AR enzymes, XR sons	Down: ADI limits
Connective tissue	Marfan fibrillin; EDS collagen	Dissection pain is an emergency
Immunopathology	ACID; HLA-B27, DR4	Type IV no antibody

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