Biochemistry and Genetics
Flash Cards

SECOND EDITION

184 high-yield cards deliver a fast and effective review for the USMLE Step 1

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McGraw Hill LANGE®

Lange FlashCards
Biochemistry & Genetics

Second Edition

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Mc Graw Hill **Medical**

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Preface

When we began to review the biochemistry and genetics material covered in the USMLE Step 1 at the end of our second year at Yale Medical School, we realized that most of the practice questions were approaching the material from a clinical perspective and not from the basic science perspective in which we had learned these topics. Although we had taken introductory biochemistry and genetics courses back in college and covered the material again during the first few months of medical school, we found ourselves studying the clinical aspects of biochemical and genetic diseases for the first time. Flipping through the highly rated biochemistry and genetics review sources, we realized that there was no gold standard review source for these high-yield topics that make up 15% of USMLE Step 1 questions.

Lange FlashCards: Biochemistry and Genetics is the result of our struggles in studying these topics for Step 1 with the clinical slant that the boards demand. These cards offer the most complete, concise, and high-yield information for the major biochemical and genetic diseases tested on Step 1 and in medical school basic science courses. We are confident that the content covered in the second version of our cards includes the most current and board-relevant information that cannot be found in any other single biochemistry and genetics review text.

We are pleased to present this information in a format modeled after *Lange FlashCards: Pathology*, our first publication in this series. Each card provides a structured presentation of a specific disease and allows students to easily compare and contrast diseases. The introductory cards in each chapter describe the basic principles of biochemistry and genetics that are board relevant and high yield. Each disease-specific card contains a clinical vignette on one side and important characteristics on the reverse side. These characteristics are organized into sections entitled biochemical or genetic defect, pathophysiology, clinical manifestations, treatment, and additional pearls. The most salient features of each disease are highlighted in bold for ease of rapid review.

We suggest using these cards as an adjunct to your biochemistry and genetics courses in medical school. Being familiar with these cards early on will be very helpful during your Step 1 review. We also encourage you to jot down your own notes in the margins and to make these cards your personal biochemistry and genetics review for the boards.

We are confident that the newly revised second edition of *Lange FlashCards: Biochemistry and Genetics* will be one of the most powerful tools to help prepare you for the boards and will serve as a resource that will bridge your basic science knowledge with the clinical aspects of disease. We wish you the best of luck on Step 1 and welcome your comments on how to improve this study tool in the next edition.

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Acknowledgments

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Christoph I. Lee, MD, earned an AB *cum laude* in English from Princeton University and an MD *cum laude* from Yale University School of Medicine. He completed his residency in diagnostic radiology at Stanford University and fellowship in breast imaging at UCLA. Dr Lee has completed a health policy fellowship in the prestigious Robert Wood Johnson Clinical Scholars program. He has previously managed a global tuberculosis initiative for Ralph Nader.

Abbreviations

1,2-DAG: 1,2-diacylglycerol
2,3-BPG: 2,3-bisphosphoglycerate
α-t: α-thalassemias
β-t: β-thalassemias
ABG: arterial blood gas
AC: adenylate cyclase
ACE: angiotensin-converting-enzyme
ACTH: adrenocorticotropic hormone
ADA: adenosine deaminase
ADP: adenosine diphosphate
ALA: aminolevulinic acid
ALL: acute lymphoblastic leukemia
ALT: alanine aminotransferase
AMP: adenosine monophosphate
Apo: apoprotein
ATP: adenosine triphosphate
AST: aspartate aminotransferase
ATP: adenosine triphosphate
AUG: adenine uracil guanine
BAL: British AntiLewisite, dimercaprol
BCKD: branched-chain α-ketoacid dehydrogenase
BSS: Bernard-Soulier syndrome
Btk: Bruton tyrosine kinase
BUN: blood urea nitrogen
CAG: cytosine adenine guanine

cAMP: cyclic adenosine monophosphate
CBC: complete blood count
CDP: cytidine diphosphate
CFTR: cystic fibrosis transmembrane conductor regulator
CGG: cytosine guanine guanine
CHF: congestive heart failure
Chr: chromosome
Cl^-: chloride ion
CMT: Charcot-Marie-Tooth (disease)
CNS: central nervous system
CoA: coenzyme A
COPRO: coproporphyrinogen
CT: computed tomography
CTG: cytosine thymidine guanine
CTP: cytosine-5′-triphosphate
dADP: deoxyadenosine diphosphate
dATP: deoxyadenosine triphosphate
dCDP: deoxycytidine diphosphate
dGDP: deoxyguanosine diphosphate
DHEA: dehydroepiandrosterone
DHT: dihydrotestosterone
DMD: Duchenne muscular dystrophy
DNA: deoxyribonucleic acid
DNAO: DNA polymerase
DNAP: DNA polymerase

MERRF: myoclonic epilepsy with ragged red fibers
MI: myocardial infarction
MRI: magnetic resonance imaging
mRNA: messenger RNA
mtDNA: mitochondrial DNA
MTP: metatarsophalangeal
NAD: nicotinamide adenine dinucleotide
NADP: nicotinamide adenine dinucleotide phosphate
NADPH: nicotinamide adenine dinucleotide phosphate hydrogen
NF1: neurofibromatosis 1
NPD: Niemann-Pick disease
NPTHM: N^5-methyl tetrahydrofolate homocysteine methyltransferase
NSAID: nonsteroidal anti-inflammatory drug
OMP: orotidine-5′-monophosphate
PBG: porphobilinogen
PPD: purified protein derivative
PRPP: phosphoribosylpyrophosphate
PT: prothrombin time
PTH: parathyroid hormone
PTT: partial thromboplastin time
RBC: red blood cell
RFLP: restriction fragment length polymorphism
RNA: ribonucleic acid
RNAP: RNA polymerase
rRNA: ribosomal ribonucleic acid

RUQ: right upper quadrant
SAM: *S*-adenosylmethionine
SCID: severe combined immunodeficiency
SSB: single-strand DNA binding
TB: tuberculosis
TGF-β: tissue growth factor β
TIBC: total iron-binding capacity
TLC: total lung capacity
TMP-SMX: trimethoprim-sulfamethoxazole
TPP: thiamine pyrophosphate
TTP: thymidine triphosphate
tRNA: transfer ribonucleic acid
UA: urinalysis
UDP: uridine 5′-diphosphate
UDPGT: uridine diphosphoglucuronosyl transferase
UMP: uridine-5′-monophosphate
URO: uroporphyrinogen
UTI: urinary tract infection
UTP: uracil-5′-triphosphate
UV: ultraviolet
VLDL: very-low-density lipoprotein
VMA: vanillylmandelic acid
vWF: von Willebrand factor
WAS: Wiskott-Aldrich syndrome
XR: x-ray

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GENERAL CONCEPTS

Citric acid cycle
Electron transport chain
NADH shuttles

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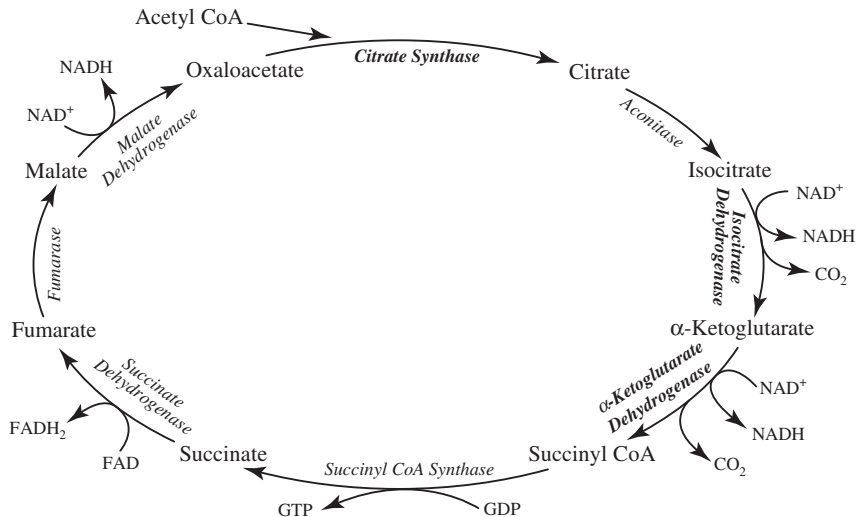
CITRIC ACID CYCLE

The citric acid cycle occurs in the mitochondrial matrix. Functions include the oxidation of acetyl CoA to CO_2, the formation of NADH and $FADH_2$ for entrance into the electron transport chain and subsequent ATP generation, and the synthesis of several important molecules, including succinyl CoA (precursor molecule of heme), oxaloacetate (early intermediate molecule in gluconeogenesis and substrate for amino acid synthesis), α-ketoglutarate (substrate for amino acid synthesis), and citrate (substrate for fatty acid synthesis).

YIELD OF THE CITRIC ACID CYCLE

Each molecule of acetyl CoA entering the citric acid cycle yields the following:

- Two CO_2
- Three NADH
- One $FADH_2$
- One GTP

Because each NADH will eventually produce 2.5 ATP and each $FADH_2$ will produce 1.5 ATP through the electron transport chain, the overall ATP yield from 1 acetyl CoA is 10 ATP (7.5 from NADH, 1.5 from $FADH_2$, and 1 from GTP).

REGULATION OF THE CITRIC ACID CYCLE

Enzyme	Inhibitors	Activators
Citrate synthase	ATP NADH Succinyl CoA	—
Isocitrate dehydrogenase	ATP NADH	ADP
α-Ketoglutarate dehydrogenase	ATP or GTP NADH Succinyl CoA	—
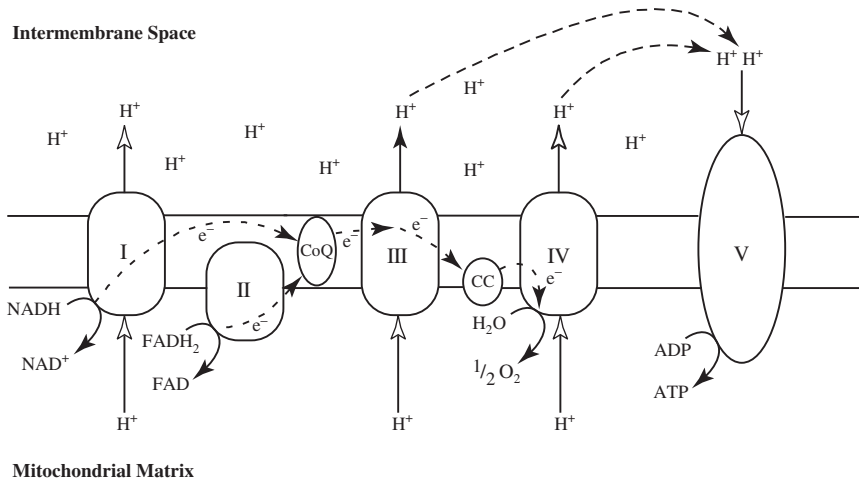
COMPONENTS OF THE ELECTRON TRANSPORT CHAIN

Complex I (NADH dehydrogenase): Contains **FMN**, which **accepts 2 e− and H+ from 2 NADH** to become the reduced **form of FMNH$_2$**; also contains iron atoms, which assist in the transfer of the e− and H+ to coenzyme Q. Inhibited by amobarbital and rotenone.

Complex II (succinate dehydrogenase): Contains iron and succinate, which oxidizes FAD to **form FADH$_2$**. Inhibited by antimycin A.

Coenzyme Q: Accepts e− from FMNH$_2$ (complex I) and FADH$_2$ (complex II). Transfers e− to complex III.

Complex III (cytochrome b): Contains **heme group**, in which the Fe^{3+} accepts the e− from coenzyme Q to become Fe^{2+}. Transfers e− to cytochrome c.

Cytochrome c: Contains **heme group**, in which the Fe^{3+} accepts the e− from complex III to become Fe^{2+}. Transfers e− to complex IV.

Complex IV (cytochrome a): Contains **heme group**, in which the Fe^{3+} accepts e− from cytochrome c to become Fe^{2+}. Transfers e− to O_2, which is combined with hydrogen to **form H$_2$O**. **Inhibited by cyanide**, **CO**, and sodium azide.

Complex V (ATP synthase): Contains a proton channel that allows for protons to cross into the matrix, using the proton gradient energy to **form ATP**. **Inhibited by oligomycin** (blocks H+ channel).

Each NADH yields 2.5 ATP; **each FADH$_2$ yields 1.5 ATP**.

THE CHEMIOSMOTIC HYPOTHESIS

Electron transport causes H+ ions to be pumped from the mitochondrial matrix into the intermembrane space, thereby resulting in the formation of an electrical and pH gradient across the inner mitochondrial membrane. The energy created by the formation of this gradient is then harnessed to form ATP as the protons travel down their gradient into the matrix through ATP synthase channel (complex V). **2, 4-dinitrophenol** acts to uncouple ATP formation from electron transport by dissipating the proton gradient.

Malate shuttle: Oxaloacetate **accepts electrons from NADH** to become malate. Malate then enters the **1** mitochondria, where it is oxidized to form NADH and oxaloacetate.
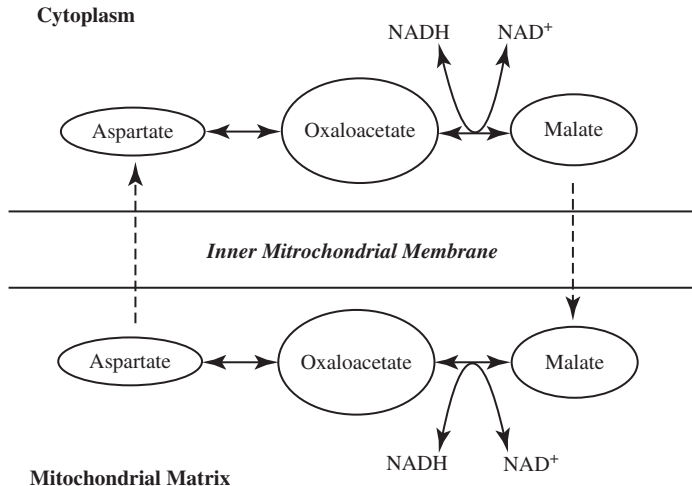
α-**Glycerol phosphate shuttle**: DHAP **accepts electrons from NADH** to become α-Glycerol phosphate. α-Glycerol phosphate enters the mitochondria, where it is oxidized to **form FADH$_2$** and DHAP. Here, only 1.5 ATPs are formed for each cytoplasmic NADH oxidized since FADH$_2$ is produced.

Cytoplasm

NADH   NAD$^+$

Dihydroxyacetone-P ←→ α-Glycerol-P

Inner Mitrochondrial Membrane

Dihydroxyacetone-P ←→ α-Glycerol-P

FADH$_2$ FAD$^+$

Mitochondrial Matrix

4
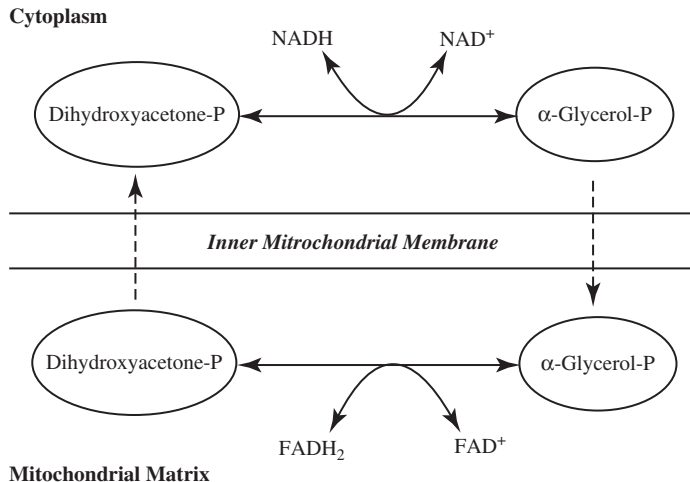
GENERAL CONCEPTS

Glycogenesis
Glycogenolysis
Glycolysis
Pyruvate metabolism
Pentose phosphate pathway
Fructose metabolism
Galactose metabolism
Gluconeogenesis
Cori cycle

DISEASES

Glycogen Storage Diseases
Von Gierke disease
Pompe disease
Cori disease
McArdle disease
Liver phosphorylase deficiency
Andersen disease
Tarui disease

Pyruvate Dehydrogenase Complex Deficiency

Glucose-6-Phosphate Dehydrogenase Deficiency

Disorders of Fructose Metabolism
Essential fructosuria
Fructose intolerance

Disorders of Galactose Metabolism
Classic galactosemia
Galactokinase deficiency

Disorders of Lactose Metabolism
Lactase deficiency

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GLYCOGENESIS
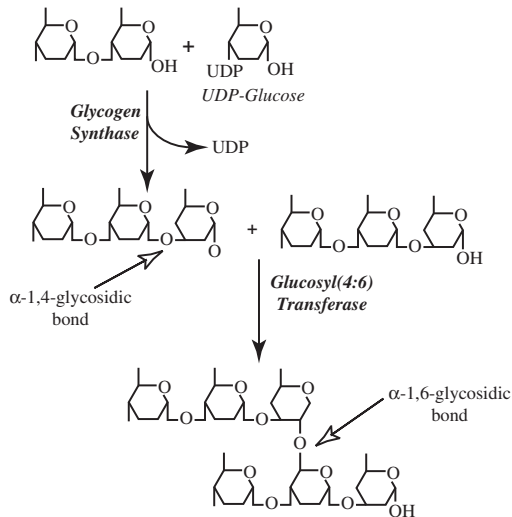
- **Location:** Glycogenesis takes place in the cytoplasm of cells in muscle, liver, and adipose tissue.
- **Substrate:** UDP-glucose.
- **Enzymes:** *Glycogen synthase* adds glucose units to the nonreducing ends of existing chains in α-1,4 linkages. *Glucosyl (4:6) transferase* transfers seven-glucose-residue-long pieces from the nonreducing ends of the chains to create internal branches with α-1,6 linkages.
- **Stimulator:** Insulin stimulates glycogenesis via dephosphorylation and thus activation of *glycogen synthase*.
- **Inhibitors:** Glucagon (liver) and epinephrine (liver and muscle) inhibit glycogenesis via the cAMP protein kinase A phosphorylation cascade, which results in phosphorylation and thus deactivation of glycogen synthase.
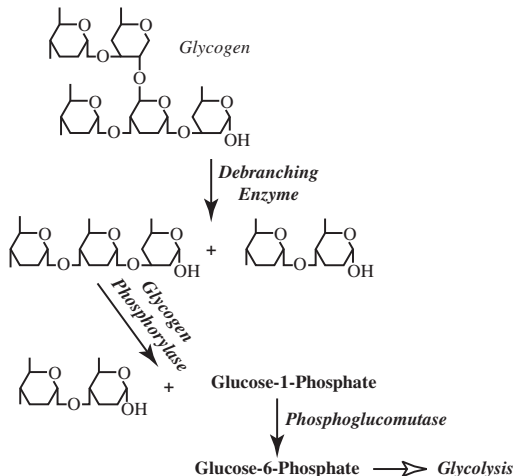
GLYCOGENOLYSIS

- **Location:** Glygogenolysis takes place in the cytoplasm of cells in muscle, liver, and adipose tissue.
- **Substrate:** Glucose-1-phosphate is released from the nonreducing ends of glycogen chains.
- **Enzymes:** *Glycogen phosphorylase* breaks α-1,4 linkages and *debranching enzyme* breaks α-1,6 linkages to release single units of glucose-1-phosphate. *Phosphoglucomutase* converts glucose-1-phosphate to glucose-6-phosphate, which is then shuttled into the glycolytic pathway.
- **Stimulators:** Glucagon (liver) and epinephrine (liver and muscle) stimulates glycogenolysis via the cAMP protein kinase A phosphorylation cascade, which results in the phosphorylation and thus activation of *glycogen phosphorylase*.
- **Inhibitors:** Insulin inhibits glycogenolysis via dephosphorylation and thus results in inactivation of *glycogen phosphorylase*.

Phase I

Glucose $\xrightarrow{\text{Hexokinase or Glucokinase}}$ Glucose-6-phosphate $\xrightleftharpoons{\text{Phosphohexose isomerase}}$ Fructose-6-phosphate $\xrightarrow{\text{Phosphofructokinase 1}}$ Fructose-1,6-bisphosphate

ATP → ADP (Hexokinase step)

ATP → ADP (Phosphofructokinase step)

Aldolase

Dihydroxyacetone phosphate $\xrightleftharpoons{\text{Triose Phosphate Isomerase}}$ Glyceraldehyde-3-phosphate

— —

Phase II

Glyceraldehyde-3-phosphate Dehydrogenase

NAD$^+$ → NADH

2-Phosphoglycerate $\xrightleftharpoons{\text{Phosphoglycerate Mutase}}$ 3-Phosphoglycerate $\xrightleftharpoons{\text{Phosphoglycerate Kinase}}$ 1,3-Bisphosphoglycerate

ADP → ATP

Enolase

Phosphoenolpyruvate $\xrightarrow{\text{Pyruvate Kinase}}$ **Pyruvate**

ADP → ATP

2

GLYCOLYSIS

GENERAL INFORMATION

- **Location:** Glycolysis takes place in the cytoplasm of cells in most body tissues.
- **Phase I:** Energy investment phase.
  - ► Converts one glucose to two G3P.
  - ► Consumes two ATP.
  - ► Includes rate-limiting step of the conversion of fructose-6-phosphate to fructose-1,6-bisphosphonate as catalyzed by *phosphofructokinase*.
- **Phase II:** Energy production phase.
  - ► Converts two G3P to two pyruvate.
  - ► Produces four ATP and two NADH.
- **Diseases:** Deficiency in any of the glycolytic enzymes leads to hemolytic anemia because RBCs depend on glycolysis for energy production and will lyse if their energy demands are not met as a result of faulty glycolysis.

REGULATION OF GLYCOLYSIS

Enzyme	Inhibitors	Activators
Hexokinase (found throughout the body)	Glucose-6-phosphate Glucagon	Insulin
Glucokinase (found in liver & pancreas)	Fructose-6-phosphate Glucagon	Insulin
Phosphofructo-kinase (rate-limiting enzyme)	Glucagon ATP Citrate	Fructose-2,6-bisphophate Insulin AMP
Pyruvate kinase	Glucagon ATP Alanine	Insulin Fructose-1,6-bisphosphonate

The Fates of Pyruvate

Cytosol

Mitochondria

Pyruvate

Pyruvate Decarboxylase

Pyruvate Carboxylase

NADH

NADH
H^+

NAD^+

Ethanol

CO_2

NAD^+
H^+

CO_2

Oxaloacetate

Lactate Dehydrogenase

Pyruvate Dehydrogenase

NAD^+

NADH
H^+

CO_2

Lactate

Acetyl CoA

8
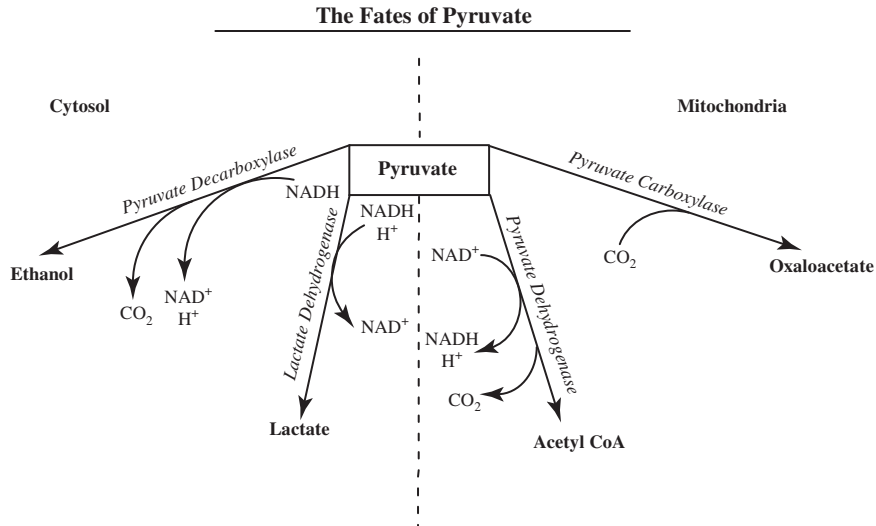
ENZYMES OF PYRUVATE METABOLISM

PYRUVATE DEHYDROGENASE

- **Location:** Mitochondria
- **Cofactors:** Thiamine pyrophosphate; FAD; NAD^+; CoA; lipoic acid
- **Products:** Acetyl CoA; CO_2; NADH
- **Regulation:** Inhibited by acetyl CoA, NADH, and ATP
- **Purpose:** Produce acetyl CoA for entry into citric acid cycle and fatty acid synthesis
- **Reaction:** Irreversible

PYRUVATE CARBOXYLASE

- **Location:** Mitochondria
- **Cofactors:** Biotin
- **Products:** Oxaloacetate
- **Regulation:** Stimulated by acetyl CoA
- **Purpose:** Produce oxaloacetate for use in citric acid cycle and gluconeogenesis
- **Reaction:** Irreversible

PYRUVATE DECARBOXYLASE

- **Location:** Cytosol of yeast and bacteria
- **Cofactors:** Thiamine pyrophosphate
- **Products:** Ethanol; NAD^+; CO_2
- **Purpose:** Replenish NAD^+ stores

LACTATE DEHYDROGENASE

- **Location:** Cytosol
- **Products:** Lactate; NAD^+
- **Regulation:** Stimulated by high NADH-NAD^+ ratio
- **Purpose:** Replenish NAD^+ stores
- **Reaction:** Reversible in liver, heart, and muscle

Glucose-6-phosphate

Glucose-6-Phosphate Dehydrogenase — $NADP^+$ → NADPH

6-Phosphogluconate

— $NADP^+$ → NADPH

Nucleotide Synthesis

Ribulose-5-phosphate — Oxidative Portion

Ribose-5-phosphate ⇄ Xylulose-5-phosphate — Nonoxidative Portion

Transketolase

Sedoheptulose-7-phosphate ⇄ Glyceraldehyde-3-phosphate

Transaldolase

Erythrose-4-phosphate ⇄ Fructose-6-phosphate — Glycolysis

Transketolase

Xylulose-5-phosphate ⇄ Glyceraldehyde-3-phosphate

2

PENTOSE-PHOSPHATE PATHWAY

- **Location:** Cytoplasm of cells of the liver, adrenal cortex, and lactating mammary glands.
- **Substrate:** Glucose-6-phosphate.
- **Oxidative portion:** Irreversible.
  - ▶ Generates two NADPH, which can then be used in fatty acid synthesis and cholesterol synthesis and for maintaining reduced glutathione inside RBCs.
- **Nonoxidative portion:** Reversible.
  - ▶ Generates intermediate molecules (ribose-5-phosphate; glyceraldehyde-3-phosphate; fructose-6-phosphate) for nucleotide synthesis and glycolysis.
- **Regulation**: Key enzyme in the pentose-phosphate pathway is *glucose-6-phosphate dehydrogenase*. Levels of *glucose-6-phosphate dehydrogenase* are increased in the liver and adipose tissue when large amounts of carbohydrates are consumed. *Glucose-6-phosphate dehydrogenase* is stimulated by $NADP^+$ and inhibited by NADPH and by palmitoyl-CoA (part of the fatty acid synthesis pathway).
- **Purpose:** Functions as an alternative route for glucose oxidation that does not directly consume or produce ATP.

Pathway of Fructose Metabolism
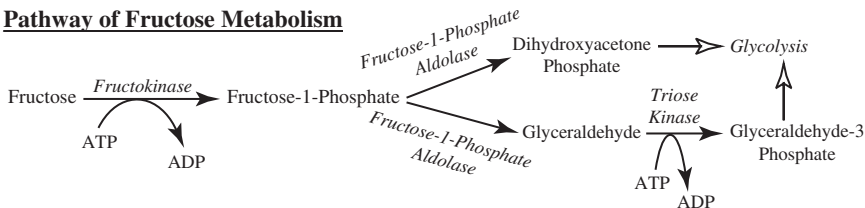
- **Location:** Fructose metabolism takes place primarily in the cytoplasm of cells of the liver.
- **Substrate:** Fructose (which is derived from breakdown of sucrose in small intestine).
- **Purpose:** Allows fructose to be converted into intermediate molecules in the glycolysis pathway. Since this pathway bypasses the rate-limiting step in glycolysis, fructose is metabolized to pyruvate more rapidly than glucose.
- **Results:** Generates 2 intermediate molecules of glycolysis for each molecule of fructose. Requires 2 ATP.

Pathway of Galactose Metabolism
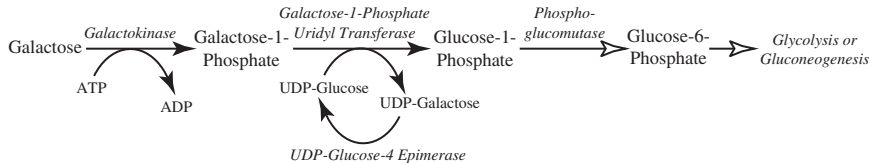
- **Location:** Galactose metabolism takes place primarily in the cytoplasm of cells of the liver.
- **Substrate:** Galactose (which is derived from breakdown of lactose in small intestine).
- **Purpose:** Allows galactose to be converted into intermediate molecules in the glycolysis or gluconeogenesis pathway.
- **Results:** Generates 1 intermediate molecule of glycolysis or gluconeogenesis for each molecule of galactose. Requires 1 ATP.

GLUCONEOGENESIS
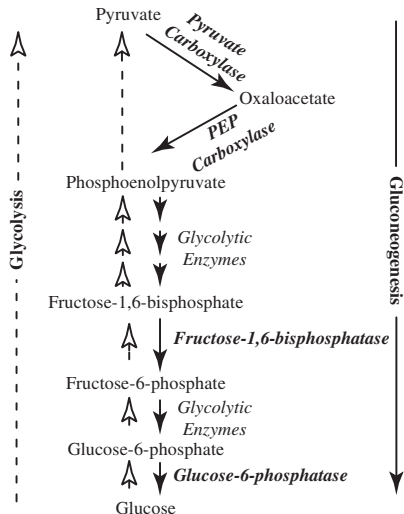
- **Location:** Liver, kidney, and intestine; **not** in skeletal muscle. The first reaction (catalyzed by pyruvate carboxylase) takes place in the mitochondria, whereas the rest of the reactions occur in the cytosol.
- **Requirements to make one glucose:**
  - ► Two pyruvate.
  - ► Four ATP and two GTP.
  - ► Two NADH.
  - ► Six H_2O.
- **Key enzymes:**
  - ► *Pyruvate carboxylase*; requires biotin.
    - ► Activators: acetyl CoA.
    - ► Inhibitors: ADP.
  - ► *PEP carboxylase.*
    - ► Inhibitors: ADP.
  - ► *Fructose-1,6-bisphosphatase.*
    - ► Activators: cAMP; glucagon.
    - ► Inhibitors: AMP; insulin; fructose-2,6-bisphosphate.
  - ► *Glucose-6-phosphatase.*
- **Diseases:** Deficiency in any of the gluconeogenic enzymes leads to hypoglycemia.

CORI CYCLE

| | MUSCLE | Glucose → → Lactate |
| | | |

MUSCLE   Glucose → → Lactate

SERUM   Glucose   Lactate

LIVER   Glucose ← ← Lactate
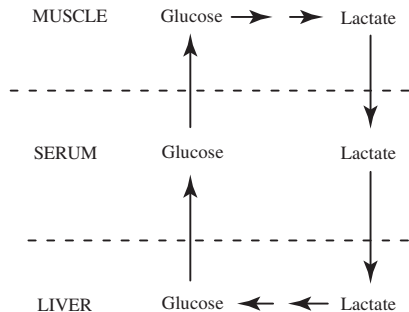
- **Description:** This biochemical cycle describes the transport of substrates, generated by gluconeogenesis, between the liver and the skeletal muscle.
- **Function:** Lactate created by active muscle is taken up by the liver and converted to glucose through gluconeogenesis. The liver releases resynthesized glucose back into the bloodstream for use by the active muscles.
- **Purpose:** This transfer of excess reducing equivalents from the muscle to the liver allows the muscle to function anaerobically, netting two ATP molecules per glycolytic cycle.

A 3-year-old boy is brought to your pediatric clinic because of restlessness and fatigue. The mother is concerned that he becomes fidgety between meals. On physical examination, you notice that the child has very fat cheeks, making his face appear "doll-like," and his abdomen is quite protuberant. The boy is short for his age, and his arms and legs are thin in comparison to his trunk. You order a series of laboratory studies, expecting to find marked hypoglycemia, elevated serum uric acid, and elevated serum lipids. If your hypothesis is correct, you believe that the child will benefit from frequent meals with cornstarch supplementation and restriction of fructose and galactose in his diet.

Von Gierke Disease (Type I)

Biochemical Defect	An **autosomal recessive** disorder that results in a **defective glucose-6-phosphatase** enzyme in the liver, kidney, and intestinal mucosa.
Pathophysiology	**Glucose-6-phosphatase is required for conversion of G6P into glucose during gluconeogenesis.** Defective G6P results in the buildup of G6P, thereby resulting in **accumulation of structurally normal glycogen in the liver** and kidney, leading to hepatomegaly. Patients are also deficient in the production of glucose from gluconeogenesis and thus become susceptible to fasting hypoglycemia resulting from glucose deficiency.
Clinical Manifestations	Affected patients present at 3-4 months of age with **hepatomegaly** or **hypoglycemia**. Patients often have "**doll-like facies**" (fat cheeks), thin extremities, short stature, and a protuberant abdomen resulting from hepatomegaly. *Lab findings:* Hypoglycemia; lactic acidosis; **hyperuricemia**; hyperlipidemia.
Treatment	Continuous nasogastric infusion of glucose or oral administration of **cornstarch**; restricted dietary intake of fructose and galactose because these molecules cannot be converted to glucose; dietary supplements of multivitamins and calcium; allopurinol to lower levels of uric acid.
Notes	The hepatic glycogen storage diseases that are characterized by hepatomegaly and hypoglycemia include **Von Gierke (type I)** as well as **liver phosphorylase deficiency** (Hers disease, **type VI**) and **phosphorylase kinase deficiency (type IX)**.

A 5-year-old girl is brought to your pediatric clinic for a routine physical. On examination, you notice that the child has not met her expected growth milestones. You also note evidence of hepatomegaly on examination. A series of initial laboratory studies reveal mild hypoglycemia, mildly elevated liver enzymes, and mild hyperlipidemia. You explain to the mother that you suspect that her daughter has a deficiency of a specific enzyme that is involved in glycogen metabolism, and you reassure her that this abnormality will likely resolve by puberty.

Liver Phosphorylase Deficiency (Hers Disease) (Type VI)

Biochemical Defect	An **autosomal recessive** disorder that results in a **defective glycogen phosphorylase** enzyme in the liver.
Pathophysiology	Glycogen phosphorylase acts to break down α-1,4 glycosidic bonds within molecules of glycogen, thereby resulting in the release of glucose-1-phosphate units, which are subsequently converted to G6P and entered into the glycolysis or gluconeogenesis pathway. **Defective glycogen phosphorylase results in the failure to efficiently breakdown glycogen**, thereby resulting in **accumulation of glycogen in the liver**, leading to hepatomegaly. Patients are also deficient in the production of glucose from gluconeogenesis and thus become susceptible to fasting hypoglycemia resulting from glucose deficiency.
Clinical Manifestations	Affected patients present in early childhood with **hepatomegaly**, **mild hypoglycemia**, and growth retardation. Patients often also have **muscle weakness**. Rare patients may have variants that involve neuropathy, myopathy, cirrhosis, or cardiomyopathy. *Lab findings:* Hypoglycemia; mildly elevated liver enzymes; hyperlipidemia.
Treatment and Prognosis	High carbohydrate diet and frequent meals to avoid hypoglycemia. This disease usually takes a mild course with most clinical and biochemical abnormalities resolving by adolescence.
Notes	**Phosphorylase kinase b deficiency (**formerly known as glycogen storage disease **type IX and VIII)** and **cAMP-dependent protein kinase deficiency** (formerly known as glycogen storage disease **type X**) are now included with glycogen storage disease type VI and present similarly to type VI disease.

A 3-month-old girl is brought to your pediatric clinic because she is not feeding well and has poor weight gain. On physical examination, you find that she has a large tongue and mild hepatomegaly. She is also significantly flaccid and hypotonic. Fearing an autosomal recessive glycogen storage disease, you order an ECG, which shows a short PR interval and a wide QRS interval. You order a series of serum studies, expecting to see elevated creatine kinase, aspartate transaminase, and lactate dehydrogenase. You fear that the child has a poor prognosis, and will likely suffer cardiopulmonary failure and death before her first birthday.

Pompe Disease (Type II)

Biochemical Defect	An **autosomal recessive** disorder caused by a deficiency of **lysosomal acid α-1, 4-glucosidase**.
Pathophysiology	**Lysosomal acid α-1,4-glucosidase** (acid maltase) **is an enzyme responsible for the degradation of glycogen in lysosomal vacuoles**. If lysosomal acid α-1,4-glucosidase is defective, there is resulting accumulation of lysosomal glycogen in the skeletal muscle, cardiac muscle, liver, and kidneys, which leads to myopathies, cardiomyopathy, and hepatic dysfunction.
Clinical Manifestations	There are several forms of Pompe disease. In *infantile-onset disease* (most severe), patients present with hypertrophic **cardiomyopathy**, hypotonia and myopathy, failure to thrive, **macroglossia** (large tongue), and hepatomegaly. Death occurs by 1 year of age. The *juvenile form* typically presents as delayed motor milestones and difficulty in walking followed by swallowing difficulties and proximal muscle weakness with death by the third decade. The *adult form* presents as a slowly progressive proximal muscle weakness with truncal involvement. There is no cardiac involvement in the juvenile or adult form. *Lab findings:* **Elevated serum creatine kinase**; **elevated aspartate transaminase**; elevated lactate dehydrogenase; muscle biopsy shows vacuoles staining positively for glycogen.
Treatment	No effective treatment for the infantile form. High-protein diet for the juvenile and adult forms. Ventilatory support as needed.
Notes	Other glycogenosis diseases are characterized by cytoplasmic accumulation of glycogen, whereas Pompe disease is the only glycogenosis disease that is characterized by lysosomal accumulation of glycogen.

A 7-year-old boy presents to your pediatric clinic complaining of muscle weakness of 1-year duration. His parents are concerned because he gets tired very quickly when playing with his classmates in the yard. He is an only child, and his mother's pregnancy was full-term with no complications. On physical examination, you note that he has moderate hepatosplenomegaly, is of short stature, and has marked muscle wasting. At his last clinic visit, serum studies revealed hypoglycemia, hyperlipidemia, a fasting ketosis, and elevated liver transaminases. You consider the possibility of a glycogen storage disease and suggest a high-carbohydrate, high-protein diet while awaiting definitive DNA-based analyses.

Cori Disease (Type III)

Biochemical Defect	An **autosomal recessive** disorder that is caused by a deficiency of **glycogen debranching enzyme, α-1,6-glucosidase**.
Pathophysiology	**Glycogen debranching enzyme, α-1,6-glucosidase**, is an enzyme that **aids in glycogen degradation by breaking α-1,6 bonds**. When this debranching enzyme is defective, glycogen breakdown is incomplete, and abnormal glycogen with short outer chains accumulates in the liver and muscle, leading to hepatomegaly. Hypoglycemia results from ineffective glycogen breakdown.
Clinical Manifestations	Patients present with **hepatosplenomegaly**, **hypoglycemia**, **hyperlipidemia**, and growth retardation. Other symptoms include short stature, **skeletal myopathy** (progressive muscle wasting), and **cardiomyopathy**. Hepatomegaly improves with age and disappears after puberty.
	Lab findings: Hypoglycemia; hyperlipidemia; elevated liver enzymes in childhood; fasting **ketosis**.
Treatment	High-carbohydrate meals with **cornstarch** or nocturnal gastric drip feedings for hypoglycemia. High-protein diet during the day plus overnight protein infusion for myopathy.
Notes	Cori disease is of high prevalence in non-Ashkenazi Jews of North African descent.

An 8-month-old boy is brought to your office by his parents, who are concerned that he is not feeding well. Examination reveals a listless child, who is small for his age. You also notice an enlarged liver and spleen on abdominal examination as well as an enlarged heart on chest x-ray. An electrocardiogram shows frequent premature ventricular contractions. When laboratory testing reveals a deficiency in the glycogen branching enzyme, you inform the parents that their son is afflicted with an autosomal recessive disorder of metabolism and recommend a consultation with a pediatric hepatologist.

Andersen Disease (Type IV)

Biochemical Defect	An **autosomal recessive** disorder that is caused by a deficiency of the **glycogen branching enzyme**, **transglucosidase**.
Pathophysiology	**Glycogen branching enzyme**, **transglucosidase**, is an enzyme that **aids in the production of glycogen**. When this enzyme is defective, long, unbranched glucose chains are formed and result in the deposition of this defective glycogen in the liver, heart, and nervous system.
Clinical Manifestations	Patients present in infancy with **hepatosplenomegaly** and **failure to thrive**. End-organ damage can lead to liver failure and cirrhosis. There are some rare neuromuscular variants, which present with muscle weakness and wasting. *Lab findings:* Elevated liver enzymes in childhood.
Treatment and Prognosis	Symptomatic treatment of liver failure, including possible liver transplantation. Prognosis is poor.
Notes	

A 22-year-old man presents to your ambulatory clinic complaining of painful muscle cramps when walking eight flights of stairs to his new apartment. On further investigation, you learn that he also experiences these severe muscle cramps after lifting weights in the gym. On several occasions, he has had reddish-purple urine after exercising. You suspect that this patient may suffer from an autosomal recessive glycogen storage disease, and you obtain a serum sample to test for elevated serum creatine kinase at rest. While awaiting the test results, you suggest that the patient avoid strenuous exercise and eat a high-protein diet.

McArdle Disease (Type V)

Biochemical Defect	An **autosomal recessive** disorder caused by a deficiency of **muscle glycogen phosphorylase**.
Pathophysiology	Muscle glycogen phosphorylase is responsible for **breaking the α-1,4 linkages of glycogen** in muscle. Deficiency of muscle phosphorylase results in deficient glycogen breakdown, leading to glycogen accumulation in muscle. Without effective glycogen breakdown, the body has to use other means to generate ATP (often through the breakdown of muscle fibers), thereby resulting in eventual muscle degradation.
Clinical Manifestations	Patients present in adulthood with **exercise intolerance** and **muscle cramps**. Symptoms are triggered by brief exercise of great intensity (eg, sprinting) or less intense but sustained activity (eg, climbing stairs). Half of patients report **burgundy-colored urine** after exercise (myoglobinuria as caused by muscle breakdown). *Lab findings:* **Elevated serum creatine kinase even at rest**.
Treatment	Avoid strenuous exercise. Augment exercise tolerance by aerobic training or by prior ingestion of glucose or sucrose. A high-protein diet may increase exercise endurance.
Notes	

A 6-year-old girl is brought to an urgent care clinic by her parents, complaining of severe muscle cramps in both legs after her weekly soccer game. Upon speaking further with the patient, you discover that she has been suffering from muscle cramps as well as nausea after every soccer practice for the last year. Her mother also reports that the patient's urine is reddish in color at times. When laboratory studies demonstrate evidence of hyperuricemia, hemolytic anemia, and elevated creatine kinase levels, you begin to suspect that the patient may be suffering from a deficiency of an enzyme in the glycolysis pathway.

Tarui Disease (Type VII)

Biochemical Defect	An **autosomal recessive** disorder caused by a deficiency of **muscle phosphofructokinase**.
Pathophysiology	Phosphofructokinase **catalyzes the conversion of fructose-6-phosphate to fructose-1, 6-diphosphate during glycolysis**. When phosphofructokinase is absent, glycolysis is significantly impaired.
Clinical Manifestations	Patients present in childhood with **exercise intolerance** and **muscle cramps and weakness after exercise**. Many patients report **burgundy-colored urine** after exercise (myoglobinuria as caused by muscle breakdown) as well as nausea and vomiting. *Lab findings:* Hyperuricemia that is worsened with exercise; hemolytic anemia; **elevated creatine kinase** levels.
Treatment and Prognosis	Avoid strenuous exercise. Consider a high-protein diet. Usually does not progress to severe disability, although a rare infantile form has been reported and is usually fatal.
Notes	Tarui disease is more prevalent among people of Ashkenazi Jewish descent.

A 4-year-old boy is brought to your pediatric clinic because his mother is concerned about a possible developmental delay. On physical examination, you find the patient to have marked hypotonia, an ataxic gait, and choreoathetosis. Ophthalmologic examination reveals poor visual tracking, grossly disconjugate eye movements, and poor pupillary response bilaterally. You order a series of laboratory tests, which reveal the presence of a lactic acidosis. You immediately become concerned that this patient may suffer from a defect of carbohydrate metabolism, and you decide to check serum levels of pyruvate to confirm your suspicion.

Pyruvate Dehydrogenase Complex Deficiency

Biochemical Defect	An **autosomal recessive** disorder that is caused by a **deficiency in the pyruvate dehydrogenase complex**.
Pathophysiology	The pyruvate dehydrogenase complex is responsible for converting pyruvate to acetyl CoA during carbohydrate metabolism. Because acetyl CoA is necessary for citrate production, a deficiency in this enzymatic complex will **limit citrate production**. Since citrate is the first substrate in the **citric acid cycle**, the cycle **cannot proceed**, and an energy deficit develops in the CNS, leading to neurologic dysfunction. A backup of substrates also develops (including lactate and pyruvate) and results in a lactic acidosis.
Clinical Manifestations	Progressive **neurologic symptoms** usually start in infancy but may be evident at birth or in late childhood. These symptoms may include developmental delay, intermittent **ataxia**, poor muscle tone, abnormal eye movements, and seizures. It is often exacerbated in alcoholics because of **thiamine deficiency**.
	Lab findings: High blood **lactate and pyruvate** levels; **lactic acidosis**.
Treatment	Increase the intake of high-fat foods with **ketogenic nutrients**.
Notes	**Lysine and leucine** are the two purely ketogenic amino acids, the catabolism of which leads to products that can be used in the citric acid cycle without having to be routed through the pyruvate dehydrogenase complex first.

A 36-year-old Mediterranean man presents to your clinic with increased fatigue and weakness of 2 days duration. He was recently tested for tuberculosis exposure and was PPD positive with a normal chest x-ray film. He just started anti-TB prophylaxis medications the week before. On physical examination, he is tachycardic, appears jaundiced, and has mild splenomegaly. You order serum studies, which show low hemoglobin, low hematocrit, and elevated indirect bilirubin. You begin to suspect that this patient suffers from an X-linked recessive disorder triggered by his current TB prophylaxis, and you decide to consult an infectious disease specialist about alternative regimens that will not cause his current symptoms.

Glucose-6-Phosphate Dehydrogenase Deficiency

Genetic Defect	An **X-linked recessive** disorder caused by a deficiency in **G6PD**.
Pathophysiology	**G6PD catalyzes the oxidation of glucose-6-phosphate to 6-phosphogluconate in the HMP shunt pathway while concomitantly reducing NADP$^+$ to NADPH.** Deficiency in G6PD leads to decreased NADPH, a required cofactor in many biosynthetic reactions. **NADPH maintains glutathione in its reduced form**, which, in turn, acts as a scavenger for dangerous oxidative metabolites in the cell and converts harmful hydrogen peroxide to water. Patients with G6PD deficiency have increased hemolysis of red blood cells, which rely heavily on G6PD activity as the only source of NADPH for protecting against oxidative stresses.
Clinical Manifestations	Most patients are asymptomatic until undergoing an oxidative stress (causes include **fava beans**, sulfamethoxazole, primaquine, anti-TB drugs), which results in hemolytic anemia. Patients may also report a history of jaundice, gallstones (from increased hemolysis), fatigue, and **splenomegaly**. *Lab findings:* Normocytic, normochromic **anemia**; hemoglobinemia; indirect bilirubinemia; decreased serum haptoglobin levels; peripheral smear shows spherocytes and **Heinz bodies** (hemoglobin precipitates within red blood cells).
Treatment	Discontinuation of precipitating agent; oxygen and bed rest.
Notes	G6PD deficiency is more prevalent among African-Americans and those of Mediterranean descent and has been associated with **protection against malaria**.

A 14-year-old boy presents for a routine physical examination to participate in high school athletics. He has no known medical history, and his family history is significant for type 2 diabetes in a maternal uncle. His physical examination is completely unremarkable. His laboratory studies are within normal limits except for positive reducing sugar found in both serum and urine. Nevertheless, his blood glucose level was normal at 85. When you inform the patient about this finding, he is concerned about possible diabetes. You assure him that it is unlikely and that further testing will most likely show a benign condition for which he needs no treatment.

Essential Fructosuria

Biochemical Defect	An **autosomal recessive** disorder caused by a **deficiency in fructokinase**.
Pathophysiology	**Fructokinase converts fructose to fructose-1-phosphate** in the fructose metabolism pathway. The deficiency of fructokinase activity in the liver and intestine significantly reduces the capacity to assimilate fructose into cells.
Clinical Manifestations	Patients are usually **asymptomatic**, and the disease comes to light as an incidental finding.
	Lab findings: Positive reducing sugar in the blood and urine after meals rich in fructose.
Treatment	No treatment is necessary.
Notes	Essential fructosuria may be confused with diabetes mellitus if the nature of the reducing sugar in the urine is not defined.

A 6-month-old girl is brought to your pediatric clinic because her mother noticed that the baby has seemed lethargic and irritable for the last several weeks. The mother had just begun feeding the baby fruit juices several weeks before this visit. On physical examination, the child is slow in her movements, mildly jaundiced, and small for her age. She also has mild hepatomegaly. You are concerned that the symptoms started after the ingestion of fruit juices, and you order serum and urine studies, which you suspect will show hypoglycemia and fructosemia. While you await the results of the laboratory tests, you tell the mother to stop giving the child any fruit juices in her diet because you believe that the patient may be suffering from an inherited enzyme deficiency that alters her metabolism of certain carbohydrates.

Fructose Intolerance

Biochemical Defect	An **autosomal recessive** disorder caused by a deficiency of **fructose-1,6-bisphosphate aldolase B** in the liver, kidney, and intestine.
Pathophysiology	**Fructose-1,6-bisphosphate aldolase catalyzes the hydrolysis of fructose-1-phosphate and fructose-1,6-bisphosphate** into three-carbon sugars (dihydroxyacetone phosphate, glyceraldehyde-3-phosphate, glyceraldehyde) in the fructose metabolism pathway. Deficiency of this enzyme causes the rapid accumulation of fructose-1-phosphate. **Fructose-1-phosphate has a toxic effect on the liver**, impeding hepatic function (eg, impaired glycolysis, glycogenolysis, and gluconeogenesis).
Clinical Manifestations	Patients are **asymptomatic until fructose or sucrose is ingested** (usually from fruit, fruit juice, table sugar, or sweetened cereal). Clinical manifestations include lethargy, irritability, jaundice, **hepatomegaly**, vomiting, and convulsions. Complications include cirrhosis and kidney failure. *Lab findings:* Hypoglycemia; fructosemia; prolonged clotting time; hypoalbuminemia; elevated bilirubin and transaminases.
Treatment	Dietary elimination of all sources of sucrose, fructose, and sorbitol.
Notes	

A 1-month-old foreign-born boy is brought to your pediatric clinic by his mother, who tells you that the child is vomiting after feedings and has been gaining weight poorly. His mother did not receive proper prenatal care, and the child did not have screening tests before or after delivery. On physical examination, the infant is small for his age, appears jaundiced, and has mild hepatomegaly. While normally you would think of possible intestinal obstruction, you notice on physical examination that the child's lenses are clouded as though he were developing cataracts. You order serum and urine studies, specifically looking for hypoglycemia, galactosuria, and aminoaciduria. You believe that the child is suffering from a deficiency of galactose-1-phosphate uridyl transferase and that the patient's diet should be limited in intake of milk and other foods rich in lactose or galactose.

Classic Galactosemia

Biochemical Defect	An **autosomal recessive** disorder caused by a deficiency of **galactose-1-phosphate uridyl transferase**.
Pathophysiology	**Galactose-1-phosphate uridyl transferase aids in the conversion of galactose-1-phosphate into glucose-1-phosphate** in the galactose metabolism pathway. A deficiency of galactose-1-phosphate uridyl transferase results in the buildup of galactose-1-phosphate, galactose, and galactitol. These substances are toxic to the parenchymal cells of the kidney, liver, lens, spleen, and brain.
Clinical Manifestations	Infants present with several nonspecific findings, including lethargy, irritability, feeding difficulties, poor weight gain, jaundice, **hepatomegaly**, ascites, **splenomegaly**, convulsions, **cataracts**, and **mental retardation**.
	Lab findings: Hypoglycemia; aminoaciduria; galactosuria; markedly reduced galactose-1-phosphate uridyl transferase activity.
Treatment	Elimination of galactose from the diet.
Notes	Neonates are routinely screened for galactosemia. The test consists of a demonstration of a reducing substance in urine specimens collected while the patient is receiving milk or formula containing lactose.

A 2-year-old foreign-born girl is brought to your pediatric clinic for a routine checkup. Her mother tells you that the child has not seen a doctor since she was born. The child's physical examination is normal, except for clouding of her eye lenses consistent with cataracts. She is of normal height and weight and has met all of her developmental milestones up to this point. While you ask the nurse to draw up a battery of immunizations, you also ask for serum studies, including a serum galactose level. While you await the results of the laboratory testing, you tell the parents to restrict galactose in the child's diet and reassure them that cataracts are the only manifestations of their child's hereditary disorder.

Galactokinase Deficiency

Biochemical Defect	A benign autosomal recessive disorder caused by deficiency of **galactokinase**.
Pathophysiology	**Galactokinase is required to phosphorylate galactose into galactose-1-phosphate** during galactose metabolism. When galactokinase is deficient, galactose builds up. In the lens of the eye, galactose reductase and aldose reductase convert this excess galactose into galactitol. **Galactitol causes the entry of water into the eye** by osmosis, leads to the **development of cataracts**.
Clinical Manifestations	In contrast to the multiple organ systems affected in classic galactosemia, infant **cataracts** are usually the sole manifestation of galactokinase deficiency.
	Lab findings: Elevated blood galactose levels.
Treatment	Dietary restriction of galactose.
Notes	

A 14-year-old Asian-American boy presents to your pediatric clinic concerned about diarrhea that has persisted for more than 1 month. He reports that the diarrhea occurs about 30 minutes after he eats his bowl of cereal with milk each morning. He states that the stools are bulky and frothy, but there is no gross blood. He also has a lot of gas and bloating after eating breakfast. He reports resolution of symptoms for the remainder of the day. On further questioning, the patient does not eat yogurt, ice cream, or any other dairy products throughout the day. You believe that the patient has a common enzyme deficiency and that his intestinal lining is not absorbing an ingested sugar properly. You suggest that he try a commercial enzyme substitute with each bowl of cereal or a different brand of milk that has the enzymes necessary for its digestion.

Lactase Deficiency

Biochemical Defect	Caused by reduced genetic expression of the enzyme **lactase-**phlorhizin hydrolase.
Pathophysiology	**Lactase**-phlorhizin hydrolase is involved in the rate-limiting step of lactose digestion. Lactose is hydrolyzed by intestinal lactase to glucose and galactose on the microvillus membrane of the intestinal adsorptive cells. Lactose that is not absorbed by the small bowel, because of the absence or deficiency of the lactase enzyme, is passed rapidly into the colon, thereby leading to the entry of water into the colon by osmosis and the development of diarrhea.
Clinical Manifestations	After ingestion of lactose-containing products (eg, milk), patients have **diarrhea**, **abdominal pain**, and **flatulence**. Stools are often bulky, frothy, and watery.
Treatment	Reduced dietary lactose intake; commercial **enzyme substitute**; alternative calcium and nutrient sources.
Notes	This common problem has a prevalence of 10%-20% among Caucasians, 80%-95% among Native Americans, 65%-75% among African-Americans, 90% among Asian-Americans, and 50% among Hispanics.

LIPID METABOLISM

GENERAL CONCEPTS

Fatty acid synthesis
Citrate shuttle
Fatty acid oxidation
Carnitine shuttle
Lipid transport
Lipoprotein and apolipoprotein function
Cholesterol synthesis
Sphingolipid synthesis
Sphingolipid degradation
Phospholipid synthesis

DISEASES

Inherited Hyperlipidemias

Familial hypercholesterolemia
Hypertriglyceridemia
Familial hyperchylomicronemia
Mixed hypertriglyceridemia
Combined hypercholesterolemia and
hypertriglyceridemia
Dysbetalipoproteinemia

Sphingolipid Storage Diseases

Hurler disease
Hunter disease
Sanfilippo syndrome
Sly syndrome
Tay-Sachs disease
Sandhoff disease
Fabry disease
Gaucher disease
Niemann-Pick disease
Farber disease
I-cell disease
Krabbe disease
Metachromatic leukodystrophy

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Malonyl Moiety — Fatty Acid Synthase Complex — $SCO[CH_2]_nCH_3$

CO_2

CoA

NADPH

NADP$^+$

Malonyl CoA Transferase

H_2O

NADPH

NADP$^+$

Malonyl CoA

Acetyl CoA Carboxylase with Biotin

ADP

ATP

Acetyl CoA

Fatty Acid Synthase Complex — $SCO[CH_2]_{(n+1)}CH_3$

After 7 Cycles — Palmitate (16C)

3
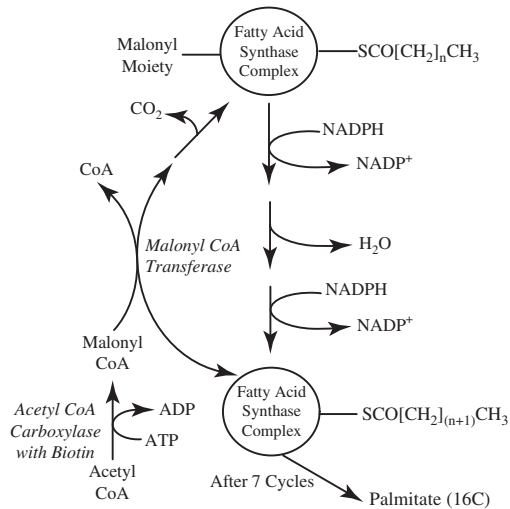
FATTY ACID SYNTHESIS

- **Location:** Fatty acid synthesis takes place in the cytosol and is carried out by a multienzyme complex called FAS.
- **Substrates** (to make one palmitate):
  - ► 8 acetyl CoA
  - ► 14 NADPH
  - ► 7 ATP
- **Products:**
  - ► 1 molecule of palmitate (16-carbon fatty acid)
  - ► 7 H_2O
- **Pathway:** Acetyl CoA is converted to malonyl CoA by *acetyl CoA carboxylase.* Malonyl CoA is transferred to FAS. Through a series of condensation, reduction, and dehydration reactions, the two carbons of malonyl CoA are added to the growing fatty acyl moiety on FAS. FAS is then recharged with another malonyl moiety, and the cycle continues. Each turn of the cycle results in the addition of a two-carbon group to the fatty acid moiety as well as the use of one ATP, one acetyl CoA, and two NADPH. When the cycle has completed seven turns, the 16-carbon fatty acid (palmitate) is released from FAS.
- **Important enzymes:**
  - ► *Acetyl CoA carboxylase*: Transforms acetyl CoA to malonyl CoA with the use of biotin and bicarbonate as cofactors. Requires one ATP.
  - ► *Malonyl CoA transferase*: Transfers the malonyl CoA molecule to FAS.
  - ► *FAS*: This collection of enzymes transfers the two carbons of malonyl CoA to the carboxyl end of the growing chain of the fatty acyl moiety. Requires two NADPH.
- **Activators: Insulin** stimulates fatty acid synthesis by dephosphorylating and, therefore, activating *acetyl CoA carboxylase*.
- **Inhibitors: Glucagon** and **epinephrine** inhibit fatty acid synthesis by inactivation of *acetyl CoA carboxylase*.

Fatty Acid
$R[CH_2]_nCO\text{--}CoA$

Acyl CoA Dehydrogenase — FAD → $FADH_2$

Enoyl CoA Hydratase — H_2O

3-Hydroxy-Acyl CoA Dehydrogenase — NAD^+ → NADH

Acyl CoA Acyltransferase — CoA → **Acetyl-CoA**

$R[CH_2]_{n-1}CO\text{--}CoA$

Electron Transport Chain

$NADH + FADH_2$

Citric Acid Cycle

3
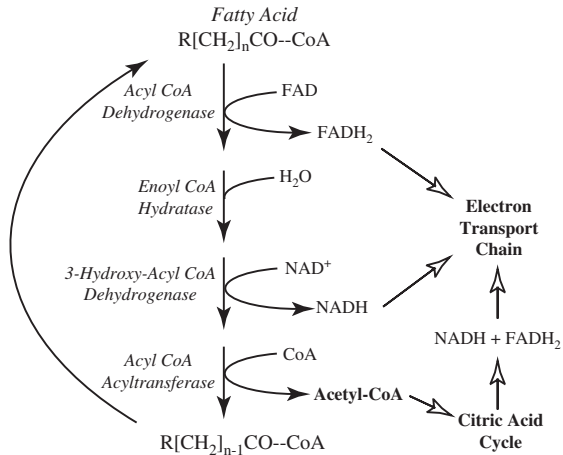
FATTY ACID OXIDATION

- **Location:** β-Oxidation takes place in the mitochondria.
- **Substrates:** Free fatty acids; H_2O.
- **Products:** One acetyl CoA, one NADH, and one $FADH_2$ for every removal of a two-carbon group from the fatty acid chain.
- **Pathway:** In the mitochondria, the fatty acid undergoes a series of oxidation and hydration reactions, which results in the removal of a two-carbon group (in the form of acetyl CoA) from the fatty acid chain as well as the formation of one NADH and one $FADH_2$, which enter the electron transport chain to form five ATP. The acetyl CoA formed will enter the citric acid cycle and then the electron transport chain, leading to the formation of another 12 ATP. The cycle continues, with each turn of the cycle removing another two-carbon group, until the formerly long-chain fatty acid has been reduced to acetyl CoA or propionyl CoA. Propionyl CoA can be converted to succinyl CoA through three enzymatic events, which require biotin and vitamin B_{12} as cofactors, and then succinyl CoA can enter the citric acid cycle.
- **Important enzymes:**
  - ► *Acyl CoA dehydrogenase*: Forms a double bond between the α and β carbon atoms in the fatty acid chain. Produces one $FADH_2$.
  - ► *Enoyl CoA hydratase*: Incorporates a water molecule into the fatty acid chain, thereby breaking the double bond between the α and β carbon atoms.
  - ► *3-Hydroxy-acyl CoA dehydrogenase*: Dehydrogenates the fatty acid chain again, thereby forming a double bond between the β carbon and the oxygen molecule. Produces one NADPH.
  - ► *Acyl CoA acyltransferase*: Cleaves acetyl CoA off the end of the fatty acid chain with the addition of CoA to the β carbon.
- **Activators: Epinephrine** stimulates β-oxidation by activating a cAMP–dependent protein kinase, which leads to the phosphorylation and thus activation of *HSL*. When activated, HSL releases fatty acids and glycerol from adipose tissue for β-oxidation.
- **Inhibitors: Insulin** inhibits β-oxidation by dephosphorylating HSL and thus inhibiting the release of fatty acids from adipose tissue.

Cytosol | Mitochondrial Matrix
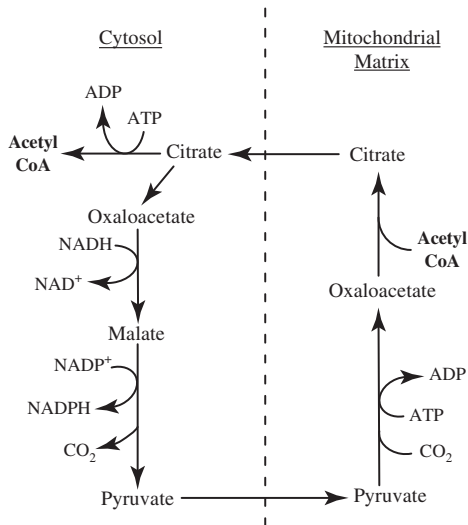
- **Description:** The citrate-malate-pyruvate shuttle functions to transport acetyl CoA from the mitochondria into the cytosol for use during fatty acid synthesis.
- **Function:** Acetyl CoA combines with oxaloacetate to form citrate, which then crosses the mitochondrial membrane. Once in the cytosol, citrate is broken down to reform acetyl CoA and oxaloacetate. Oxaloacetate is then transported back into the mitochondria in the form of pyruvate. During this process, two ATP and one NADH are used, while one NADPH is formed.
- **Purpose:** Fatty acid synthesis takes place in the cytosol and uses acetyl CoA as a substrate. Because acetyl CoA is primarily formed in the mitochondria (usually by *pyruvate dehydrogenase*), the citrate shuttle is necessary to transport acetyl CoA into the cytosol, where fatty acid synthesis occurs. Furthermore, the citrate shuttle produces NADPH, which is subsequently used in the process of fatty acid synthesis.

CARNITINE SHUTTLE
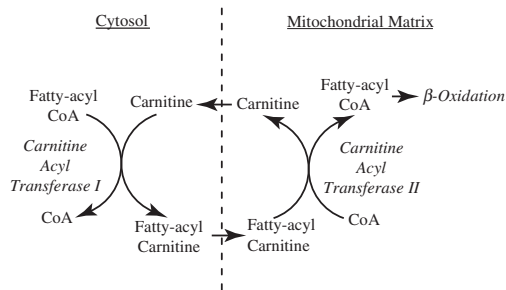
- **Description:** The carnitine transport system shuttles long-chain fatty acids from the cytosol into the mitochondria.
- **Function:** The fatty acyl chain is enzymatically attached to carnitine in the cytosol via *carnitine acyl transferase I*, and then shuttled across the mitochondrial membrane. Once inside the mitochondria, the fatty acids are released from carnitine by the enzyme, *carnitine acyl transferase II*.
- **Purpose:** Because long-chain fatty acids are unable to enter the mitochondria, the carnitine transport system allows for the movement of fatty acids in the mitochondrial matrix where fatty acid oxidation occurs.
- **Diseases:** Inherited defects in the carnitine shuttle present with hypoglycemia, muscle pain, and muscle atrophy because of the accumulation of fat in muscle tissue. Affected infants benefit from being fed fat with medium-chain triacylglycerols (eg, butter fat) because medium-sized fatty acids can bypass the carnitine shuttle.
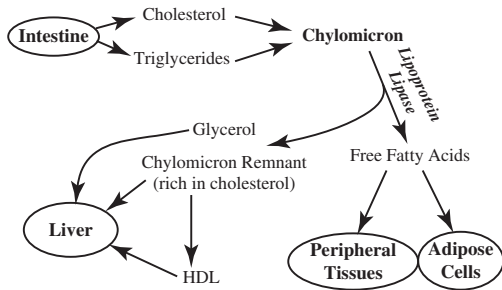
- **Pathway:** Dietary cholesterol and triglycerides are absorbed from the intestinal lumen into the mucosal cells of the small intestine, where they are incorporated into chylomicrons and released into the bloodstream. Chylomicrons are degraded by LPL, which is present on the capillary endothelium of muscle and adipose tissue, into glycerol, free fatty acids, and a chylomicron remnant. The free fatty acids are either stored in adipose cells or taken up by muscle or other peripheral tissues. The glycerol is transferred to the liver. The remnant of the chylomicron, which is rich in cholesterol molecules, is then either directly taken up by the liver through endocytosis or transported to the liver by HDL.
- **Fates of dietary cholesterol and triglycerides:**
  - ▶ **Free fatty acids:** Either used as fuel in muscle or other peripheral tissues or stored as triacylglycerols in adipose tissue.
  - ▶ **Glycerol:** Transferred to the liver where it is used in glucose synthesis.
  - ▶ **Chylomicron remnant:** Absorbed by the liver where the cholesterol within the remnant is either converted to bile acids or transformed to VLDLs.
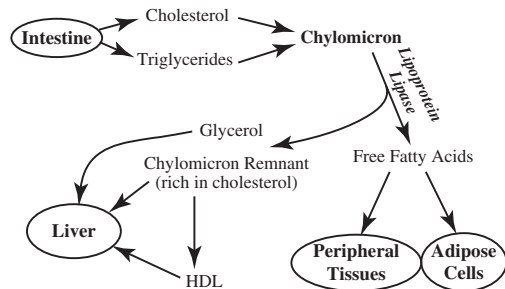
- **Pathway:** The liver secretes VLDL, which is then broken down into free fatty acids and LDL by *lipoprotein lipase*. The free fatty acids are taken up by the peripheral tissues for fuel or are stored in the adipose cells. LDL is absorbed either by the liver or the peripheral tissues through an **LDL receptor**. If absorbed by the peripheral tissues, LDL is degraded intracellularly into cholesterol and cholesterol esters, which are then released into the bloodstream. The cholesterol esters are picked up by HDL with the help of the *cholesterol ester transfer protein* and transported out of the bloodstream and back into the liver.
- **Fates of products of endogenous lipid secretion:**
  - ▸ **VLDL:** Broken down to free fatty acids and LDL by *lipoprotein lipase*.
  - ▸ **LDL:** Absorbed by liver or peripheral tissues via LDL receptors. Once in liver, LDL reduces the synthesis of cellular cholesterol by inhibiting *HMG coenzyme A reductase*. Intracellular LDL also decreases the synthesis of LDL receptors, thereby decreasing LDL uptake into the liver and other tissues and thereby increasing LDL levels in the bloodstream.
  - ▸ **Cholesterol esters:** Attached to HDL by *cholesterol ester transfer protein* and transported back to liver.

LIPOPROTEIN FUNCTION

Lipoprotein	Source	Function	Associated Enzymes or Receptors	Consequences of Excess Lipoprotein
Chylomicron	Secreted by intestine	Transports exogenous lipids to liver, adipose tissue, and peripheral tissues	Broken down by *lipoprotein lipase* into glycerol, free fatty acids, and chylomicron remnants	Pancreatitis Eruptive xanthomas Lipemia retinalis
VLDL	Secreted by liver	Transports endogenous triglycerides, LDL, and cholesterol esters from the liver to other tissues	Broken down by *lipoprotein lipase* into free fatty acids and LDL particles	Pancreatitis
LDL	Formed from breakdown of VLDL particles	LDL particles are absorbed by tissues when cellular cholesterol is needed	Absorbed into cells via the *LDL receptor*, which is down-regulated by increased LDL levels within the cell	Atherosclerosis Arcus corneae Xanthomas
HDL	Secreted by liver	Transports cholesterol to liver where it is secreted into bile or to steroid hormone-producing tissues where it is utilized in steroid hormone production	Works in conjunction with *cholesterol ester transfer protein*, which binds free cholesterol esters in the bloodstream, to transport cholesterol back to the liver	None

3

APOLIPOPROTEIN FUNCTIONS

Apolipoprotein	Function in Lipid Metabolism	Associated with Lipoproteins	Associated Metabolic Diseases
A (Apo A-I, A-II, A-IV)	A-I: activates *LCAT*, which acts to trap cholesterol esters within HDL A-II and A-IV: interact with *PLTP* to transfer phospholipids to HDL	All Apo As are found in HDL	A-I: defects lead to HDL deficiencies A-II and A-IV: defects lead to hypercholesterolemia
B (Apo B-48, B-100)	B-48: involved in synthesis and secretion of chylomicrons from small intestine B-100: binds LDL receptor to facilitate LDL binding	B-48: chylomicrons B-100: VLDL; LDL	B-48: deficiency leads to abetalipoproteinemia (unable to absorb dietary fats) B-100: defective B-100 leads to increased LDL levels
C (Apo C-I, C-II, C-III)	C-I: inhibits *cholesterol ester transfer protein* C-II: activates *lipoprotein lipase* C-III: inhibits *lipoprotein* lipase	C-I: VLDL, HDL; chylomicrons C-II: VLDL; chylomicrons C-III: VLDL	C-I: increased levels lead to hypercholesterolemia CII: deficiencies lead to hyperlipoproteinemia type Ib C-III: increased levels lead to hypertriglyceridemia
E (Apo E2, E3, E4)	Synthesized in liver; act to transport triglycerides and cholesterol to the liver	Found in chylomicrons and VLDLs	Deficiency results in dysbetalipoproteinemia

CHOLESTEROL SYNTHESIS

Acetyl CoA + Acetoacetic CoA

HMG-CoA Synthase

↓

HMG CoA

⟋ 2 NADPH

HMG-CoA Reductase ⟍ 2 NADP⁺

⟍ CoA

↓

Mevalonic Acid

↓

↓

↓
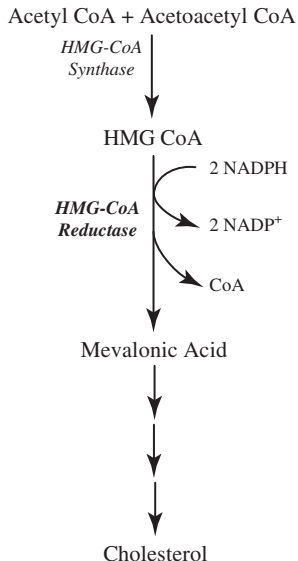
Cholesterol

- **Location:** Cholesterol synthesis takes place in the liver and intestinal mucosa.
- **Substrates:** Acetyl CoA; acetoacetyl CoA.
- **Products:**
  - ▶ **Cholesterol:** Oxidized to bile acids in liver; precursor for steroid hormones.
  - ▶ **Mevalonic acid:** Precursor for terpenes (eg, vitamins A and K, coenzyme Q).
- **Regulation:** *HMG CoA reductase* is inhibited by high levels of cholesterol. This enzyme is the pharmacologic target of lovastatin and other drugs in that class.
- **Circulation:** Two-thirds of plasma cholesterol is esterified by *LCAT,* an enzyme activated by apo A. Cholesterol esterification by *LCAT* traps cholesterol in HDL and prevents membrane cholesterol uptake, which can lead to alterations in membrane permeability.

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SPHINGOLIPID SYNTHESIS

Serine + Palmitoyl-CoA

↓

Sphingosine

Acylation Step

↓

Ceramide

UDP-galactose
or
UDP-glucose

Phosphatidyl
choline

UDP

Diacylglycerol

Galactocerebroside
+
Glucocerebroside

Gangliosides
+
Sulfatides
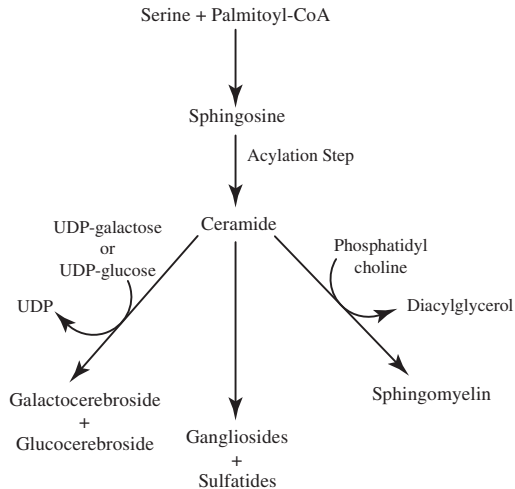
Sphingomyelin

- **Location:** Sphingolipid synthesis occurs in the cytosol.
- **Substrates:** Serine; palmitoyl CoA.
- **Products:**
  - ▶ **Sphingomyelin:** Principal lipid of nervous tissue membranes.
  - ▶ **Gangliosides:** Acidic glycosphingolipids found in ganglion cells of the nervous system.
  - ▶ **Sulfatides:** Acidic glycosphingolipids found primarily in nervous tissue.
  - ▶ **Cerebrosides:** Neutral glycosphingolipids found primarily in the CNS myelin.
- **General pathway:** There are two phases in sphingolipid synthesis. The first phase involves the formation of the ceramide core, which is produced by the combination of palmitoyl-CoA, serine, and a fatty acyl-CoA molecule. There are several possible pathways in the second phase of sphingolipid synthesis, which result in the formation of the different sphingolipids. In general though, the second phase involves the addition of a specific compound (eg, phosphocholine, glucose, galactose, sulfate, etc) to the hydroxyl group on the terminal carbon of the ceramide molecule.
- **Degradation:** Normally degraded by lysosomes.

Flow diagram of sphingolipid degradation:

G_{M1} ganglioside → (G_{M1}-β-galactosidase) → **G_{M2} ganglioside** → (Hexosaminidase A) → **G_{M3} ganglioside** → (Neuraminidase) → **Lactosylceramide**

Globoside → (β-hexosaminidase A and B) → **Globotriaosylceramide** → (α-galactosidase A) → **Lactosylceramide**

Lactosylceramide → (GalCer-β-galactosidase) → **Glucosylceramide** → (Glucocerebrosidase) → **Ceramide**

Sphingomyelin → (Sphingomyelinase) → **Ceramide**

Digalactosylceramide → (α-galactosidase A) → **Galactosylceramide** → (β-galactosylceramidase) → **Ceramide**

Sulfatide → (Arylsulfatase A) → **Galactosylceramide**

Ceramide → (Acid Ceramidase) → **Sphingosine**

IMPORTANT ENZYMES IN SPHINGOLIPID DEGRADATION

Enzyme	Action	Associated Sphingolipid Storage Disease	Accumulated Substance Seen with Deficiency
G_{M1}-β-galactosidase	Breaks down G_{M1} ganglioside to G_{M2} ganglioside	G_{M1} gangliosidosis	G_{M1} ganglioside
Hexosaminidase	Breaks down G_{M2} ganglioside to G_{M3} ganglioside	Tay-Sachs disease	G_{M2} ganglioside
Neuraminidase	Breaks down G_{M3} ganglioside to lactosylceramide	Sialidosis	G_{M3} ganglioside
GalCer-β-galactosidase	Breaks down lactosylceramide to glucosylceramide	No clear associated syndrome	Lactosylceramide
Glucocerebrosidase	Breaks down glucosylceramide to ceramide	Gaucher disease	Glucosylceramide
β-Hexosaminidase A and B	Breaks down globoside to globotriaosylceramide	Sandhoff disease	Globoside
α-Galactosidase A	Breaks down globotriaosylceramide to lactosylceramide Breaks down digalactosylceramide to galactosylceramide	Fabry disease	Globotriaosylceramide Digalactosylceramide
Sphingomyelinase	Breaks down sphingomyelin to ceramide	Niemann-Pick disease	Sphingomyelin
Acid ceramidase	Breaks down ceramide to sphingosine	Farber disease	Ceramide
Arylsulfatase A	Breaks down sulfatide to galactosylceramide	Metachromatic leukodystrophy	Sulfatide
β-Galactosylceramidase	Breaks down galactosylceramide to ceramide	Krabbe disease	Galactosylceramide
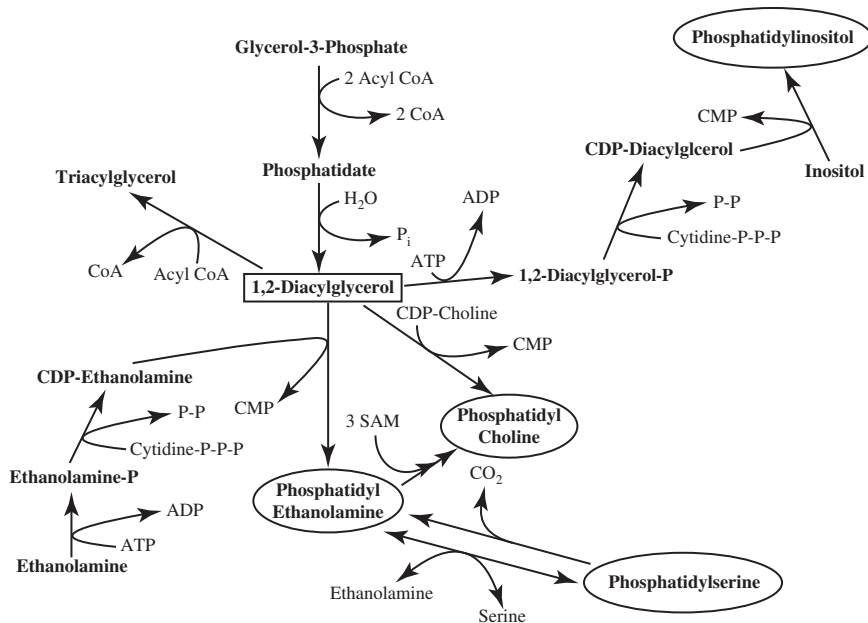
PHOSPHOLIPID SYNTHESIS

- **Location:** Phospholipid synthesis occurs in the cytosol in the cells of the liver, intestine, and adipose tissue.
- **Main substrate:** (1,2-DAG) (which is derived from glycerol-3-phosphate).
- **Products:**
  - ▶ **Phosphatidylinositol:** Negatively charged phospholipid; when phosphorylated, it plays a major role in cell signaling.
  - ▶ **Phosphatidyl choline:** Most abundant phospholipid; it is neutral; acts as key component of lipoproteins, as well as membranes of cells in several types of tissues; may have a role in cell-signaling.
  - ▶ **Phosphatidyl ethanolamine:** Found in membranes in the cells of the nervous tissue (particularly white matter of the brain).
  - ▶ **Phosphatidylserine:** Acidic phospholipid found mostly in membranes of myelin cells.
- **General pathway:** All phospholipids are derived from 1, 2-DAG. The addition of a phosphorylated ethanol-amine group to 1,2-DAG results in phosphatidyl ethanolamine. The addition of an activated choline group to 1,2-FAG results in phosphatidyl choline. The addition of an inositol group to phosphorylated 1,2-DAG results in phosphatidylinositol. Phosphatidylserine is formed by the exchange of a serine group for the etha-nolamine group on phosphatidyl ethanolamine.
- **Degradation:** Normally degraded by a family of enzymes known as *phospholipases*.

A 31-year-old man presents with complaints of sharp retrosternal chest pain when lifting heavy objects or walking up several flights of stairs. The pain lasts for about 2 minutes at a time and radiates up to his left jaw. He reports that the pain is relieved by rest. The patient reports that his father and two paternal uncles had heart attacks during their 30s. His symptoms and ECG are consistent with stable angina. While you prescribe nitroglycerin to treat the angina, you also order a serum lipid panel because you are concerned that this patient may have a codominant genetic disorder that is putting him at a very high risk for early-onset atherosclerotic heart disease.

Familial Hypercholesterolemia (Type IIa)

Biochemical Defect	Causes include a **codominant** genetic disorder resulting from mutations in the gene for the **LDL receptor** or an **autosomal dominant** genetic disorder associated with **defective apoprotein B-100**, a protein that facilitates binding of LDL to the LDL receptor.
Pathophysiology	When LDL receptors or apoprotein B-100 are deficient, LDL is unable to be taken into the liver for processing. This results in **increased plasma LDL levels**, leading to intracellular and extracellular deposits of cholesterol, which result in xanthomas and xanthelasmas as well as premature atherosclerotic disease. Also, because the liver senses decreased LDL levels, it responds by secreting more IDL and VLDL (LDL precursors), resulting in increased LDL production.
Clinical Manifestations	Homozygotes develop **severe atherosclerosis with heart disease in early or middle age**. Other symptoms include **tendon xanthomas** of the Achilles and knuckle extensor tendons, **tuberous xanthomas** (soft, painless nodules) on elbows and buttocks, and **xanthelasmas** (barely elevated deposits of cholesterol on eyelids).
	Lab findings: Elevated serum cholesterol level of 275-500 mg/dL and **elevated LDL** level; normal plasma triglycerides; normal HDL and VLDL levels.
Treatment	Low-fat, low-cholesterol diet and exercise; **HMG-CoA reductase inhibitor** (atorvastatin or simvastatin) in combination with **cholestyramine**; nicotinic acid can be added as a third agent.
Notes	The **homozygous form** of the LDL receptor mutation is rare (1:1 000 000); however, HMG-CoA reductase inhibitors are ineffective in treating the homozygous form of this disorder.

A 34-year-old man presents to your clinic complaining of chronic, recurrent abdominal pain. He has a history of pancreatitis, but his current symptoms do not suggest an acute process. Upon taking a family history, you discover that several members of his family, including his mother and two sisters suffer from an inherited metabolic disease. On funduscopic examination, you discover the presence of lipemia retinalis. Abdominal examination shows moderate hepatosplenomegaly. You are concerned that this patient may have a genetic disorder predisposing him to attacks of abdominal pain. You order serum studies, looking for elevated fasting plasma triglycerides, along with tests for elevated amylase and lipase. In addition to a low-fat diet and exercise, you also start the patient on gemfibrozil.

Familial Hypertriglyceridemia

Biochemical Defect	Familial hypertriglyceridemia **(type IV)** is an **autosomal dominant** disorder, but the underlying mutation has not been identified.
Pathophysiology	Pathophysiology involves both reduced catabolism of triglyceride-rich lipoproteins and **overproduction of VLDL** in the liver.
Clinical Manifestations	Usually **asymptomatic,** but **eruptive xanthomas** (small nonpainful orange-red papules) and **lipemia retinalis** may appear with triglyceride levels >1000 mg/dL. Also associated with an increased risk of vascular disease.
	Lab findings: Elevated fasting plasma triglycerides (200-750 mg/dL), elevated VLDL, elevated total cholesterol.
Treatment	Fat-free diet; niacin, gemfibrozil, and/or fish oil supplements.
Notes	Obesity, inactivity, alcohol use, and insulin resistance are associated with hypertriglyceridemia.

A 45-year-old man with a medical history significant for obesity and diabetes mellitus presents to your clinic complaining of an abnormal rash on his body. Physical examination reveals small orange-red papules on his scalp, elbows, and knees that are not painful to the touch. You order serum studies, which demonstrate elevated triglyceride levels as well as elevated levels of chylomicrons and VLDL. You explain to the patient that he likely has a partial genetic deficiency of an enzyme involved in lipid metabolism, and you start the patient on gemfibrozil and fish oil supplements.

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Familial Hyperchylomicronemia and Mixed Hypertriglyceridemia

Biochemical Defect	**Familial hyperchylomicronemia (type I)** is an **autosomal recessive** disorder caused by an absence of either LPL (type Ia) or apoprotein C-II (type Ib).
	Mixed hypertriglyceridemia (type V) is a heterogeneous disorder caused by a partial deficiency (as opposed to total deficiency) in either LPL or apoprotein C-II.
Pathophysiology	Apo C-II activates LPL, which then hydrolyzes chylomicrons. A deficiency or absence in either apo C-II or LPL results in the accumulation of **chylomicrons** in the plasma.
Clinical Manifestations	Usually **asymptomatic**, but **eruptive xanthomas** (small nonpainful orange-red papules), pancreatitis, and **lipemia retinalis** may appear with triglyceride levels >1000 mg/dL.
	Lab findings: **Elevated fasting plasma triglycerides** (>750 mg/dL) associated with **chylomicronemia**. Type V will also have evidence of elevated VLDL.
Treatment	Lifelong fat-free diet; niacin, gemfibrozil, or fish oil supplements.
Notes	Obesity, inactivity, alcohol use, and insulin resistance are associated with hypertriglyceridemia.

A 38-year-old woman presents to your clinic 1 month after having been admitted to the hospital and **3** treated for a myocardial infarction. Although she is feeling well during this visit, she is concerned about what may have led to a heart attack so early in her life. She eats a regular diet and exercises twice a week. On physical examination, you notice cholesterol deposits in the palmar creases of both her hands. She also has two very small tuberous xanthomas near her buttocks. You believe that this patient suffers from an autosomal recessive disease and you order serum lipid studies, expecting to find elevated VLDL and IDL levels in the presence of normal LDL and HDL levels. You believe that the patient may benefit from niacin and clofibrate treatment.

Dysbetalipoproteinemia

Biochemical Defect	Dysbetalipoproteinemia **(type III)** is an **autosomal recessive** disorder resulting from homozygosity for apo E-2, the binding-defective form of apo E.
Pathophysiology	Apo E is involved in the hepatic uptake of chylomicron, VLDL, and IDL remnants. Defective apo E results in elevations in both VLDL triglyceride and VLDL cholesterol levels.
Clinical Manifestations	Tuberous xanthomas; **striae palmaris** (deposits of cholesterol in palmar creases) are pathognomonic; vascular disease is present usually by the fifth decade.
	Lab findings: **Elevated VLDL and IDL**; chylomicron remnants in plasma; normal LDL and HDL.
Treatment	Niacin and fibrates.
Notes	

A 52-year-old man presents to your primary care office for establishment of care. He tells you that his past medical history includes peripheral arterial disease, borderline diabetes mellitus, and high cholesterol. Family history is significant for early-onset coronary artery disease as well as hyperlipidemia in several family members. Routine laboratory studies reveal moderately elevated total cholesterol levels as well as moderately elevated triglyceride levels. You begin to suspect that this patient's early vascular disease may be related to an overproduction of apolipoprotein B-100 and you suggest that he begin treatment with an HMG-CoA reductase inhibitor.

Familial Combined Hyperlipidemia

Biochemical Defect	Familial combined hyperlipidemia **(type IIb)** is an **autosomal dominant** disorder; the underlying defect is currently unknown although a defective locus has been discovered on chromosome 1q21. The proband (initial case discovered within a family) typically has combined hyperlipidemia or isolated hypertriglyceridemia.
Pathophysiology	The defect results in the overproduction of apo B-100 lipoproteins, which results in the increased circulation of VLDL particles in the blood.
Clinical Manifestations	**Type IIb:** Usually asymptomatic until **premature vascular disease** appears by fifth decade; **insulin resistance**; patients usually do not have xanthomas. *Lab findings:* Moderately elevated **triglyceride and total cholesterol levels**.
Treatment	**HMG-CoA reductase inhibitors** (ie, statins), cholestyramine (ie, bile sequestrants), and/or niacin.

Notes

A 1-year-old boy is brought to the pediatric ophthalmology clinic because his pediatrician noticed **3** corneal clouding on a routine physical examination. While evaluating the patient, you notice that he is small for his age, has a large tongue, and has mild coarsening of his facial features. On ophthalmologic examination, you find bilateral corneal opacities and papilledema. You believe that the patient may be suffering from an autosomal recessive trait caused by a deficiency in a lysosomal enzyme. Although the patient may benefit from symptomatic treatment for his eyes, you fear that his prognosis is grim and that he will likely die in childhood.

Hurler Disease

Biochemical Defect	An **autosomal recessive** disorder caused by deficiency in the enzyme α-ʟ-**iduronidase**.
Pathophysiology	α-ʟ-**iduronidase is a lysosomal enzyme necessary for the breakdown of GAGs.** When this enzyme is deficient, there is a **buildup of dermatan sulfate** and **heparan sulfate** (GAGs that are linked to proteins in connective tissue). Dermatan sulfate and heparan sulfate tend to accumulate in the skin and bones (leading to physical deformities), and in the heart, liver, and brain (leading to abnormal functioning of these organs).
Clinical Manifestations	Affected infants are normal at birth but exhibit mild coarsening of facial features and growth retardation in the first year. Distinguishing features include **coarse facies**, **joint stiffness**, short stature, and **valvular heart disease**. Other symptoms include hepatosplenomegaly, **corneal clouding**, large tongue, developmental delay, dwarfism, hearing loss, and mental retardation. *Lab findings:* Dermatan sulfate and heparan sulfate in the urine.
Treatment and Prognosis	Symptomatic therapies currently include corneal transplantation, heart valve replacement, and physical therapy for joint contractures. Bone marrow transplantation and enzyme replacement are experimental. Death usually occurs before age 10.
Notes	**Scheie syndrome** is an adult variant of Hurler disease that is also caused by a deficiency of α-ʟ-iduronidase. Hurler disease, Scheie syndrome, Hunter disease, Sly syndrome, and Sanfilippo disease are considered mucopolysaccharidoses.

An 8-year-old boy is referred to your rheumatologic clinic by his pediatrician, who had noticed prominent joint stiffness during a recent visit. On physical examination, you find that the patient has coarse facial features, a large tongue, a small jaw, and marked hepatosplenomegaly. He also has a distinctive nonpainful, pebbly skin lesion on his upper back. When asked to perform movements, he exhibits remarkable joint stiffness for his age and is unable to touch his toes from a standing position. You order a urinalysis, looking for dermatan sulfate and heparan sulfate, which you suspect will be present in the urine if the patient has a particular X-linked recessive disorder. If this turns out to be the case, you will inform the parents of their child's rare disorder and you plan to invite them to join a promising clinical trial for enzyme replacement therapy, which may improve the child's symptoms.

Hunter Disease

Biochemical Defect	An **X-linked recessive** disorder caused by deficiency in the enzyme **iduronate sulfatase**.
Pathophysiology	**Iduronate sulfatase** is a lysosomal enzyme that is involved in the breakdown of GAGs. When this enzyme is deficient, there is a **buildup of dermatan sulfate** and **heparan sulfate** (GAGs that are linked to proteins in connective tissue) as in Hurler disease. Dermatan sulfate and heparan sulfate tend to accumulate in the skin and bones, leading to physical deformities, and in the heart, liver, and brain, leading to abnormal functioning of these organs.
Clinical Manifestations	As in Hurler disease, affected Hunter disease infants are normal at birth but develop **coarse facies**, growth retardation, joint stiffness, hepatosplenomegaly, large tongue, small jaw, mental retardation, and valvular heart disease as they age. Unlike Hurler disease, patients with Hunter disease have **retinal degeneration but no corneal clouding**, mild or no mental retardation, and distinctive **pebbly skin lesions**.
	Lab findings: Dermatan sulfate and heparan sulfate in the urine.
Treatment	Symptomatic therapies currently include heart valve replacement and physical therapy for joint contractures. Bone marrow transplantation has been unsuccessful, and enzyme replacement therapy is experimental.
Notes	Hurler disease, Scheie syndrome, Hunter disease, Sly syndrome, and Sanfilippo disease are considered mucopolysaccharidoses.

A mother returns to your pediatric clinic with her 3-year-old son to receive test results from the previous visit. The patient was last seen 2 weeks ago for progressive behavioral problems, including lashing out at other children in the playground. During your initial history and physical examination, you learned that the patient is an only child and the mother's pregnancy was full term and noncomplicated. The child's medical history is significant for a seizure disorder and a developmental delay. On physical examination, you noticed that the child had mildly coarse facial features. Laboratory testing demonstrates elevated heparan sulfate in the patient's serum. When the mother asks you about her child's condition, you tell her that he suffers from a rare autosomal recessive disorder caused by defective breakdown of glycosaminoglycans.

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Sanfilippo Disease

Biochemical Defect	An **autosomal recessive** disorder caused by a deficiency in a number of lysosomal enzymes (usually **heparan *N*-sulfatase**) involved in GAG catabolism.
Pathophysiology	**Heparan *N*-sulfatase is a lysosomal enzyme that is involved in the breakdown of GAGs.** When this enzyme is deficient, there is a **buildup of heparan** (a GAG that is linked to proteins in connective tissue). Heparan sulfate tends to accumulate in the skin and bones (leading to physical deformities), and in the liver and brain (leading to abnormal functioning of these organs).
Clinical Manifestations	Affected infants present with severe mental retardation, mild coarse facies, **progressive behavioral problems**, and **CNS disease** in the form of seizures.
Treatment and Prognosis	Psychotropic drugs to control behavior. Patients can survive into the third or fourth decade, although they will suffer from progressive CNS disease.
Notes	Hurler disease, Scheie syndrome, Hunter disease, Sly syndrome, and Sanfilippo disease are considered mucopolysaccharidoses.

A 6-year-old boy is brought to your office for establishment of care. The patient's mother states that her child has been generally well, although he has had two cases of walking pneumonia in the last 2 years, which were successfully treated with antibiotics. On physical examination, you note that the child is short for his age and that he has coarse facies. Spinal examination reveals mild kyphosis. When you ask the mother how the child has been doing in school, she admits that he is behind his classmates in reading and writing and that his teachers have wondered if he has some form of a learning disability. You begin to suspect that the child has a rare autosomal recessive disorder caused by a deficiency in β-glucuronidase.

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Sly Syndrome

Biochemical Defect	An **autosomal recessive** disorder caused by a **deficiency of β-glucuronidase.**
Pathophysiology	**β-Glucuronidase is a lysosomal enzyme that is involved in the breakdown of GAGs.** In particular, β-glucuronidase is responsible for the removal of β-D-glucuronic acid moieties from the nonreducing end of GAGs. When β-glucuronidase is deficient, there is a buildup of GAGs in the skin, bones, and brain leading to skeletal deformities as well as mental retardation and bone marrow malfunctioning.
Clinical Manifestations	Patients present in infancy with **short stature**, **coarse facies**, and spinal deformities (kyphosis or scoliosis). CNS disease is manifested as **mental retardation**. Bone marrow malfunctioning is manifested as **recurrent infections** as well as hepatosplenomegaly. In its most severe form, hydrops fetalis can result prior to birth.
Treatment and Prognosis	Supportive treatment with physical therapy to treat skeletal deformities. Survival to middle age is possible with milder forms of the disease.
Notes	Hurler disease, Scheie syndrome, Hunter disease, Sly syndrome, and Sanfilippo disease are considered mucopolysaccharidoses.

A 7-month-old boy of Ashkenazi Jewish descent is brought to your pediatric clinic for lethargy. On physical examination, you notice that the child has an exaggerated startle reaction to noise while otherwise appearing quite limp and sleepy. He has a fixed gaze and a larger-than-normal head size. On funduscopic examination, you identify macular pallor with a distinctive cherry-red spot. You begin to suspect that this patient may suffer from an autosomal recessive disorder that results in a progressive neurologic disease and death by age 3.

3

Tay-Sachs Disease

Biochemical Defect	An **autosomal recessive** disorder caused by a deficiency in the enzyme **hexosaminidase A**.
Pathophysiology	**Hexosaminidase A is a lysosomal enzyme that is involved in the breakdown of gangliosides**, a type of glycolipid that contains neuraminic acid and is found in high concentration in the ganglion cells of the CNS. When this enzyme is deficient, there is the **accumulation of GM_2 gangliosides**, which are toxic to neuronal cells and lead to progressive neurologic damage.
Clinical Manifestations	There are several different clinical forms of this disorder. The *infantile form* is a neurodegenerative disease characterized by macrocephaly, loss of motor skills, **increased startle reaction** to noise (hyperacusis), hepatosplenomegaly, and macular pallor with **cherry-red spot on retinal examination**. The *juvenile-onset* form presents with dementia and ataxia. The *adult-onset* form is characterized by childhood clumsiness, progressive motor weakness in adolescence, spinocerebellar or lower motor neuron symptoms in adulthood, and the eventual development of psychosis.
Treatment and Prognosis	Supportive treatment for symptoms. The infantile form usually results in death by age 3; the juvenile form results in death by age 15.
Notes	Screening for Tay-Sachs disease carriers is recommended among Ashkenazi Jews because 1 in 30 people of this descent carries the allele for this disease.
	Tay-Sachs disease and Sandhoff disease are considered GM_2 gangliosidoses.

A 7-year-old boy presents to your pediatric clinic with an unspecified history of seizures. The parents are concerned that the seizures have affected their child's ability to function physically. They tell you that, over the last 2 years, the patient's motor skills have progressively degenerated. On physical examination, you note that the child has an ataxic gait and is unable to write without shaking. Ophthalmologic examination is significant for macular pallor with a cherry-red spot. You tell the parents that you believe that their son is suffering from an autosomal recessive disorder caused by defects in two lysosomal enzymes.

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Sandhoff Disease

Biochemical Defect	An **autosomal recessive** disorder caused by defects in β-**hexosaminidase A and B**.
Pathophysiology	**Hexosaminidase A and B are lysosomal enzymes, which are involved in the breakdown of gangliosides**, a type of glycolipid that contains neuraminic acid and is found in high concentration in the ganglion cells of the CNS. When this enzyme is deficient, there is the **accumulation of GM_2 gangliosides**, which are toxic to neuronal cells and lead to progressive neurologic damage.
Clinical Manifestations	Sandhoff disease is nearly identical to Tay-Sachs disease in that it is a **fatal** neurodegenerative disorder. In its *infantile form*, it is characterized by macrocephaly, loss of motor skills, seizures, and macular pallor with **cherry-red spot on retinal examination**. In its *later-onset variants*, patients suffer from progressive visceral and degenerative CNS disease. Unlike Tay-Sachs disease, Sandhoff disease patients **do not have hepatosplenomegaly** or bony dysplasias, and the course of the disease is more rapid.
Treatment	Supportive treatment for symptoms.
Notes	Tay-Sachs disease and Sandhoff disease are considered GM_2 gangliosidoses.

You receive a call to your pediatric genetics clinic from a colleague, who works in an adult genetics **3** clinic. He tells you that she is caring for a 30-year-old patient, who has developed the slow onset of dementia as well as gait ataxia over the last 2 years. Neurologic workup for causes of early-onset Parkinson disease has been unrevealing, and your colleague is beginning to suspect that his patient may suffer from a genetic disease. You suspect that this patient may suffer from a disorder that is related to an enzyme deficiency involved in the breakdown of gangliosides that can present with one of three clinical subtypes, and you recommend that your colleague assess the levels of β-galactosidase activity in his patient.

GM₁ Gangliosidosis

Biochemical Defect	An **autosomal recessive** disorder caused by a **deficiency in β-galactosidase**.
Pathophysiology	**β-Galactosidase is a lysosomal enzyme that is involved in the breakdown of gangliosides**, a type of glycolipid that contains neuraminic acid and is found in high concentration in the ganglion cells of the CNS. When this enzyme is deficient, there is the **accumulation of GM₁ gangliosides**, which are toxic to neuronal cells and lead to progressive neurologic damage.
Clinical Manifestations	There are **three clinical subtypes** of GM₁ gangliosidosis. Type 1 (**infantile**) manifests at birth with hepatosplenomegaly, coarse facies, macular cherry-red spots, and CNS dysfunction. Type 2 (**juvenile**) presents within the first 3 years of life and is not marked by organomegaly or macular spots, but does have coarse facies and skeletal deformities. Type 3 (**adult**) is marked by a normal childhood; however, dementia and CNS degeneration with gait ataxia develop by middle age.
Treatment and Prognosis	No effective treatment is currently available. The infantile subtype is usually fatal by age 2.
Notes	

A 13-year-old boy presents to your pediatric clinic complaining of episodic burning pain in his hands, feet, arms, and legs after playing soccer. These painful episodes occur only after strenuous exercise or when he is sick with the flu. On physical examination, you notice telangiectatic skin lesions on his back that are dark red, punctate, and nonblanching with pressure. He states that these lesions have grown in size and become more numerous over the years. His neurologic examination is normal. You order a battery of serum studies, which show elevated BUN and creatinine, suggesting that the patient's kidneys are damaged. You believe that he may be suffering from an X-linked recessive disorder that is associated with a lysosomal enzyme deficiency, and you prescribe phenytoin and carbamazepine for treatment of his painful burning episodes while you await further genetic testing.

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Fabry Disease

Biochemical Defect	An **X-linked** recessive disorder that results from a deficiency of the enzyme α-galactosidase A.
Pathophysiology	α-**Galactosidase A** is a lysosomal enzyme that is involved in cleaving the terminal α-galactosyl moiety from globotriaosylceramide (trihexosylceramide), which is a key step in **glycosphingolipid metabolism**. When this enzyme is deficient, **globotriaosylceramide (ceramide trihexoside) accumulates** in the skin, heart, kidneys, and CNS, leading to abnormal functioning of these organs.
Clinical Manifestations	The disease presents in childhood with angiokeratomas (telangiectatic skin lesions), acroparesthesia, and **hypohidrosis** (sweating less than usual). **Angiokeratomas** are small, punctate, and dark red to blue-black, do not blanch with pressure, and increase in size and number with age. The **acroparesthesia** presents as episodic burning pain of the hands, feet, and proximal extremities that is precipitated by exercise, fatigue, or fever. **Corneal and lenticular lesions** are detectable on slit-lamp examination, with tortuosity of conjunctival and retinal vessels. Patients may eventually develop heart failure and renal failure as well.
	Lab findings: Elevated serum BUN and creatinine.
Treatment	Phenytoin and carbamazepine diminish acroparesthesia; dialysis and kidney transplantation for renal failure.
Notes	Fabry disease, Gaucher disease, and Niemann-Pick disease are classified as neutral glycosphingolipidoses.

A 13-year-old Swedish boy presents to your clinic complaining of increased forgetfulness. He has **3** been held back in school several times and has just recently begun forgetting common, everyday facts. On further questioning, he informs you that he has also become more injury prone, sustaining small fractures over the last 2 years while playing sports. On physical examination, you find moderate hepatosplenomegaly. Neurologic examination shows defects in his lateral gaze tracking. These findings lead you to suspect that he may suffer from an autosomal recessive disorder that is associated with a lysosomal enzyme deficiency. Given the patient's history, you believe that the definitive diagnosis will require a bone marrow biopsy, which may demonstrate characteristic "wrinkled tissue paper"–appearing lipid-laden macrophages in the bone marrow.

Gaucher Disease

Biochemical Defect	An **autosomal recessive** disorder that results from a deficiency of the enzyme **acid β-glucosidase** (β-glucocerebrosidase).
Pathophysiology	Acid β-glucosidase is responsible for cleaving glucosylceramide into ceramide during **glycosphingolipid catabolism**. When this enzyme is deficient, **glucosylceramide** (glucocerebroside) **accumulates** in the brain, liver, spleen, and bone marrow, causing damage to those organs. In the bone marrow specifically, there is the infiltration of **Gaucher cells** (lipid-laden macrophages), which leads to infarction, necrosis, and cortical bone destruction.
Clinical Manifestations	There are multiple clinical forms of this disorder. Patients exhibit **hepatosplenomegaly** as well as variable manifestations in the CNS and viscera. **Type I** (adult form) presents in early adulthood with rapidly progressive, myoclonic **seizures** and **aseptic necrosis** with fractures of the femoral head. **Type II** (infantile form) presents early with **slowly progressive CNS involvement** and mental retardation. **Type III** (juvenile form) presents in adolescence with **dementia**.
	Lab findings: Mild anemia and thrombocytopenia; bone marrow biopsy reveals Gaucher cells (characteristic **wrinkled tissue paper–appearing** macrophages).
Treatment	Cerezyme, a recombinantly produced acid β-glucosidase, is the treatment of choice. Symptomatic management of the blood cytopenias; joint replacement surgeries.
Notes	Gaucher disease type I is the most common and most compatible with life. Fabry disease, Gaucher disease, and Niemann-Pick disease are classified as neutral glycosphingolipidoses.

A 1-year-old boy and his mother return to your pediatric genetics clinic to receive results from a bone marrow biopsy performed several days earlier. The patient had initially been referred to you by his pediatrician, who was concerned about the patient's seizures and general spastic movements. Your initial physical examination demonstrated possible diminished vision in both eyes, dyspnea, hepatosplenomegaly, and a general failure to thrive. The bone marrow biopsy showed characteristic "foam cells" containing sphingomyelin and cholesterol. With this information, you inform the mother that her child has an autosomal recessive genetic disorder associated with a lysosomal enzyme deficiency. Although there is no specific treatment, you inform the mother about possible clinical trials involving bone marrow transplantation and enzyme replacement therapy.

3

Niemann-Pick Disease

Biochemical Defect	An **autosomal recessive** disorder caused by deficiency of the enzyme **sphingomyelinase**.
Pathophysiology	Sphinogomyelinase is a lysosomal enzyme that is responsible for converting sphingomyelin to ceramide during **glycosphingolipid catabolism**. When this enzyme is deficient, **sphingomyelin accumulates** in the histiocytic lysosomes **(foam cells)** of the brain, liver, spleen, bone marrow, and lung, leading to dysfunction of these organs.
Clinical Manifestations	Two clinical variants exist. **NPD type A** presents in the first 6 months of life with rapidly progressive **CNS deterioration** (seizures), spasticity, and failure to thrive. **NPD type B** has a later onset. In both types, patients develop **mental retardation**, **hepatosplenomegaly**, osteoporosis, and macular degeneration. There is also **progressive pulmonary disease**, which eventually leads to the development of pulmonary hypertension and cor pulmonale.
	Imaging: Reticular infiltrative pattern on chest x-ray film.
Treatment and Prognosis	Experimental treatments include hepatic or bone marrow transplantation and enzyme therapy. Death usually occurs during adolescence from pulmonary disease.
Notes	Fabry disease, Gaucher disease, and Niemann-Pick disease are classified as neutral glycosphingolipidoses.

A 3-month-old girl and her mother present to your pediatrics clinic for an urgent care visit. The mother states that she has noted that her child has developed swollen glands and joints over the last few weeks. She also states that the child often chokes when feeding. Upon physical examination, you note the presence of fatty nodules in multiple joints on the child's body as well as mild hepatosplenomegaly. While examining the child, she begins to cry and you appreciate a hoarseness to the child's cry that is unusual. You begin to worry that this child may suffer from a rare autosomal recessive disorder that is related to an abnormal accumulation of ceramide in the patient's macrophages.

Farber Disease

Biochemical Defect	An **autosomal recessive** disorder caused by deficiency of the enzyme, **acid ceramidase**.
Pathophysiology	**Acid ceramidase** is a lysosomal enzyme that is responsible for converting ceramide to sphingosine during **glycosphingolipid catabolism**. When this enzyme is deficient, **ceramide accumulates** in the histiocytic lysosomes **(foam cells)** of the musculoskeletal system, throat, liver, and central nervous system, leading to dysfunction of these organs.
Clinical Manifestations	Patients tend to present with the disease within the **first few months of life**, although phenotypic variability has had some patients presenting later in childhood. Symptoms include developmental delay, **arthritis with joint swelling and contracture**, **hoarseness**, dysphagia, and hepatosplenomegaly.
Treatment and Prognosis	Supportive treatment for symptoms. There are multiple clinical forms with variable prognoses, although most patients die of the disease by age 3.
Notes	

A 6-month-old boy is admitted to your pediatric service for evaluation of failure to thrive. The child has been small for his age and quite lethargic since birth. He has not met his developmental milestones. On initial physical examination, you notice the child has significantly coarse facial features as well as significant deterioration of his gums. Fundoscopic examination reveals corneal clouding. When serum studies reveal highly elevated levels of lysosomal enzymes in the plasma, you immediately become concerned that the child may suffer from an autosomal recessive disorder caused by a deficiency in a lysosomal phosphotransferase.

3

I-Cell Disease

Biochemical Defect	An **autosomal recessive** disorder caused by a deficiency in the enzyme *N*-acetylglucosamine-1-phosphotransferase.
Pathophysiology	*N*-acetylglucosamine-1-phosphotransferase is **involved in the development of the mannose-6-phosphate signal, which serves to sort lysosomal enzymes into the lysosomes** during enzyme production. When this enzyme is deficient, there is defective cell targeting of lysosomal hydrolases, which leads to numerous enzymes being secreted outside the cell and accumulation of their substrate mucopolysaccharides outside the cell.
Clinical Manifestations	Small, lethargic infants with mental retardation, corneal clouding, coarse facies, and **gingival hypoplasia**.
	Lab findings: Greatly **elevated serum levels of lysosomal enzymes**; absence of mucopolysacchariduria.
Treatment	Symptomatic treatment.
Notes	I-cell disease is categorized as a mucolipidosis.

A 22-year-old man presents to your neurology clinic for an initial evaluation of seizures. He states that he developed his first seizure 6 months ago. He describes the seizures as whole-body jerks that last a few seconds. On neurologic examination, you note macular cherry-red spots as well as mild gait ataxia. You tell the patient that his symptoms of myoclonic seizures in conjunction with his findings on neurologic examination may be consistent with a metabolic disorder that is caused by an abnormality in the degradation of glycoproteins.

3

Sialidosis

Biochemical Defect	An **autosomal recessive** disorder caused by a deficiency in the enzyme, **sialidase**.
Pathophysiology	Sialidase **involved in the degradation of glycoproteins with sialic acid moieties**. When this enzyme is deficient, there is defective degradation of sialyloligosaccharides, resulting in the abnormal accumulation of these glycoproteins in lysosomes in the cells of the musculoskeletal system, central nervous system, and reticuloendothelial system.
Clinical Manifestations	There are two clinical forms of the disorder. **Type I** presents in early adulthood with **myoclonic seizures**, gait instability, and **macular cherry-red spots**. **Type II** presents in early childhood with coarse facies, skeletal abnormalities, hepatosplenomegaly, and developmental delay. Only some patients with type II disease will have macular cherry-red spots.
Treatment and Prognosis	Supportive treatment of symptoms. Type I form of the disease is usually fatal by age 35, whereas type II form of the disease is fatal by age 2.
Notes	

A 9-month-old girl is brought to your pediatric clinic by her parents, who noticed that she has been **3** increasingly irritable. Her mother also tells you that she has noticed some stiff and jerky movements of the child's extremities. On physical examination, you discover that the patient is small for her age and has hyperactive deep tendon reflexes and marked hamstring rigidity. She does not have much of a startle reflex, suggesting possible diminished visual or hearing acuity. Her suck reflex is also quite weak. Laboratory serum studies are within normal limits. You begin to wonder whether this child might suffer from a leukodystrophy disorder associated with demyelination in the CNS, and you refer the child and her family to a medical geneticist.

Krabbe Disease

Biochemical Defect	An **autosomal recessive** disorder caused by a deficiency in the enzyme **galactosylcerami-dase** (galactosylceramide β-galactosidase).
Pathophysiology	**Galactosylceramidase** is a lysosomal enzyme that catalyzes the conversion of galactosyl-ceramide (galactocerebroside) to ceramide during **glycosphingolipid catabolism**. When this enzyme is deficient, there is an **accumulation of galactosylceramide** (galactocerebro-side) **and galactosyl sphingosine in the brain**, leading to neuronal damage (white matter globoid cells on gross pathology) and **demyelination**.
Clinical Manifestations	Optic atrophy **(blindness)**; deafness; **spasticity** or paralysis; mental retardation; seizures.
Treatment and Prognosis	Symptomatic treatment. This disease is usually fatal in childhood.
Notes	Krabbe disease and metachromatic leukodystrophy are classified as the leukodystrophies.

A 30-month-old white boy is brought to your pediatric clinic because of deterioration in his ability to stand and walk. The infant was born full term without any complications during pregnancy. He had met all developmental milestones up to this point. On standing the patient up, you find a wide-based gait and ataxia. The child also has mildly hyperreflexive deep tendon reflexes. The parents were also concerned about possible seizure-like activity 1 week ago. A lumbar puncture shows increased protein, thereby ruling out cerebral palsy. You become concerned about an autosomal recessive leukodystrophy that tends to present in this fashion, and you set out to diagnose this disorder by demonstrating a deficiency of arylsulfatase A in nucleated cells.

Metachromatic Leukodystrophy

Biochemical Defect	An **autosomal recessive** disorder caused by deficiency of the lysosomal enzyme, **arylsulfatase A**.
Pathophysiology	Arylsulfatase A is involved in the conversion of galactosylceramide sulfate to galactosylceramide during **glycosphingolipid catabolism**. When this enzyme is deficient, there is an **accumulation of galactosylceramide sulfate or sulfatide** in the nervous system (especially CNS white matter and myelinated peripheral nervous system tracts), kidney, and liver.
Clinical Manifestations	There are several clinical variations of this disorder. *The infantile form* presents by age 2 with regression of developmental milestones and **mental retardation**. The *juvenile and adult forms* present with **ataxia** (gait disturbances), mental regression, **optic atrophy**, peripheral neuropathy, and seizures. In adults, **behavioral disturbances** such as psychosis and **dementia** are common.
	Lab findings: Metachromasia of nerves with staining on microscopic examination.
Treatment and Prognosis	Later-onset diseases respond to bone marrow transplantation. The infantile and juvenile forms of the disease are usually fatal by age 10.
Notes	Krabbe disease and metachromatic leukodystrophy are classified as the leukodystrophies. **Adrenal leukodystrophy** is a rare, fatal X-linked recessive disorder characterized by the defective breakdown of very long-chain fatty acids, resulting in the accumulation of cholesterol esters in the CNS white matter, peripheral nerves, adrenal cortex, and testes. Patients present in early childhood with gait deterioration, spasticity resulting from demyelination, seizures, loss of vision, and Addison disease caused by adrenal gland degeneration.

AMINO ACID METABOLISM

GENERAL CONCEPTS

Amino acid function and structure
Overview of amino acid degradation
Deamination of amino acids
Transport of ammonium to liver
Urea cycle
Derivatives of amino acid carbon skeletons
Breakdown of branched-chain amino acids
Metabolism of phenylalanine
Metabolism of methionine
Derivatives of amino acids

DISEASES

Alkaptonuria
Cystinuria
Hartnup disease
Homocystinuria
Maple syrup urine disease
Phenylketonuria

4

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AMINO ACID FUNCTION

- Amino acids are **required for synthesis of proteins** and function as a nitrogen source for several important substances.
- The breakdown of both dietary and tissue proteins yields nitrogen-containing substrates and carbon skeletons.
- The nitrogen-containing substrates are used in the biosynthesis of purines, pyrimidines, neurotransmitters, hormones, porphyrins, and nonessential amino acids.
- Some amino acids cannot be synthesized by the body and must be ingested via food. These amino acids are called **essential amino acids** and include phenylalanine, valine, tryptophan, threonine, isoleucine, methionine, histidine, leucine, and lysine.
- The carbon skeletons are used as a fuel source in the citric acid cycle, used for gluconeogenesis, or used in fatty acid synthesis.

NONPOLAR VERSUS POLAR AMINO ACIDS

	Side Chain	Amino Acid	
Nonpolar	Aliphatic	Glycine Alanine Valine	Leucine Isoleucine Proline
	Aromatic	Phenylalanine Tryptophan	
	Sulfur containing	Methionine	
Polar	Basic	Lysine Arginine Histidine	
	Acidic	Aspartic acid Glutamic acid	
	Uncharged	Serine Threonine Cysteine (contains sulfur) Tyrosine (aromatic)	Glutamine Asparagine

4

OVERVIEW OF AMINO ACID DEGRADATION

- There are several steps involved in the degradation of amino acids.
  1. The α-amino group must be removed from the amino acid. This can be done either via transamination or oxidative deamination (see card 57).
  2. Once the α-amino group is removed from the amino acid, the ammonia moiety must then be transported to the liver for metabolism into urea. This transport occurs with the help of alanine and glutamine (see card 58).
  3. Once in the liver, the ammonia moiety is transformed into urea via the urea cycle (see card 59).
  4. The remaining carbon skeleton are then degraded into intermediates of the citric acid cycle or can be used as building blocks for other molecules (see card 60).
  5. The branched-chain amino acids (valine, isoleucine, leucine) require specific enzyme complexes in order to be fully degraded (see card 61).

TRANSAMINATION
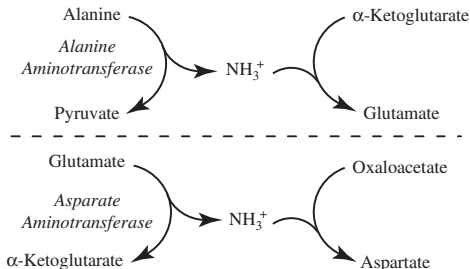
- **Location:** Many tissues, especially liver, skeletal muscle, and kidney.
- **Cofactors:** Pyridoxal phosphate (vitamin B_6).
- **Purpose:** Deamination is the first step in amino acid metabolism and can occur either through transamination or oxidative deamination. In transamination, enzymes, known as aminotransferases, act to remove the amino group from specific amino acids and transfer them to another molecule. Almost every amino acid has a specific aminotransferase. ALT and AST are shown here.
  - ► **ALT:** Transfers amino group from alanine to α-ketoglutarate, resulting in the formation of glutamate and pyruvate.
  - ► **AST:** Transfers amino group from glutamate to oxaloacetate, resulting in the formation of aspartate and α-ketoglutarate.

4

DEAMINATION OF AMINO ACIDS

OXIDATIVE DEAMINATION

Glutamate $\xrightarrow[\text{NAD(P)}^+ \quad \text{NAD(P)H} \quad \text{NH}_4^+]{\textit{Glutamate Dehydrogenase}}$ α-Ketoglutarate
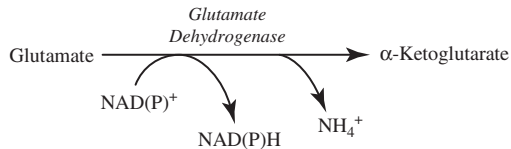
- **Location:** Liver and kidney.
- **Cofactors:** NAD^+ or $NADP^+$.
- **Purpose:** Deamination is the first step in amino acid metabolism and can occur either through transamination or oxidative deamination. Oxidative deamination acts to remove the amino group from glutamate and release it as ammonia.
- **Regulation:**
  - *Stimulators:* ADP and GDP activate glutamate dehydrogenase.
  - *Inhibitors:* ATP and GTP inhibit glutamate dehydrogenase.

Alanine Shuttle

Glutamine Shuttle
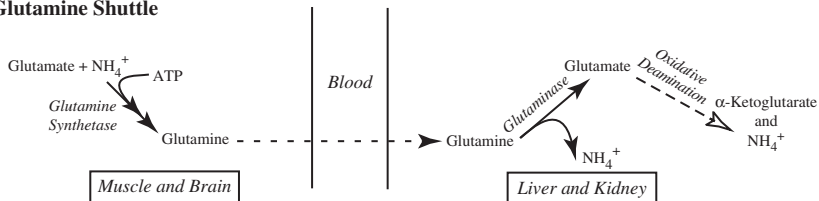
TRANSPORT OF AMMONIUM TO LIVER FOR UREA SYNTHESIS

ALANINE SHUTTLE

- **Location:** Skeletal muscle and liver.
- **Important enzyme:** Alanine transaminase.
- **Purpose:** To transport α-amino groups that have been removed from amino acids to the liver for metabolism from the skeletal muscle.
- **Pathway:**
  - ► In the skeletal muscle:
    - ► The ammonia moiety is transferred from the amino acid to α-ketoglutarate to form glutamate with the help of the enzyme family of transaminases.
    - ► The ammonia moiety is then subsequently transferred from glutamate to pyruvate to form alanine with the help of alanine transaminase.
  - ► Alanine then travels from skeletal muscle through the bloodstream to the liver.
  - ► In the liver:
    - ► Alanine combines with α-ketoglutarate to form pyruvate and glutamate, thereby transferring the ammonia moiety to glutamate.
    - ► Through the process of oxidative deamination, the ammonia moiety is then released from glutamate and enters the urea cycle.

GLUTAMINE SHUTTLE

- **Location:** Skeletal muscle, brain, kidney, and liver.
- **Important enzymes:** Glutamine synthetase; glutaminase.
- **Purpose:** To transport free ammonium moieties formed in the tissues to the liver for metabolism.
- **Pathway:**
  - ► In the skeletal muscle or brain:
    - ► Glutamate combines with the ammonia moiety to form glutamine. This reaction requires one ATP.
  - ► Glutamine then travels through the bloodstream to the liver or kidney.
  - ► In the liver or kidney:
    - ► The ammonia moiety is removed from glutamine by glutaminase, to form glutamate and an ammonium ion. This ammonium ion can then be directly excreted by the kidney.
    - ► Through the process of oxidative deamination, another ammonia moiety is then released from glutamate and can enter the urea cycle in the liver.
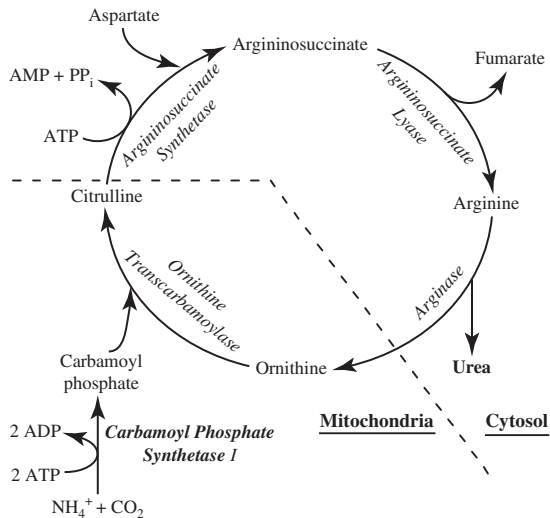
UREA CYCLE

- **Location:** Cytosol and mitochondria of hepatocytes.
- **Substrates:** NH_3 (as derived from oxidative deamination of glutamate); CO_2; aspartate; three ATP.
- **Products:** Urea; fumarate; H_2O.
- **Purpose:** The urea cycle allows for the excretion of NH_4^+ by transforming ammonia into urea, which is then excreted by the kidneys.
- **Important enzymes:**
  - ► *Carbamoyl phosphate synthetase I:* Converts ammonium and bicarbonate into carbamoyl phosphate. This is the rate-limiting step in the urea cycle. This reaction requires two ATP and occurs in the mitochondria.
  - ► *Ornithine transcarbamoylase:* Combines ornithine and carbamoyl phosphate to form citrulline. Located in mitochondria.
  - ► *Argininosuccinate synthetase:* Condenses citrulline with aspartate to form arginosuccinate. This reaction occurs in the cytosol and requires one ATP.
  - ► *Argininosuccinate lyase:* Splits argininosuccinate into arginine and fumarate. Occurs in the cytosol.
  - ► *Arginase:* Cleaves arginine into one molecule of urea and ornithine in the cytosol. The ornithine is then transported back into the mitochondria for entry back into the cycle.
- **Regulation:** *Carbamoyl phosphate synthetase I* catalyzes the rate-limiting step of the cycle and is stimulated by *N*-acetylglutamate.
- **Diseases:** Hyperammonemia occurs when there is a deficiency in one of more of the urea cycle enzymes, causing insufficient removal of NH_4^+. Ammonia intoxication leads to CNS deterioration in the form of mental retardation, seizure, coma, and death.

DEGRADATION OF AMINO ACID CARBON SKELETONS

- After the ammonia moiety has been removed from the amino acid, the carbon skeleton remains. The amino acid carbon skeletons undergo a series of reactions in order to be used as a fuel source or they can be used as building blocks to make other molecules.
- The different amino acids can thus be grouped by what citric acid cycle intermediate they become.
- An amino acid carbon skeleton can be considered ketogenic, glucogenic, or both. If an amino acid is ketogenic, its carbon skeleton will be used for ketogenesis. If an amino acid is glucogenic, its carbon skeleton will be used for glucogenesis. Lysine and leucine are strictly ketogenic. Isoleucine, phenylalanine, tryptophan, and tyrosine are both glucogenic and ketogenic. All other amino acids are strictly glucogenic.

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Acetyl CoA	α-Ketoglutarate	Fumarate	Oxaloacetate	Pyruvate	Succinyl CoA
Isoleucine	Arginine	Phenylalanine	Asparagine	Alanine	Isoleucine
Leucine	Glutamate	Tyrosine	Aspartate	Cysteine	Methionine
Lysine	Glutamine			Glycine	Threonine
Phenylalanine	Histidine			Serine	Valine
Tryptophan	Proline			Threonine	
Tyrosine				Tryptophan	

DERIVATIVES OF AMINO ACIDS

Amino Acid	Derivatives
Tyrosine	Thyroid hormones
	Dopa (eventually gives rise to dopamine, norepinephrine, epinephrine, and melanin)
Methionine	*S*-Adenosylmethionine
	Homocysteine
	Cysteine
Tryptophan	Niacin
	Serotonin
	Melatonin
Glutamate	GABA
Glycine	Porphyrin (heme synthesis)
Arginine	Creatine
	Nitric oxide
	Urea
Histidine	Histamine
Phenylalanine	Tyrosine

Valine
Isoleucine
Leucine

Branched-chain
aminotransferase
with
pyridoxal
phosphate

α-Ketoglutarate

Glutamate

Branched-chain α-ketoacids
(derivatives of valine, isoleucine, leucine)

4

Branched-chain
α-ketoacid dehydrogenase
with
lipoate and
thiamine-pyrophosphate

$NAD^+ + CoA$

$NADH + CO_2$

Branched-chain
acyl-CoA of leucine

Branched-chain acyl-CoA
of isoleucine

Branched-chain
acyl-CoA of valine

Acetoacetyl CoA ⇢ Acetyl CoA

Propionyl CoA ⇢ Succinyl CoA

Fatty Acid Synthesis

Citric Acid Cycle

61

DEGRADATION OF BRANCHED-CHAIN AMINO ACIDS

- **Location:** Mitochondria of skeletal muscle cells.
- **Substrates:** Valine/isoleucine/leucine; α-ketoglutarate; NAD^+; CoA.
- **Products:** Succinyl CoA; propionyl CoA; acetyl CoA; acetoacetyl CoA; NADH; CO_2; glutamate.
- **Overview of pathway:** Branched-chain amino acids (valine, isoleucine, leucine) require the use of two common enzyme complexes to catalyze their degradation. The products of degradation are intermediates in the pathways for fatty acid synthesis or the citric acid cycle and hence are converted to energy.
- **Important enzymes:**
  - ► *Branched-chain aminotransferase:* Transfers the α-amino group from the branched-chain amino acid to α-ketoglutarate, thereby forming a molecule of glutamate as well as a branched-chain α-ketoacid. This enzyme uses pyridoxal phosphate as a cofactor.
  - ► *Branched-chain α-ketoacid dehydrogenase:* A multienzyme complex that decarboxylates the branched-chain α-ketoacid into a branched-chain acyl-CoA analog of the respective branched-chain amino acid through a series of reactions. This enzyme complex requires lipoate and thiamine pyrophosphate as cofactors. These reactions result in the formation of an NADH as well as a CO_2.
- **Diseases:** When branched-chain α-ketoacid dehydrogenase is deficient, maple syrup urine disease results (see card 67).

METABOLISM OF PHENYLALANINE
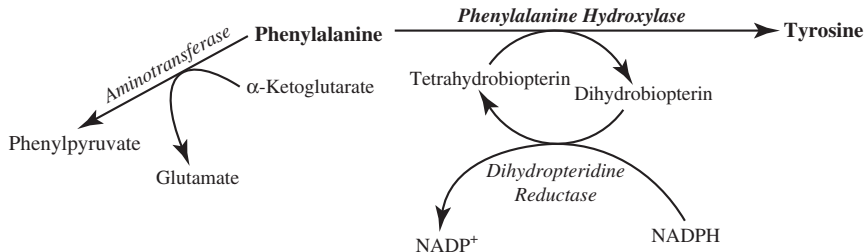
- **Overview of pathway:** Phenylalanine can be converted into one of two products. If the α-amino group is removed from phenylalanine, it is transformed into phenylpyruvate, which is eventually broken down into fumarate and entered into the citric acid cycle. Alternatively, phenylalanine can be used to synthesize tyrosine. The conversion of phenylalanine to tyrosine is catalyzed by *phenylalanine hydroxylase*.
- **Important enzymes:**
  - ▶ *Phenylalanine hydroxylase:* Hydroxylates phenylalanine to tyrosine. Requires tetrahydrobiopterin and O_2 as cofactors.
  - ▶ *Dihydrobiopterin reductase:* Regenerates tetrahydrobiopterin by reducing dihydrobiopterin to form tetrahydrobiopterin. Requires a molecule of NADPH.
- **Diseases:** When *phenylalanine hydroxylase* or *dihydropteridine reductase* is deficient, phenylketonuria results (see card 68).

N^5-methyl-tetrahydrofolate → Tetrahydrofolate

Methionine → S-Adenosyl-methionine → S-Adenosyl Homocysteine → **Homocysteine** → Methionine

S-Adenosylmethionine Synthetase · ATP · $P_i + PP_i$

Methyltransferase · R · $R-CH_3$

Methyltransferase (with Vitamin B$_{12}$)

Cystathionine Synthase (with Pyridoxal Phosphate) · Serine · H_2O

Cystathionine → → **Cysteine**
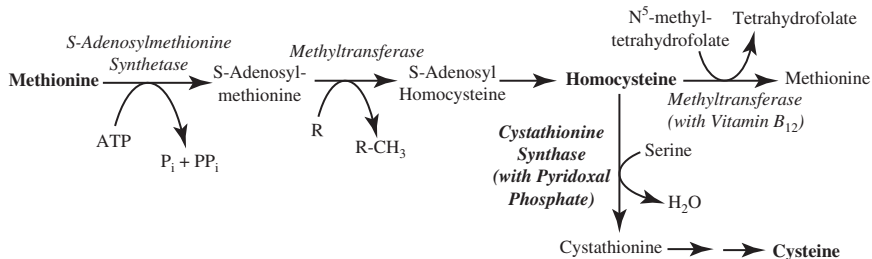
- **Overview of pathway:** Methionine is the precursor for the formation of SAM, which is used as a methylating agent in many reactions. Furthermore, after several more reactions, methionine can be transformed into homocysteine, which can then either be converted back to methionine (with the help of N^5-methyl-tetrahydrofolate and *methyltransferase* with vitamin B$_{12}$) or can be converted into cysteine with the help of *cystathionine synthase.*
- **Important enzymes:**
  - ▶ *S-Adenosylmethionine synthetase:* Converts methionine to SAM. Uses one ATP.
  - ▶ *Methyltransferase:* Converts excess homocysteine back into methionine. Requires vitamin B$_{12}$ as cofactor as well as a molecule of N^5-methyl-tetrahydrofolate.
  - ▶ *Cystathionine synthase:* Combines serine and homocysteine to form cystathionine, which is eventually converted to cysteine. Requires pyridoxal phosphate as a cofactor.
- **Diseases:** When either *cystathionine synthase* or *methyltransferase* is deficient or there is a decreased affinity of *cystathionine synthase* for pyridoxal phosphate (which results in decreased function of the enzyme), homocystinuria results (see card 66).

A 25-year-old man presents to your office for an initial visit complaining of pain and swelling in his knee joints. He has just moved to the area and tells you that has avoided physicians most of his young life. He reports that his knee pain is a chronic issue along with chronic back pain. On physical examination, he has limited range of motion of both his spine and knees. He also has dark spots in his conjunctiva and nasal bridge. On further questioning, you learn that the water in his toilet bowl turns black if he forgets to flush it after urination. You order x-ray films of his back and knees and send his urine for analysis, expecting to find premature arthritic changes on x-ray film and elevated urine homogentisic acid in the urinalysis.

4

Alkaptonuria

Biochemical Defect	An **autosomal recessive** disorder associated with a mutation on chromosome 3 that results in the defective formation of **homogentisic acid oxidase**.
Pathophysiology	Homogentisic acid oxidase is responsible for the degradation of tyrosine. When this enzyme is defective, there is a buildup of tyrosine, phenylalanine (precursor to tyrosine), and homogentisic acid (intermediate in tyrosine breakdown). The accumulation of **homogentisic acid** causes degeneration of cartilage, leading to a dark blue **discoloration of connective tissue** (ochronosis) and degenerative joint disease.
Clinical Manifestations	Increased **pigmentation** of ears, nasal bridge, conjunctiva, neck, and anterior thorax; arthralgias and incapacitating **arthritis** of knee joints, spine, and fingers.
	Lab findings: Elevated urine homogentisic acid; **dark urine** caused by polymers of homogentisate.
	Imaging: Premature arthritic changes and cartilaginous calcifications seen on x-ray film.
Treatment	Symptomatic treatment of arthritis.
Notes	

A 14-year-old boy presents to the emergency room complaining of sudden severe, intermittent right flank pain associated with nausea and vomiting. Physical examination is remarkable for a slight fever, tachycardia, and tenderness in the right upper quadrant of the abdomen and right flank. His routine urinalysis shows hematuria. After three-way films of the abdomen revealing a radiopaque stone in the area of the right kidney, you begin treating him for kidney stones. When further urinalysis testing reveals the presence of cysteine crystals, you begin to wonder whether this patient might suffer from an autosomal recessive disorder that is associated with abnormal renal and intestinal transport of four amino acids.

4

Cystinuria

Biochemical Defect	An **autosomal recessive** disorder that results in the formation of a **defective amino acid transporter** in the renal tubule and intestinal epithelial cells.
Pathophysiology	The amino acid transporter is responsible for transporting **cysteine, ornithine, lysine, and arginine**. Defective tubular reabsorption of these amino acids in the kidneys results in **increased cysteine in the urine**, which can precipitate and cause kidney stones.
Clinical Manifestations	Cysteine **kidney stones** presenting with severe, intermittent flank pain and hematuria.
	Lab findings: Increased urinary excretion of cysteine, ornithine, arginine, and lysine on urine amino acid chromatography; **hematuria** and cysteine crystals (hexagonal) on cooling of acidified urine sediment.
	Imaging: Radiopaque kidney stones on CT scan.
Treatment	Low-methionine diet; increased fluid intake; acetazolamide to alkalinize the urine.
Notes	**Cystinosis** is a rare disorder characterized by the intralysosomal accumulation of free cysteine in body tissues. One variant of cystinosis is the infantile (nephropathic) autosomal recessive form, which manifests as **Fanconi syndrome**. Fanconi syndrome is characterized by renal proximal tubular dysfunction, leading to hypophosphatemia, renal glycosuria, generalized amino aciduria, and hypokalemia. Clinical manifestations include growth retardation, vomiting, rickets, polyuria, dehydration, metabolic acidosis, and photophobia. Death usually occurs as a result of uremia or infection by age 10.

A 32-year-old man presents to your primary care practice complaining of a rash on his face and neck. He reports that the rash is usually worse after he spends the day outside. On further questioning, he also reveals that he has been feeling more irritable than usual. Physical examination is significant for mild photophobia, an ataxic gait, and the presence of a scaly, red rash on the face, back of the neck, and extensor surfaces of his limbs. You feel as though his symptoms are rather consistent with niacin (vitamin B_6) deficiency, although he reports eating a healthy and well-balanced diet. You prescribe nicotinic acid supplements and concurrently refer him to a geneticist for workup of a rare autosomal recessive disease that causes defective transport of certain amino acids in the intestine and kidney.

4

Hartnup Disease

Genetic Defect	A rare **autosomal recessive** disorder that results in the **mutation of a sodium-dependent transport channel of neutral amino acids** (ie, tryptophan).
Pathophysiology	The neutral amino acid transport channel is **present in both the proximal tubule of the nephron and the brush border of the small intestine**. If this transport channel is defective, neutral amino acids cannot be absorbed in the intestine or reabsorbed by the kidney after filtration, thereby resulting in a **relative deficiency of the neutral amino acids, such as tryptophan**. If the body is deficient in tryptophan (a precursor for niacin), symptoms can arise that **mimic niacin deficiency** (ie, pellagra).
Clinical Manifestations	Symptoms appear intermittently and tend to decrease with age. Symptoms include a **photosensitive dermatitis** that affects face, neck, and extensor surfaces of limbs and neurologic signs (headaches; **personality disturbances**; photophobia; mental retardation; **cerebellar ataxia**).
	Lab findings: **Renal aminoaciduria**; indoles in the urine.
Treatment	Nicotinic acid supplements.
Notes	

A 7-year-old boy presents to your pediatric clinic complaining of diminished visual acuity. He was born in Southeast Asia and immigrated to the United States 1 year ago. On physical examination, you find that he has lenticular dislocation on ophthalmologic examination and abnormally long fingers. His concerned parents also report that he was far behind his peers in terms of developmental milestones and seems to suffer from some mild mental retardation. While you await an emergent pediatric ophthalmology consult, you order serum and urine studies, expecting elevated serum methionine and urine homocysteine levels. You suspect that the patient will need high-dose pyridoxine, cysteine, folate supplements, and a methionine-restricted diet.

4

Homocystinuria

Biochemical Defect	An **autosomal recessive** disorder that is caused by a **defect in cystathionine synthase** or in NPTHM. The disorder can be caused by either a deficiency of either enzyme or **decreased affinity of cystathionine synthase for pyridoxal phosphate (vitamin B$_6$)**, a necessary cofactor for the enzyme.
Pathophysiology	Homocysteine is converted to either methionine by NPTHM or to cystathionine (and eventually cysteine) by cystathionine synthase (with vitamin B$_6$). If either NPTHM or cystathionine synthase is defective, homocysteine will accumulate. Homocysteine is a toxin to the vascular endothelium, leading to increased atherosclerosis and increased platelet adhesiveness to the vessel wall and thus increased incidence of thrombus formation. Elevated homocysteine levels also interfere with normal collagen formation, thereby resulting in ocular and skeletal malformations.
Clinical Manifestations	Marfanoid appearance with elongated limbs; can cause mental retardation, neuropsychiatric dysfunction, **osteoporosis**, and characteristic **lens dislocation** (ectopia lentis). Patients with this disorder are at increased risk for **thromboembolism** and coronary artery disease.
	Lab findings: Increased methionine in serum; excess **homocysteine in urine**.
Treatment	Enzyme deficiency: **Decreased methionine** and increased cysteine and folate in diet.
	Decreased affinity of synthase for pyridoxal phosphate: **high-dose** vitamin B$_6$ in diet.
Notes	Homocystinuria can also result in response to a deficiency of vitamin B$_{12}$, which is needed for normal functioning of NPTHM.

A concerned mother brings her 4-day-old boy to the pediatric emergency room because he is vomiting her breast milk. On further questioning, she tells you that the child is urinating regularly, but that the urine has a strange odor reminiscent of pancake syrup. On physical examination, the child is afebrile; however, you note that his Moro reflex is absent and that his muscle tone is rigid. When laboratory studies suggest the presence of a metabolic acidosis, you decide to admit the child to the pediatric intensive care unit and tell his mother that the child's symptoms are likely associated with a rare genetic disorder associated with defective breakdown of certain amino acids.

4

Maple Syrup Urine Disease

Biochemical Defect	An **autosomal recessive** disorder resulting in a **defect of the BCKD**.
Pathophysiology	BCKD is the second enzyme in the pathway of the **breakdown of the three branched-chain amino acids: isoleucine, leucine, and valine**. When this enzyme is defective, branched-chain ketoacids build up, resulting in a metabolic acidotic state. Also, the elevated levels of these **ketoacids are toxic to the brain** and lead to brain edema with gliosis and white matter demyelination.
Clinical Manifestations	Symptoms include those associated with **metabolic acidosis**, psychomotor retardation (muscular rigidity, loss of Moro reflex), **brain damage**, and a **maple syrup odor of the urine** (caused by branched-chain amino acids in urine).
	Lab findings: Increased serum and urine levels of branched-chain amino acids (isoleucine, leucine, valine).
Treatment and Prognosis	Protein-modified diet restricting intake of branched-chain amino acids; dialysis; thiamine supplementation.
	Associated with high mortality rate.
Notes	

A 2-year-old boy with blonde hair and blue eyes presents to your pediatric clinic after just having immigrated from outside the United States. The child appears small for his age and has slight microcephaly. His parents report some concern about possible developmental delays. Physical examination is significant for hypertonia and hyperreflexia in all limbs. In addition to ordering a CBC and urinalysis, you order a Guthrie test, which you suspect will be positive. While you await the results of the laboratory testing, you tell the parents that the patient will likely need to avoid foods containing Nutrasweet.

Phenylketonuria

Biochemical Defect	An **autosomal recessive** disorder caused by multiple loss-of-function mutations in **phenylalanine hydroxylase** or decreased tetrahydrobiopterin, a cofactor for the enzyme.
Pathophysiology	**Phenylalanine hydroxylase** is **responsible for converting phenylalanine into tyrosine**. When this enzyme is deficient, phenylalanine builds up. High levels of phenylalanine lead to severe **brain damage** by competitively inhibiting amino acid transport required for protein synthesis, impairing polyribosome stabilization, reducing myelin production, and decreasing the formation of norepinephrine and serotonin. Phenylalanine is also a competitive inhibitor of tyrosinase, a key enzyme in the pathway of melanin synthesis, and thereby leads to hypopigmentation of the hair and skin.
Clinical Manifestations	Mental and **growth retardation**; microcephaly; decreased pigmentation **(blonde and blue-eyed)**; eczema; "mousy" body odor; heavy perspiration; **musty urine** odor; hypertonia, hyperreflexia.
	Lab findings: **Phenylketones** detected **in urine** (phenylacetate, phenyllactate, and phenylpyruvate); positive Guthrie test (measures phenylalanine in blood) at birth.
Treatment	Decreased intake of phenylalanine (avoid aspartame, which is found in Nutrasweet) and increased dietary tyrosine (essential amino acids for patients with this disorder).
Notes	**Histidinemia** is an autosomal recessive disorder caused by a defect in histidine-α-deaminase, which results in defective breakdown of histidine. Thus, there are elevated levels of histidine in the blood. The disorder is characterized by both hearing and speech deficits.

GENERAL CONCEPTS

Nucleotide and base structure
Origin of atoms of purine and pyrimidine rings
Purine and pyrimidine nucleotide synthesis
Purine and pyrimidine nucleotide degradation
Deoxyribonucleotide synthesis
Thymidylate synthesis

DISEASES

Adenosine deaminase deficiency
Lesch-Nyhan syndrome
Orotic aciduria

5

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NUCLEOTIDES AND BASES

- A nucleotide contains a sugar (deoxyribose or ribose), a base (purine or pyrimidine), and at least one phosphate group.
- A nucleotide is a nucleoside (sugar with a base in glycosidic linkage to C1) with phosphate group(s) in an ester linkage to C5.
- Purines include adenine and guanine and have two rings; pyrimidines include cytosine, thiamine, and uracil and have one ring.
- Adenine has an ammonia group on its rings, whereas guanine has a ketone group.
- Thymine (found in DNA) and uracil (found in RNA) are similar in that they both have ketone groups, but thymine has an extra methyl group on its ring.
- Bonds between guanine and cytosine (three hydrogen bonds) are stronger than bonds between adenine and thymine (two hydrogen bonds).

Pyrimidines
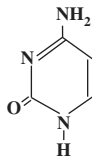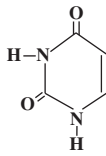
Cytosine   *Uracil*   *Thymine*

Purines

5
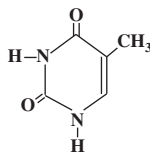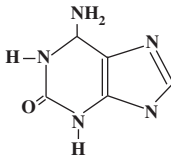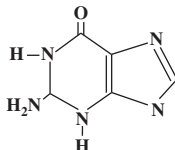
Adenine   *Guanine*

ORIGINS OF ATOMS IN THE PURINE AND PYRIMIDINE RINGS

PYRIMIDINE RING
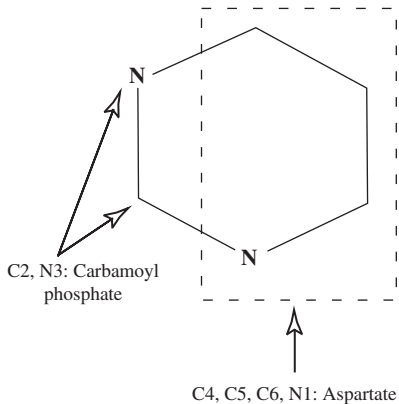
C2, N3: Carbamoyl phosphate

C4, C5, C6, N1: Aspartate

PURINE RING

C6: Respiratory CO_2

N1: Aspartate

C4, C5, N7: Glycine

N^{10}-formyl Tetrahydrofolate

N^{10}-formyl Tetrahydrofolate

N3, N9: Glutamine

DE NOVO PURINE NUCLEOTIDE SYNTHESIS

Ribose-5-Phosphate

PRPP Synthetase — ATP → AMP

PRPP

Glutamine PRPP Amidinotransferase — Glutamine → Glutamate

5-Phosphoribosylamine

IMP

ADP ATP — *IMP Dehydrogenase*

GTP → GDP — *Adenylosuccinate Synthetase*

GMP

AMP

5
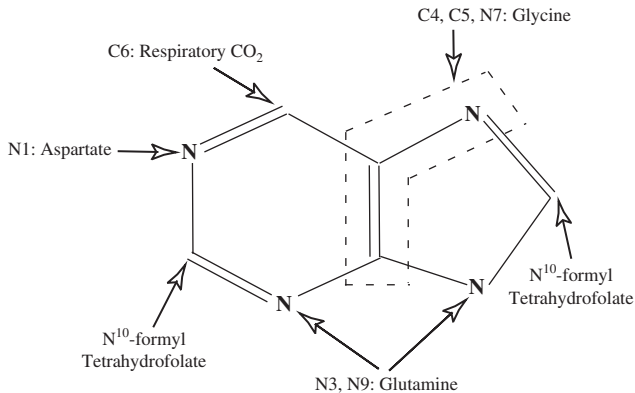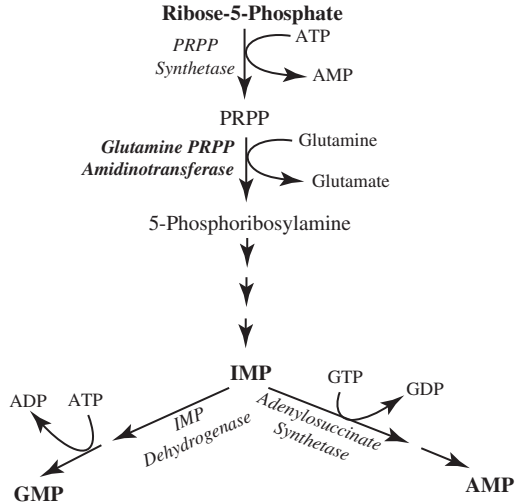
DE NOVO PURINE NUCLEOTIDE SYNTHESIS

- **Location:** Purine synthesis occurs in all tissues.
- **Substrates:** Ribose-5-phosphate; glycine; glutamine; H_2O; ATP; CO_2; aspartate.
- **Products:** GMP; AMP; glutamate; fumarate; H_2O.
- **Overview of pathways:**
  - ► Ribose-5-phosphate (as provided by the pentose-phosphate pathway) is converted into PRPP by *PRPP synthetase*, in a step requiring one ATP.
  - ► In the committed step in the process, an α-amino group is then added to PRPP from glutamine to form 5-phosphoribosylamine. This reaction is catalyzed by *glutamine PRPP amidinotransferase.*
  - ► A series of nine reactions results in the formation of IMP.
  - ► IMP can then be transformed either to GMP by *IMP dehydrogenase*, or to AMP by *adenylosuccinate synthetase*.
- **Regulation of important enzymes:**
  - ► *PRPP synthetase:* Inhibited by AMP, IMP, and GMP.
  - ► *Glutamine PRPP amidinotransferase:* Inhibited by AMP, IMP, and GMP.
  - ► *IMP dehydrogenase:* Inhibited by GMP.
  - ► *Adenylosuccinate synthetase:* Inhibited by AMP.
- **Pharmacologic inhibitors:** Although not shown, tetrahydrofolate is involved in two reactions of de novo purine synthesis. Folic acid analogs, such as methotrexate, inhibit the formation of tetrahydrofolate and thus interfere with purine synthesis.

PURINE SALVAGE PATHWAYS

- **Location:** Purine synthesis via the salvage pathways occurs in all tissues.
- **Substrates:** Hypoxanthine; PRPP; guanine; adenine.
- **Products:** GMP; AMP; IMP.
- **Overview of pathways:**
  - ▶ Bases from degraded nucleic acids can be converted back into purine nucleotides via the salvage pathways.
  - ▶ Hypoxanthine can be combined with PRPP (which acts as the donor of ribose-5-phosphate) to form IMP in a reaction catalyzed by *HGPRT*. IMP can subsequently be transformed into AMP or GMP via the last few steps of the pathway of de novo purine synthesis.
  - ▶ *HGPRT* also catalyzes the reaction which combines PRPP with guanine to form GMP.
  - ▶ *Adenine phosphoribosyltransferase* converts adenine and PRPP to form AMP.
- **Regulation of important enzymes:**
  - ▶ *HGPRT:* Inhibited by IMP and GMP.
  - ▶ *Adenine phosphoribosyltransferase:* Inhibited by AMP.
- **Diseases:** Deficiency of *HGPRT* leads to Lesch-Nyhan syndrome (see card 77), which is characterized by self-mutilation and CNS deterioration.

CO_2

Carbamoyl Phosphate Synthetase II — Glutamine + 2 ATP

Glutamate + 2 ADP → Orotic acid

Carbamoyl phosphate

Orotate Phosphoribosyl Transferase — PRPP → PP_i

Aspartate Transcarbamoylase — Aspartate

Dihydroorotate Dehydrogenase

Carbamoyl aspartate

Orotidine monophosphate

OMP Decarboxylase → CO_2

Dihydroorotase — H_2O

→ NADH

NAD$^+$

UMP → UTP — *CTP Synthetase* → CTP

Dihydroorotate

2 ATP

2 ADP

Glutamine + ATP

Glutamate + ADP

5
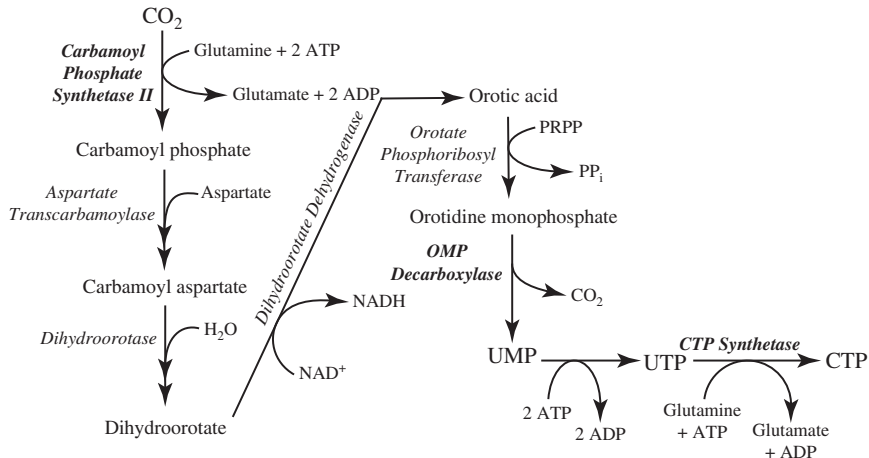
PYRIMIDINE NUCLEOTIDE SYNTHESIS

- **Location:** De novo pyrimidine synthesis occurs in the cytosol of cells in all tissues.
- **Substrates:** CO_2; glutamine; ATP; aspartate; H_2O; NAD^+; PRPP.
- **Products:** UTP; CTP; glutamate; NADH; CO_2.
- **Overview of Pathways:**
  - ► CO_2 and glutamine are combined to form carbamoyl phosphate. This reaction is catalyzed by *carbamoyl phosphate synthetase II*, which is the major regulated step for this pathway.
  - ► Carbamoyl phosphate is then combined with water and aspartate before being subsequently dehydrogenated in a series of reactions to form orotic acid.
  - ► The ribose-5-phosphate ring is then attached to orotic acid by *orotate phosphoribosyl transferase*, to form OMP.
  - ► OMP is decarboxylated to form UMP by *OMP decarboxylase*.
  - ► UMP can then be phosphorylated to form UTP.
  - ► UTP can subsequently be converted to CTP with the addition of an amino group that is donated by glutamine. The conversion of UTP to CTP is catalyzed by *CTP synthetase*.
- **Regulation of important enzymes:**
  - ► *Carbamoyl phosphate synthetase II:* Inhibited by UTP; activated by ATP and PRPP.
  - ► *Orotidylate (OMP) decarboxylase:* Inhibited by UMP and CMP.
  - ► *CTP synthetase:* Inhibited by CTP.
- **Pyrimidine synthesis via salvage pathways:** Pyrimidines can be salvaged from orotic acid, uracil, and thymine but not from cytosine. Salvage is accomplished by the enzyme *pyrimidine phosphoribosyl transferase.*
- **Diseases:** Deficiencies in *orotate phosphoribosyl transferase* or *OMP decarboxylase* can lead to orotic aciduria (see card 78), which is characterized by growth retardation and anemia.

PURINE NUCLEOTIDE DEGRADATION
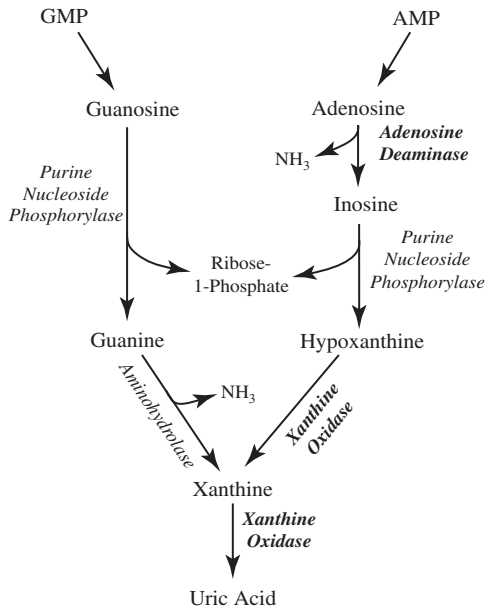
- **Location:** Purine degradation takes place in most tissues.
- **Substrates:** AMP; GMP.
- **Product:** Uric acid (excreted in the urine).
- **Overview of pathways:**
  - ► AMP and GMP are dephosphorylated to form their respective nucleosides, adenosine and guanosine.
  - ► Adenosine is then deaminated by *adenosine deaminase* to form inosine.
  - ► The sugar ring, ribose-1′-phosphate is then removed from inosine and guanosine by *purine nucleoside phosphorylase* to form hypoxanthine and guanine, respectively.
  - ► Guanine is then deaminated by *aminohydrolase* to form xanthine, while hypoxanthine is oxidized to form xanthine.
  - ► Xanthine is further oxidized by *xanthine oxidase* to form uric acid, which is excreted in the urine.
- **Diseases and treatments:**
  - ► Deficiency of *adenosine deaminase* results in severe combined immune deficiency (see card 76).
  - ► Allopurinol is a *xanthine oxidase* inhibitor that is used to treat hyperuricemia and gout.

5

PYRIMIDINE NUCLEOTIDE DEGRADATION

Surplus Nucleotides

Uracil or Cytosine → Thymine

reduction, ring-opening, deamination-decarboxylation

$CO_2 + NH_4^+$
β-Alanine

$CO_2 + NH_4^+$
β-Aminoisobutyrate

Acetyl CoA

Succinyl CoA

Citric Acid Cycle
Fatty Acid Synthesis
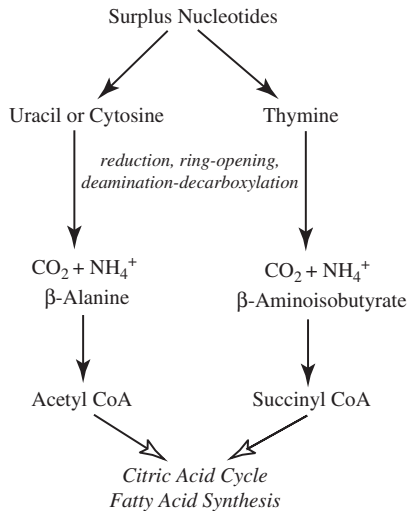
- **Location:** Pyrimidine degradation can take place in many tissues.
- **Substrates:** UTP; CTP; TTP.
- **Products:** CO_2; NH_4^+; β-alanine; β-aminobutyrate.
- **Purpose:** Unlike purine nucleotides, pyrimidine nucleotides can be completely degraded into precursors for intermediates of other metabolic processes, such as the citric acid cycle.
- **Overview of pathways:**
  - ► Nucleotides are degraded to their base forms of uracil, cytosine, and thymine.
  - ► Through a three-step process of reduction, ring-opening and deamination-decarboxylation that requires a series of enzymes, the bases are broken down into a ammonium ion, carbon dioxide, and a carbon skeleton (either β-alanine or β-aminoisobutyrate).
  - ► Subsequent degradation of these carbon skeletons results in molecules of acetyl CoA and succinyl CoA, which can subsequently be entered into the pathways for fatty acid synthesis or the citric acid cycle.

DEOXYRIBONUCLEOTIDE SYNTHESIS

Ribonucleoside Diphosphate

Deoxyribonucleoside Diphosphate
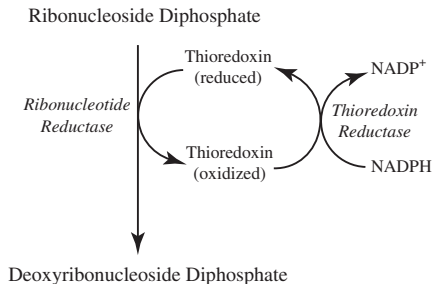
- **Location:** Deoxyribonucleotide synthesis occurs in all tissues.
- **Substrates:** ADP; CDP; UDP; GDP; NADPH.
- **Products:** dADP; dCDP; dUDP; dGDP.
- **Overview of pathways:**
  - ▶ *Ribonucleotide reductase* acts to reduce the ribonucleotide to a deoxyribonucleotide. The two sulfhydryl groups of thioredoxin provide reducing power for *ribonucleotide reductase*, and thioredoxin becomes oxidized in the process.
  - ▶ In a reaction requiring NADPH, *thioredoxin reductase* converts the oxidized thioredoxin back to its reduced state so that it can be reused by *ribonucleotide reductase*.
- **Regulation of *ribonucleotide reductase*:** Allosterically inhibited by dATP and other deoxynucleotide triphosphates.

5

THYMIDYLATE SYNTHESIS
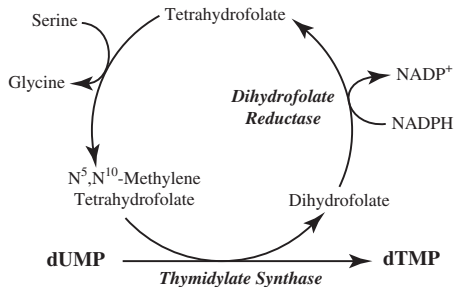
- **Location:** Deoxythymidylate (dTMP) synthesis occurs in all body tissues.
- **Substrates:** dUMP; NADPH; serine.
- **Products:** dTMP; glycine.
- **Overview of pathways:**
  - ► *Thymidylate synthase* catalyzes a reaction in which a one-carbon unit from N^5, N^{10}-methylene tetrahydrofolate (FH_4) is transferred to C5 on the uracil ring of dUMP.
  - ► Concurrently, FH_4 is oxidized to dihydrofolate to reduce the methylene group on dUMP to a methyl group, thereby forming dTMP.
  - ► FH_4 must be regenerated from dihydrofolate for this process to continue. *Dihydrofolate reductase* converts dihydrofolate to tetrahydrofolate with the aid of NADPH. Tetrahydrofolate is then remethylated with the aid of serine to form FH_4, which can subsequently be used again by *thymidylate synthase*.
- **Pharmacologic inhibitors:** Folic acid analogs (such as methotrexate) act to inhibit *dihydrofolate reductase*, which results in a lack of tetrahydrofolate and thus inhibition of this pathway.

A 2-month-old male infant has been referred to your pediatric genetics practice for failure to thrive and repeated infections. Over the last month, the child was admitted to the hospital twice for the treatment of bacterial and viral pneumonias as well as for positive fungal growth from past stool samples. While hospitalized, the child was found to have a significantly deficient lymphocyte count. The child's older brother and older sister are in good health. The patient's mother notes that **5** her father's sister died before the age of 1 as a result of repeated illnesses. You suspect that the child has an immune deficiency and will not be able to survive past his first birthday without extraordinary treatment. You inform the concerned parents that the child may need a bone marrow transplantation and raise the possibility of experimental gene therapy.

Adenosine Deaminase Deficiency

Biochemical Defect	An **autosomal recessive** disorder that results in a **defect of ADA**.
Pathophysiology	**ADA is involved in converting adenosine to inosine during purine degradation**. When ADA is deficient, adenosine accumulates. This accumulation of adenosine eventually results in an excess of dATP, which serves to **inhibit ribonucleotide reductase**, a key enzyme in the synthesis of DNA. Defective DNA synthesis results in deficient lymphoid differentiation and results in **dysfunctional T and B cells**.
Clinical Manifestations	Adenosine deaminase deficiency accounts for half of the autosomal recessive cases of **SCID**. SCID is associated with severe and repeated **fungal, bacterial, viral, and protozoal infections** during the first year of life. The disorder commonly presents with *Pneumocystis carinii* pneumonia and failure to thrive. Graft-versus-host disease will often develop after transfusions.
Treatment and Prognosis	**Bone marrow transplantation** as a source of stem cells. Administration of exogenous ADA prognosis (ADA conjugated to polyethylene glycol) may improve immunologic function and clinical status. ADA **gene therapy** is also used with limited success. Affected infants rarely survive beyond 1 year without treatment.
Notes	SCID can also be inherited by autosomal recessive RAG-1 or RAG-2 mutations, by mutations in the DNA-dependent tyrosine kinase gene, or as an **X-linked recessive disorder that results in defective IL-2 receptors on T cells**.

A 2-year-old boy presents to your pediatric clinic without having been seen by a pediatrician since 6 months of age. His parents are concerned about his propensity for biting himself and strange writhing body movements. On physical examination, the patient is quite spastic in his movements with marked hyperreflexia in all limbs. His fingers are notably disfigured from his constant self-biting. When questioned further, the mother admits that the child produces reddish-orange urine in his diapers but states that this has been a constant phenomenon since birth. You ask the nurse to collect urine from the child, suspecting marked hyperuricemia and uric acid crystals on analysis. You start the child on allopurinol and suggest that the parents see a dentist about removing the child's newly forming front teeth.

Biochemical Defect	An **X-linked recessive** disease that results from a deficiency of **HGPRT**.
Pathophysiology	HGPRT is an enzyme involved in the **salvage purine synthesis pathway**, which catalyzes the reaction that combines PRPP with either hypoxanthine or guanine to form IMP or GMP, respectively. When HGPRT is deficient, hypoxanthine and guanine are degraded to form uric acid instead of IMP and GMP, leading to **hyperuricemia**. Hyperuricemia then leads to nephrolithiasis and arthritis. IMP and GMP levels are decreased and PRPP levels are increased, leading to stimulation of the de novo purine synthesis pathway. **Excessive levels of purines** can lead to **CNS damage** and neurologic problems.
Clinical Manifestations	**Self-mutilative behavior**; aggression; spasticity; choreoathetosis (involuntary writhing); kidney stones; arthritis; hyperreflexia; **gout**; **mental retardation**; orange or red urine. *Lab findings:* **Hyperuricemia**; uric acid crystals in urine.
Treatment	**Allopurinol** (xanthine oxidase inhibitor) can prevent problems related to hyperuricemia but has no effect on behavior or neurologic abnormalities.
Notes	**Primary gout** is caused by inherited errors of metabolism that result in increased levels in uric acid. Although many of these mutations are not characterized, some cases of primary gout are caused by a partial deficiency of HGPRT. Symptoms of gout include acute arthritis (especially in the big toe, or podagra) and obstructive nephropathy. Gout is treated with colchicines and NSAIDs for acute relief and allopurinol for prevention.

A 2-month-old girl presents to the pediatric clinic for a follow-up visit. She was seen 2 weeks ago for a routine physical examination and was found to have a hypochromic megaloblastic anemia at that time. She was started on iron, folic acid, and vitamin B_{12}. According to her serum studies, she has been unresponsive to this treatment regimen. On physical examination, she is small for her age and has sparse hair. She looks rather pale and lethargic. When a urine study shows a specific crystalluria, you **5** begin to suspect that this child may suffer from a rare autosomal recessive disorder of pyrimidine synthesis.

Orotic Aciduria

Biochemical Defect	An **autosomal recessive** disorder of pyrimidine synthesis that is caused by **mutations** in the bifunctional enzyme, **UMP synthase**.
Pathophysiology	UMP synthase is composed of two different enzymes: **orotate phosphoribosyl transferase** and **orotidylate (OMP) decarboxylase**. UMP synthase is involved in the conversion of orotic acid into UMP by the addition of a ribose-5′-monophosphate ring during **de novo pyrimidine synthesis**. When UMP synthase is defective, orotic acid builds up and the synthesis of nucleic acids is impaired, leading to **deficient hematopoiesis and growth**.
Clinical Manifestations	Symptoms of anemia (lethargy, **weakness**, pallor); **growth retardation**; neurologic abnormalities.
	Lab findings: **Orotic acid crystalluria** in urine; peripheral blood smear shows **hypochromic megaloblastic anemia**.
Treatment	Supplementation of synthetic **uridine and cytidine** (supplies pyrimidine nucleotides needed for RNA and DNA synthesis).
Notes	

GENERAL CONCEPTS

Heme synthesis
Heme degradation
Hemoglobin structure and function

DISEASES

Acute intermittent porphyria
Congenital erythropoietic porphyria
Porphyria cutaneous tarda
Hereditary coproporphyria
Lead poisoning

6

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Heme

Succinyl CoA + glycine

ALA Synthase

Aminolevulinic Acid

ALA Dehydrase

Porphobilinogen

Uroporphyrinogen I Synthetase

Preuroporphyrinogen

Uroporphyrinogen III Cosynthetase

Uroporphyrinogen III

Fe^{2+} *Ferrochelatase*

Protoporphyrin IX

Mitochondria

Protoporphyrinogen IX

Coproporphyrinogen Oxidase

Coproporphyrinogen III

Cytosol

Uroporphyrinogen Decarboxylase

6

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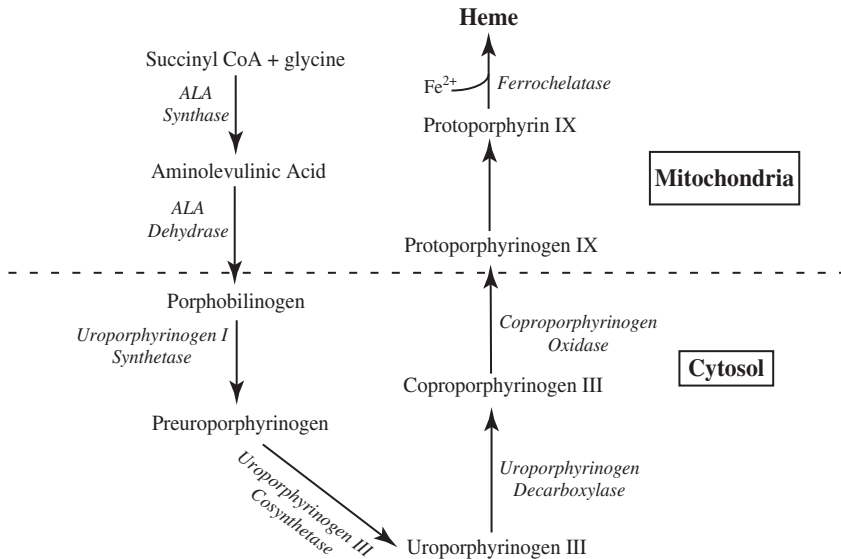
HEME SYNTHESIS

- **Location:** Heme synthesis takes place in the cytosol and mitochondria of cells of the liver and bone marrow.
- **Substrates:** Succinyl A CoA; glycine; Fe^{2+}.
- **Product:** Heme.
- **Overview of pathways:**
  - ► Succinyl CoA and glycine are combine by *ALA synthase* to form aminolevulinic acid.
  - ► Aminolevulinic acid is subsequently dehydrated by *ALA dehydrase* to form porphobilinogen.
  - ► A series of reactions in the cytosol of the cell results in the transformation of porphobilinogen to protoporphyrinogen IX, which is subsequently transferred back into the mitochondria of the cell.
  - ► In the mitochondria of the cell, protoporphyrinogen IX is converted to protoporphyrin IX.
  - ► Iron is added to protoporphyrin IX by the enzyme, *ferrochelatase*, to form heme.
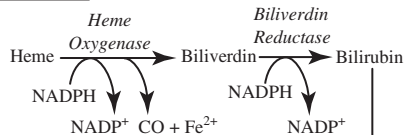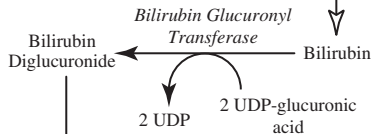- **Regulation:** *ALA synthase*, the primary regulating enzyme of heme synthesis, is inhibited by high levels of hemin (a heme derivative).
- **Diseases and toxicities:**
  - ► Deficiencies in any of the heme synthesis enzymes leads to a porphyria.
  - ► Lead inhibits *ferrochelatase* and *ALA dehydrase*, leading to deficient heme synthesis with a resulting anemia and other symptoms of lead poisoning.
  - ► Barbiturates and other drugs that induce the cytochrome P-450 system can lead to the activation of *ALA synthase*. Activation of the cytochrome P-450 system leads to decreased heme levels, which results in enhanced *ALA synthase* activity. Use of these drugs can precipitate clinical manifestations of porphyrias.

Macrophage

Heme $\xrightarrow{\textit{Heme Oxygenase}}$ Biliverdin $\xrightarrow{\textit{Biliverdin Reductase}}$ Bilirubin

NADPH $\rightarrow$ NADP$^+$ CO + Fe^{2+}

NADPH $\rightarrow$ NADP$^+$

- -

Liver

Bilirubin Diglucuronide $\xleftarrow{\textit{Bilirubin Glucuronyl Transferase}}$ Bilirubin

2 UDP   2 UDP-glucuronic acid

- -

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Intestine

Bilirubin Diglucuronide (in Bile) $\longrightarrow$ Bilirubin $\nearrow$ Urobilinogen $\downarrow$ Stercobilin
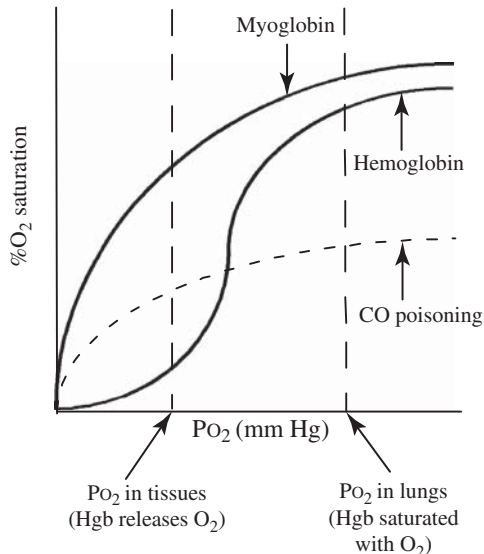
HEME DEGRADATION

- **Location:** Various components of heme degradation occur in the cells of the reticuloendothelial system, liver, and intestine.
- **Substrates:** Heme; NADPH; 2 UDP-glucuronic acid.
- **Products:** Urobilinogen (excreted in urine); stercobilin (excreted in feces); carbon monoxide (CO); Fe^{2+}.
- **Overview of pathway:**
  - ► RBCs are engulfed by cells of the reticuloendothelial system. The globin is recycled into amino acids, which in turn are catabolized into intermediates of the citric acid cycle and fatty acid oxidation.
  - ► Heme is oxidized; the heme ring is opened by *heme oxygenase*. The oxidation occurs on a specific carbon, producing the linear tetrapyrrole biliverdin, ferric iron (Fe^{3+}), and CO.
  - ► In the next reaction, a second bridging methylene is reduced by *biliverdin reductase*, producing bilirubin.
  - ► Bilirubin is then transported in the serum by albumin to the liver, where it is conjugated with glucuronate by *bilirubin glucuronyl transferase* and excreted in the bile.
  - ► In the intestine, bilirubin is deconjugated and converted to urobilinogen and stercobilin. Some urobilinogen is reabsorbed and excreted as urobilin in the urine. Most urobilinogen is oxidized in the feces to stercobilin.
- **Diseases:** In patients with abnormally high red cell lysis or obstructive liver damage, bilirubin can accumulate, leading to the clinical manifestation of jaundice.

HEMOGLOBIN STRUCTURE AND FUNCTION

- Hgb is a heme protein that is found in erythrocytes and is responsible for binding oxygen in the lung and transporting the bound oxygen throughout the body where it is used in aerobic metabolism.
- Hgb is composed of four polypeptide subunits (two α and two β).
- Oxygen binds at each of the four heme groups of the Hgb molecule.
- Hgb exists in two forms:
  - ► In the T (taut) form, the protein has a low affinity for oxygen and promotes oxygen unloading.
  - ► In the R (relaxed) form, the protein has a high affinity for oxygen (up to 300 times higher than in T form).

HGB-O_2 DISSOCIATION CURVE

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REGULATION

- The T (taut) form of hemoglobin, and thus oxygen unloading, is activated by the following:
  - ▶ Increased Cl^-.
  - ▶ Decreased pH (increased H^+).
  - ▶ Increased CO_2.
  - ▶ Increased temperature.
  - ▶ Increased levels of 2,3-BPG, seen in chronic hypoxemia or anemia (eg, emphysema or high altitude).
- Carbon dioxide binding favors the T (taut) form of Hgb and binds to the amino acids in the globin chain at the N terminus rather than to heme.
- Hgb, unlike myoglobin, exhibits positive cooperativity and negative allostery. This accounts for the sigmoid shape of the oxygen dissociation curve.

CO POISONING

- CO poisoning shifts the oxygen dissociation curve to the left and plateaus the curve because it has 200 times greater affinity for hemoglobin compared with oxygen.
- CO poisoning is reversible with the administration of large quantities of oxygen.
- CO poisoning causes headaches, dizziness, weakness, nausea and vomiting, chest pain, confusion, loss of consciousness, and death.

METHEMOGLOBIN

- Methemoglobin is an oxidized form of hemoglobin (ferric, Fe^{3+}) that cannot bind oxygen as readily.
- Formation of methemoglobin by amyl nitrite (oxidizes Fe^{2+} to Fe^{3+}) compound is used as a treatment for cyanide poisoning because methemoglobin can bind and sequester cyanide.

A 26-year-old woman presents to the emergency room complaining of severe abdominal pain. This is her fourth visit for the same complaint over the last calendar year. She has a history of epilepsy for which she takes several medications, including valproic acid, which was added to her regimen within the last year. Recent testing has included a normal CT scan of the abdomen, a normal endoscopy, and a negative colonoscopy. Upon taking a more detailed history, you learn that she has no vomiting or diarrhea but has not taken in food for the last 2 days because of pain. Your physical examination is significant for hypoactive deep tendon reflexes and a prominent left footdrop. You begin to wonder whether she may suffer from an autosomal dominant disorder involving a defect in the biosynthesis of heme, and you decide to test her urine for elevated porphobilinogen and ALA.

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Biochemical Defect	An **autosomal dominant** disorder that results from a defect in **uroporphyrinogen I synthetase**.
Pathophysiology	Uroporphyrinogen I synthetase is involved in the **biosynthesis of heme**. Specifically, it catalyzes the **conversion of PBG to preuroporphyrinogen**. When this enzyme is deficient, PBG and **ALA accumulate**, resulting in neurologic damage. Although the mechanism of disease is not well understood, PBG is thought to be neurotoxic and ALA may promote oxidative **damage to the CNS**.
Clinical Manifestations	Symptoms include intermittent, recurrent **abdominal pain** (resulting from autonomic dysregulation), **neuropsychiatric signs** and symptoms (blurred vision, hallucinations, hyporeflexia; peripheral neuropathy), and urine that darkens on exposure to air. Patients are *not* **photosensitive**. *Lab findings:* Elevated urine and plasma porphobilinogen and aminolevulinic acid; hyponatremia.
Treatment	**Hemin** (acts to decrease the synthesis of ALA synthase and thus decrease PBG and ALA accumulation); **discontinuation of precipitating factors** (exogenous and endogenous gonadal steroids; alcohol; **barbiturates**; valproate; low-calorie diets).
Notes	Symptomatic AIP results in patients who have the defective enzyme as well as exposure to drugs or environmental situations (such as fasting) that stimulate heme synthesis.

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A 32-year-old woman presents to your primary care clinic for an urgent care visit. She reports that she has had multiple episodes of crampy, episodic abdominal pain over the last 6 months. The abdominal pain is associated with nausea and constipation. She denies any new medications or significant change in her diet, although she does note that she has been trying to lose weight as of late and will go on 3- to 4-day stretches of fasting. Her husband, who has accompanied her to the appointment, also notes that she is often hysterical and seems to hallucinate during the attacks of abdominal pain. Physical examination is notable for hypoactive deep tendon reflexes. Her **6** abdominal examination is unremarkable, although you do make note of several blisters on her extremities. You initiate routine testing for abdominal symptoms, which is unremarkable. Upon reviewing her case with a specialist, you decide to send a stool sample to evaluate for elevated levels of coproporphyrins as you suspect that her symptoms may be related to a defect in the process of heme synthesis.

Hereditary Coproporphyria

Biochemical Defect	An **autosomal dominant** disorder that results from a defect in **coproporphyrinogen oxidase**.
Pathophysiology	Coproporphyrinogen oxidase is involved in the **biosynthesis of heme**. Specifically, it catalyzes the **conversion of coproporphyrinogen III to proprotoporphyrinogen IX**. When this enzyme is deficient, the precursors of heme (ie, porphobilinogen and ALA **accumulate**, resulting in central and peripheral neurologic damage as well as skin damage due to deposition of porphyrin precursors in the skin.
Clinical Manifestations	Symptoms include episodic recurrent, colicky **abdominal pain** (resulting from autonomic dysregulation), **psychiatric symptoms**, and autonomic neuropathies, which can manifest as **seizures**, constipation, hypertension, or **peripheral neuropathy**. Patients *are* **photosensitive** and can develop blisters with long-term sun exposure.
	Lab findings: Elevated stool and urinary coproporphyrins; hyponatremia.
Treatment	**Hemin** (acts to decrease the synthesis of ALA synthase and thus decrease PBG and ALA accumulation); **discontinuation of precipitating factors** (exogenous and endogenous gonadal steroids; alcohol; **barbiturates**; valproate; low-calorie diets); seizure control as needed.
Notes	Symptomatic hereditary coproporphyria results in patients who have the defective enzyme as well as exposure to drugs or environmental situations (such as fasting) that stimulate heme synthesis.

A mother brings her 6-month-old boy to your pediatric clinic for his first well-baby visit. The pregnancy was full term and uncomplicated; however, since the birth, the mother has not been able to visit the pediatric clinic until now. The mother is concerned about several vesicular lesions on the child's face and hands that developed a few days earlier after a prolonged outing at a neighborhood picnic. On physical examination, you notice several friable bullae on the child's face and hands and mild splenomegaly on abdominal examination. The child also has more hair than normal on the forearms, face, and hands. You consult the pediatric geneticist, who suggests ordering special laboratory studies to check for uroporphyrin or coproporphyrin in the serum and urine.

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Congenital Erythropoietic Porphyria

Biochemical Defect	An **autosomal recessive** disorder characterized by markedly **deficient activity of URO III cosynthetase**.
Pathophysiology	URO III cosynthetase is involved in the conversion of preuroporphyrinogen to uroporphyrinogen III during the **biosynthesis of heme**. When this enzyme is deficient, **uroporphyrin I and coproporphyrin I** (isomers/derivatives of preuroporphyrinogen) **accumulate** in the bone marrow, erythrocytes, teeth, plasma, and urine. Porphyrin deposition in the teeth leads to discoloration, whereas increased levels of erythrocyte porphyrins lead to **increased hemolysis** and splenomegaly. Porphyrins can also damage the bone marrow, leading to an **increased susceptibility to infections**. Porphyrin deposition in the skin results in the formation of oxygen-free radicals, which can then damage cells and lead to **photosensitivity**.
Clinical Manifestations	Severe **cutaneous photosensitivity** in early infancy with the appearance of friable bullae and vesicles. Other skin symptoms include skin thickening, focal pigmentation abnormalities, and facial and extremity hypertrichosis. Patients also suffer from disfigurement of face and hands, **reddish-brown teeth**, and **splenomegaly**.
	Lab findings: Elevated levels of uroporphyrin I and coproporphyrin I in the urine.
Treatment	**Blood transfusion** to suppress erythropoiesis; splenectomy to reduce hemolysis; β-carotene supplementation (free radical scavenger); possible bone marrow transplantation in severe cases.
Notes	

A 32-year-old man presents to your free clinic complaining of bullae formation on his forearms, hands, and face. He is an intravenous drug user and has not seen a physician for years. He tells you that he had similar problems as a child and that his brother has similar skin issues. On physical examination, you note small white plaques interspersed among fluid-filled vesicles and bullae over his face, hands, and forearms. The patient had recently become homeless and has been spending more time in the sun. The neurologic examination is completely benign. Besides ordering a series of laboratory studies, including tests for HIV and hepatitis, you also decide to order studies looking **6** for elevated porphyrins in the urine. You advise the patient to continue to return to the free clinic, believing that his skin condition can be treated with repeated phlebotomy.

Porphyria Cutaneous Tarda

Biochemical Defect	An **autosomal dominant** disorder that is characterized by a deficiency in hepatic **URO decarboxylase**. Sporadic cases of this disorder can also occur.
Pathophysiology	URO decarboxylase is involved in the **heme biosynthetic pathway**. It is responsible for converting uroporphyrinogen III to coproporphyrinogen III. When hepatic URO decarboxylase is defective, uroporphyrinogen III accumulates, resulting in the deposition of excess porphyrins in the skin. Excess porphyrin deposition in the skin results in the formation of oxygen free radicals, which can then damage cells and lead to photosensitivity.
Clinical Manifestations	Cutaneous **photosensitivity** as evidenced by fluid-filled vesicles and bullae over sun-exposed areas of face, the dorsum of hands and feet, forearms, and legs. Often, small white plaques (**milia**) will precede vesicle formation. Other skin manifestations include hypertrichosis, hyperpigmentation, and skin thickening. There are *no* neurologic manifestations. *Lab findings:* **Elevated porphyrins** in the plasma and urine; urinary ALA slightly increased; urinary **PBG level is normal**.
Treatment	Repeated phlebotomy to reduce hepatic iron; low-dose chloroquine; stop use of alcohol, iron supplements, and estrogen, all of which can exacerbate symptoms.
Notes	HIV and hepatitis can precipitate symptom onset.

A 36-year-old man presents to your walk-in clinic complaining of recurrent abdominal pain, constipation, muscle pain, and headaches over the last 3 months. He reports no medical history or significant family history. After further questioning, you learn that he started working for a contractor several months ago and has been stripping and remodeling old warehouses. On physical examination, you see a bluish tinge to the gum-tooth line in his mouth and a significant ankle drop on the left side. You order serum studies and a peripheral blood smear, expecting to find microcytic hypochromic anemia with basophilic stippling on smear. You advise the patient to pursue safer working **6** conditions and decide to inform the proper authorities of the patient's working conditions.

Lead Poisoning

Biochemical Defect	Increased levels of lead in the blood leads to the inhibition of sulfhydryl-dependent enzymes such as γ-aminolevulinic acid dehydratase and ferrochelatase, which are enzymes involved in heme synthesis.
Pathophysiology	Inorganic lead is absorbed via lungs and GI tract. Elevated levels of lead disrupt hemoglobin synthesis, leading to an increase in FEP (eg, ALA), which contribute to oxidative damage to several organ systems, including demyelination and axonal degeneration in nervous system, decreased erythrocyte survival time, increased hemolysis, renal toxicity, and hypertension.
Clinical Manifestations	**Abdominal pain** (lead colic); **constipation**; irritability; difficulty concentrating; arthralgia; myalgia; encephalopathy; anorexia; decreased libido; **"lead line"** (a bluish pigmentation seen at the gum-tooth line); peripheral **neuropathy** (extensor weakness or wrist/ankle drop).
	Lab findings: **Elevated serum lead level**, elevated FEP level, **microcytic hypochromic anemia**; **basophilic stippling** on peripheral blood smear.
	Imaging: Lead lines on x-ray film of long bone epiphyses.
Treatment	Reduction of lead exposure; chelation with **succimer** (2,3-dimercaptosuccinic acid) if blood lead levels <80 µg/dL; other pharmacologic treatments include vitamin C, calcium-edetic acid, penicillamine, and dimercaprol.
Notes	

GENERAL CONCEPTS

Steroidogenesis in the adrenal cortex
Structure, function, and regulation of adrenal hormones

DISEASES

21β-hydroxylase deficiency
17α-hydroxylase deficiency
11β-hydroxylase deficiency
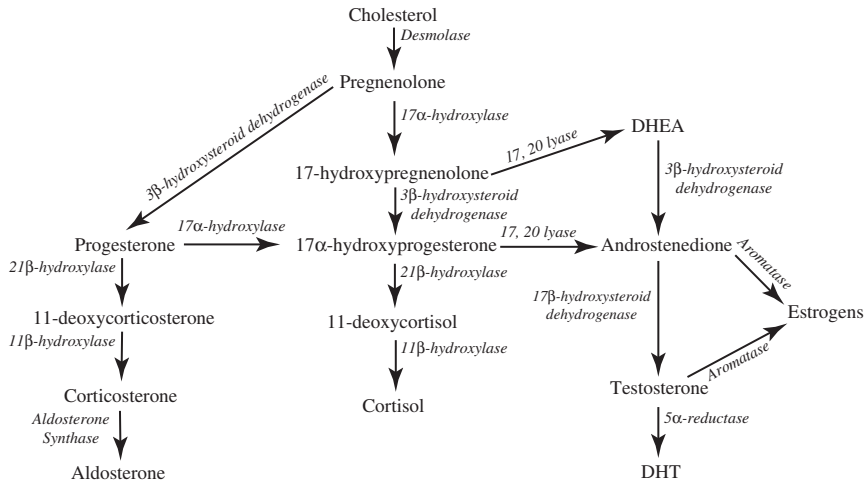3β-hydroxysteroid dehydrogenase deficiency
Androgen insensitivity syndrome

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Cholesterol
Desmolase

Pregnenolone

3β-hydroxysteroid dehydrogenase

17α-hydroxylase

17-hydroxypregnenolone

17, 20 lyase → DHEA

3β-hydroxysteroid dehydrogenase

Progesterone

17α-hydroxylase → 17α-hydroxyprogesterone *17, 20 lyase* → Androstenedione

21β-hydroxylase

3β-hydroxysteroid dehydrogenase

11-deoxycorticosterone

11β-hydroxylase

21β-hydroxylase

11-deoxycortisol

11β-hydroxylase

17β-hydroxysteroid dehydrogenase

Aromatase → Estrogens

Corticosterone

Aldosterone Synthase

Cortisol

Testosterone

Aromatase → Estrogens

Aldosterone

5α-reductase

DHT

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| Enzyme	Action	Pertinent Clinical Fact
Desmolase	Converts cholesterol to pregnenolone	N/A
3β-hydroxysteroid dehydrogenase	Converts: • pregnenolone to progesterone • 17-hydroxypregnenolone to 17α-hydroxyprogesterone • DHEA to androstenedione	Defect leads to deficiency of aldosterone, cortisol, and adrenal androgens (see card 94)
17α–hydroxylase	Converts: • pregnenolone to 17-hydroxypregnenolone • progesterone to 17α-hydroxyprogesterone	Defect leads to deficiency of cortisol and adrenal androgens (see card 92)
21β–hydroxylase	Converts: • progesterone to 11-deoxycorticosterone • 17α-hydroxyprogesterone to 11-deoxycortisol	Defect leads to deficiency of aldosterone and cortisol (see card 91)
11β–hydroxylase	Converts: • 11-deoxycorticosterone to corticosterone • 11-deoxycortisol to cortisol	Defect leads to deficiency of aldosterone and cortisol (see card 93)
17, 20 lyase	Converts: • 17-hydroxypregnenolone to DHEA • 17α-hydroxyprogesterone to androstenedione	Defect leads to clinical syndrome similar to defect in 17α–hydroxylase
17β-hydroxysteroid dehydrogenase	Converts androstenedione to testosterone	Defect leads to deficiency of testosterone and, hence, impaired virilization of males
Aldosterone synthase	Converts corticosterone to aldosterone	N/A
5α–reductase	Converts testosterone to DHT	Pharmacologic inhibitors of this enzyme are used to treat prostate cancer and benign prostatic hypertrophy
Aromatase	Converts testosterone and androstenedione to estrogens	Pharmacologic inhibitors of this enzyme are used to treat breast and ovarian cancer

Cortisol
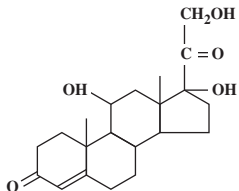
Aldosterone

Dehydroepiandrosterone

Androstenedione

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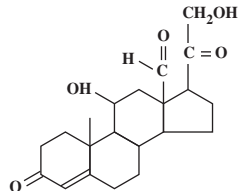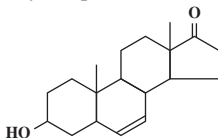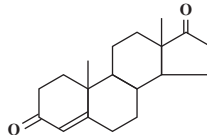
FUNCTION AND REGULATION OF ADRENAL HORMONES

Hormone	Site of Release	Action	Regulation
Aldosterone	Zona glomerulosa of adrenal cortex	Increases renal Na^+ reabsorption; increases renal K^+ and H^+ secretion	Stimulators: angiotensin II; hyperkalemia; ACTH
Cortisol	Zona fasciculata of adrenal cortex	Stimulates gluconeogenesis; immunosuppressant; anti-inflammatory; increases GFR; inhibits bone formation	Stimulator: ACTH inhibitor: cortisol
Androgens (dehydroepiandrosterone, androstenedione)	Zona reticularis of adrenal cortex	Females: pubic and axillary hair growth Males: same as testosterone	Stimulator: ACTH inhibitor: cortisol

You deliver a baby girl to a 40-year-old woman. On examination of the child at birth, you notice that her genitalia are abnormal. The child's sex had been confirmed as female by karyotype from an amniocentesis performed during the pregnancy; however, you observe that the child has a penis-like clitoris and scrotum-like labia. When further evaluation reveals that the child is hypotensive and hyponatremic, you begin to suspect that she may suffer from an autosomal recessive disorder that leads to defective steroid synthesis in the adrenal gland.

21 β-Hydroxylase Deficiency

Genetic Defect	An autosomal recessive mutation on chromosome 6 that results in a **deficiency of 21 β-hydroxylase**.
Pathophysiology	21β-hydroxylase is involved in the synthesis of aldosterone (converts progesterone to 11-deoxycorticosterone) and the synthesis of cortisol (converts 17-hydroxyprogesterone to 11-deoxycortisol). Without 21β-hydroxylase, there is a **deficiency of aldosterone and cortisol** as well as a buildup of progesterone and 17-hydroxyprogesterone. These intermediate molecules will then be shunted toward the synthesis of DHEA and androstenedione, leading to an **excess of adrenal androgens**.
Clinical Manifestations	**Masculinization** of external genitalia of female fetuses; **hypotension**; precocious puberty with premature appearance of pubic and axillary hair; suppression of gonadal function in females; hypovolemia as a result of **"salt wasting."**
	Lab findings: Hyperkalemia; hyponatremia; low cortisol levels; elevated levels of ACTH.
Treatment	Replacement of glucocorticoids and mineralocorticoids; symptomatic treatment of masculinization with antiandrogen therapy.
Notes	21β-hydroxylase deficiency is considered one of the **congenital adrenal hyperplastic syndromes**, along with 17α-hydroxylase deficiency and 11β-hydroxylase deficiency. In all of these disorders, there is hyperplasia of the adrenal cortex as a result of increased ACTH levels. Increased levels of ACTH are released from the pituitary in response to negative feedback from the decreased cortisol levels associated with these disorders.

A 17-year-old girl presents to your office expressing concern over the fact that she has not achieved menarche. She also tells you that she has not developed breasts or grown axillary or pubic hair. Physical examination is significant for a blood pressure of 180/100, normal-appearing female external genitalia, and lack of breast development. You send for laboratory studies, which reveal decreased K^+ levels and elevated HCO_3^- levels. You tell the patient that she will need to be treated for hypertension and will also need hormone replacement therapy.

17α-Hydroxylase Deficiency

Genetic Defect	An autosomal recessive mutation that results in a **deficiency of 17α-hydroxylase**.
Pathophysiology	17α-hydroxylase is involved in the synthesis of adrenal androgens and cortisol (converts pregnenolone to 17-hydroxypregnenolone and converts progesterone to 17α-hydroxyprogesterone). Without 17α-hydroxylase, there is a **deficiency of cortisol and adrenal sex hormones** as well as a buildup of progesterone and pregnenolone. These intermediate molecules will then be shunted toward the synthesis of aldosterone and other mineralocorticoids, leading to an excess of mineralocorticoids.
Clinical Manifestations	**Hypertension**; fluid retention; **lack of onset of puberty** (no axillary/pubic hair growth; no secondary sex characteristics development); patients appear female.
	Lab findings: Hypokalemia; metabolic alkalosis; low cortisol levels; elevated ACTH levels.
Treatment	Replacement of glucocorticoids and adrenal sex hormones; treatment of hypertension.
Notes	17α-hydroxylase deficiency is considered one of the **congenital adrenal hyperplastic syndromes**, along with 21β-hydroxylase deficiency and 11β-hydroxylase deficiency. In all of these disorders, there is hyperplasia of the adrenal cortex as a result of increased ACTH levels. Increased levels of ACTH are released from the pituitary in response to negative feedback from the decreased cortisol levels associated with these disorders.

A 9-year-old girl is brought to your pediatric clinic for her annual checkup. She is a new patient, and her mother tells you that the child has been healthy over the past year except for some occasional complaints of headaches. On physical examination, you find that the patient has a blood pressure of 176/104, pubic and axillary hair, and masculinized female external genitalia. You tell the patient's mother that you suspect that the girl may have a rare enzymatic deficiency, and you refer the patient to a geneticist.

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11β-Hydroxylase Deficiency

Genetic Defect	An autosomal recessive mutation that results in a **deficiency of 11β-hydroxylase**.
Pathophysiology	11β-hydroxylase is involved in the synthesis of aldosterone (converts 11-deoxycorticosterone to corticosterone) and cortisol (converts 11-deoxycortisol to cortisol). Without 11β-hydroxylase, there is a **deficiency of cortisol and aldosterone** as well as a buildup of 11-deoxycorticosterone and other aldosterone and cortisol precursors (eg, progesterone and pregnenolone). These aldosterone and cortisol precursors will then be shunted toward the synthesis of DHEA and androstenedione, leading to an **excess of adrenal androgens**. 11-deoxycorticosterone has weak mineralocorticoid activity and will, therefore, lead to **hypertension** through salt and water retention.
Clinical Manifestations	**Masculinization** of external genitalia of female fetuses; **hypertension**; precocious puberty with premature appearance of pubic and axillary hair; suppression of gonadal function in females. *Lab findings:* Low cortisol levels; elevated ACTH levels.
Treatment	Replacement of glucocorticoids; treatment of masculinization with antiandrogen therapy; treatment of hypertension.
Notes	11β-hydroxylase deficiency is considered one of the **congenital adrenal hyperplastic syndromes**, along with 21β-hydroxylase deficiency and 17α-hydroxylase deficiency. In all of these disorders, there is hyperplasia of the adrenal cortex as a result of increased ACTH levels. Increased levels of ACTH are released from the pituitary in response to negative feedback from the decreased cortisol levels associated with these disorders.

A baby boy is born to a 33-year-old woman. Within several hours of his birth, the child goes into hypovolemic shock, and he is transferred to the neonatal intensive care unit. Despite your best efforts at resuscitation, the child dies during his first week of life. In an attempt to understand why the baby died, an autopsy and several genetic tests are performed. When one of the genetic tests shows a mutation that would have resulted in the complete deficiency of aldosterone, cortisol, and adrenal androgens, you explain to the grief-stricken parents that their child died from a rare enzyme deficiency that interferes with normal steroid synthesis in the adrenal cortex.

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3β-Hydroxysteroid Dehydrogenase Deficiency

Etiology	An autosomal recessive mutation that results in a **deficiency of 3β-hydroxysteroid dehydrogenase**.
Pathophysiology	3β-hydroxysteroid dehydrogenase is involved in the synthesis of aldosterone, cortisol, and adrenal androgens (converts pregnenolone to progesterone and 17-hydroxypregnenolone to 17-hydroxyprogesterone). Without 3β-hydroxysteroid dehydrogenase, there is a **deficiency of aldosterone, cortisol, and adrenal androgens**. Without aldosterone or any molecules with mineralocorticoid activity, there is no salt and water retention, leading to extreme hypovolemia and hypotension.
Clinical Manifestations	Severe "salt wasting" in urine, with resultant hypovolemia, usually leading to hypovolemic shock early in life.
	Lab findings: Hyponatremia; hyperkalemia; elevated ACTH levels; low cortisol levels.
Treatment and Prognosis	Glucocorticoid, mineralocorticoid, and sex hormone replacement therapy. Most patients suffer an early death.

Notes

A 1-year-old baby girl is brought to your pediatric surgical clinic. The mother reports that she has noticed a small lump in her child's left groin region for the last 3 months. It is stable in size and is nontender. She states that otherwise her child has been healthy and her physical examination (with the exception of the mass in the child's groin) is unremarkable. You decide to take the child to surgery to excise the mass. When pathology reveals that the mass is consistent with a testes and laboratory studies reveal normal testosterone levels, you begin to wonder if this patient may have an X-linked genetic defect that results in the loss of function of a specific cell receptor.

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Androgen Insensitivity Syndrome

Etiology	An X-linked recessive mutation that results in a **loss of function in the androgen receptor**.
Pathophysiology	Androgens are produced by the adrenal gland as well as the sex organs. In response to the binding of androgens to androgen receptors on cell surfaces, the cell undergoes activation and specific gene transcription (eg, for embryological gonadal development) ensues. In the case of a defective androgen receptor in XY patients, the cell does not respond to the androgen signals and embryo does not develop the normal external male sex organs and appears female.
Clinical Manifestations	Presence of **inguinal mass noted in infancy**, later found to be undescended testes in a phenotypic female; if the disorder is not discovered in childhood, it may come to light when the patient presents with **primary amenorrhea**.
	Lab findings: XY on karyotype in a phenotypic female; **normal levels of testosterone and dihydrotestosterone**.
Treatment	Hormone replacement therapy (primarily of estrogen if the patient identifies with the female gender); psychological support.

Notes

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FUNCTION AND SOURCES OF VITAMINS

| Vitamin	Solubility	Source	Function
A	Fat	Carrots; leafy greens (eg, spinach); sweet potato	Synthesis of rhodopsin; cell differentiation and growth; antioxidant
B_1	Water	Whole grains; breads; cereals	Precursor for TPP; involved in nerve conduction
B_2	Water	Bread; cereals; milk	Precursor for FAD and FMN
B_3	Water	Chicken; fish; whole grains; cereals	Precursor for NAD and NADP
B_5	Water	Chicken; beef; cereals; potatoes	Constituent of coenzyme A and fatty acid synthase
B_6	Water	Cereals; soy; liver	Precursor for pyridoxal phosphate; involved in heme synthesis
B_{12}	Water	Liver; fruits; meats	Cofactor in methionine metabolism and in propionyl coenzyme A metabolism
C	Water	Citrus fruits; peppers; broccoli	Facilitates collagen synthesis; increases iron absorption in GI tract
D	Fat	Fish; milk; cereals; skin production via sunlight	Increases Ca^{2+} through increased absorption in kidney and GI tract
E	Fat	Cereals; almonds; vegetable oils	Antioxidant
K	Fat	Leafy green vegetables (eg, spinach); cabbage	Facilitates γ-carboxylation of clotting factors II, VII, IX, and X

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FUNCTION AND SOURCES OF MINERALS

Micronutrient	Source	Function
Biotin	Liver; fruits; meats	Cofactor for pyruvate carboxylase, propionyl coenzyme A carboxylase, and acetyl coenzyme A carboxylase
Folic Acid	Leafy green vegetables; cereals; whole grain breads	Cofactor for 1-carbon transfers (eg, in methionine and nucleotide synthesis)
Iron	Cereals; beans; beef; eggs	Key component of heme synthesis as well as enzymes of the electron transport chain
Calcium	Milk; cheese; yogurt; cereals; spinach	Component of skeletal system; involved in activation of coagulation cascade; necessary for muscle contraction and nerve function
Iodine	Processed food; iodized salt	Necessary for synthesis of thyroid hormone
Magnesium	Leafy green vegetables; almonds; fish	Binds ATP to facilitate many ATP-mediated reaction; stabilizes membrane function in heart and muscle cells
Phosphorus	Milk; meat; eggs; cereals	Component of nucleic acids, cell membranes and skeletal system
Zinc	Red meat; cereals; fish	Acts as cofactors for multiple enzyme complexes involved in immune and nerve function

FUNCTION OF MACRONUTRIENTS

Macronutrient	kcal/g	% Caloric Intake	Function
Carbohydrates	4	50-60	Metabolized to glucose, which is used as fuel; fibers assist in bowel elimination
Fats	9	30	Precursor for prostaglandin and leukotriene synthesis; carrier molecules for fat-soluble vitamins
Proteins	4	10-20	Source of 9 essential amino acids for synthesizing proteins and other nitrogen-containing substances

8

METABOLISM OF ETHANOL
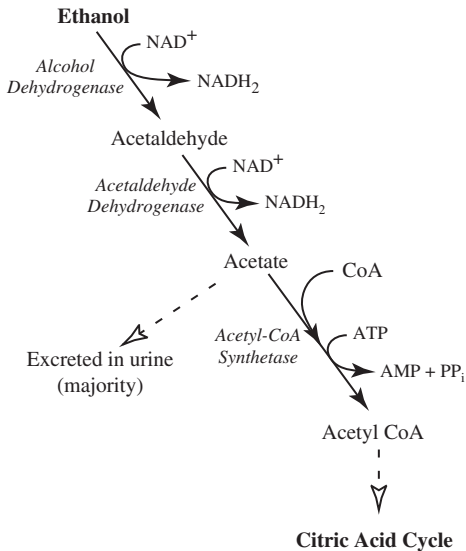
- **Location:** Cells of the kidney and liver.
- **Substrates:** Ethanol, two NAD^+.
- **Products:** Acetate, two $NADH_2$.
- **Overview of pathway:**
  - ► Ethanol is oxidized to acetaldehyde by *alcohol dehydrogenase*, in a reaction requiring one NAD^+.
  - ► Acetaldehyde is an unstable compound that is prone to forming free radical structures, and thereby damaging nearby tissues, it is subsequently oxidized to acetate by *acetaldehyde dehydrogenase*. Again, this reaction requires one NAD^+.
  - ► Acetate can either be excreted in the urine (which occurs in the majority of cases) or can be transformed into acetyl CoA and entered into the citric acid cycle.
- **Important enzymes:**
  - ► *Alcohol dehydrogenase:* Requires NAD^+ and zinc to catalyze the reaction; acts via zero-order kinetics.
  - ► *Acetaldehyde dehydrogenase:* Requires NAD^+ to function; inhibited by disulfiram, which has been marketed as a drug to treat alcoholism.

On your first day of working at a refugee camp clinic in Southwest Asia, a 3-year-old boy is brought to see you. His mother tells you that he has developed dark patches of flaky skin on his body. You also notice that the boy has pitting edema of his lower extremities and a protuberant abdomen, while his arms show signs of muscle wasting. You suspect that the boy's edema and skin changes are likely due to poor nutrition caused by his social situation.

Kwashiorkor and Marasmus

Etiology and Epidemiology	**Kwashiorkor:** Caused by the **inadequate intake of protein** in the setting of adequate calorie intake; typically seen in underdeveloped countries in children about 1 year of age, when weaning begins.
	Marasmus: Caused by the **inadequate intake of calories**; typically seen in underdeveloped countries in children younger than 1 year, when breast milk is supplemented with calorie-deficient cereals.
Pathophysiology	Malnutrition affects every organ system in the human body. Initial effects include loss of body weight, fat stores, and muscle mass. Protein mass is lost from several organs, including the heart, liver, and kidneys. Respiratory function is depressed as respiratory muscles atrophy, leading to decreased tidal volume. Cardiac output is decreased. Hepatic function also suffers, leading to **decreased albumin production** (especially **marked in kwashiorkor**, thereby causing the characteristic edema). The immune system is also depressed with decreased numbers of T lymphocytes and impaired complement and granulocytic activity, leading to increased susceptibility to infection.
Clinical Manifestations	**Kwashiorkor: Skin changes** (dark, flaky patches); diarrhea; **stunted growth**; increased susceptibility to infections; **pitting edema**; hepatomegaly.
	Marasmus: Muscle wasting; increased susceptibility to infections; **stunted growth**; weakness; anemia.
Treatment	Nutritious diet; mineral/electrolyte/vitamin supplementation.
Notes	

A 75-year-old man presents to your evening clinic complaining of worsening night vision. Medical history is significant for constipation, for which he uses mineral oil laxatives, and he notes that he has suffered from at least three bouts of the common cold over the past 4 months. Physical examination reveals scattered white patches on his conjunctiva as well as two poorly healed cuts on his left hand, which he states he incurred 2 weeks ago while cutting vegetables. You assure this man that his night blindness will likely improve with treatment and recommend that he seek alternative therapy for his constipation.

Vitamin A (Retinol) Deficiency

Etiology and Epidemiology	Causes include fat malabsorption syndromes (pancreatic insufficiency, cholestatic liver disease, celiac sprue, inflammatory bowel disease, gastrectomy), mineral oil laxative abuse, and malnutrition. In the United States, vitamin A deficiency occurs most commonly in the elderly or urban poor.
Function	There are several derivatives of vitamin A, which are involved in multiple different metabolic processes. 11-*cis*-retinol is involved in the **synthesis of rhodopsin**, the visual pigment in retinal cells. Retinoic acid acts to regulate **cell growth and differentiation**. β-Carotene, a precursor for vitamin A, has been known to act as an **antioxidant**.
Clinical Manifestations	Early symptoms include **night blindness**, poor wound healing, increased susceptibility to infection, and Bitot spots (white patches on the conjunctiva). Later symptoms include hyperkeratinization and resulting **skin dryness**, ulceration and keratinization of the cornea, and complete blindness.
Treatment and Prognosis	Treat with vitamin A supplementation (30 000 IU daily for 1 week for early deficiency; 20 000 IU/kg for 5 days for late deficiency). Early signs of deficiency can often be reversed with supplementation.
Notes	Vitamin A toxicity occurs with ingestion of more than 50 000 IU per day of vitamin A for longer than 3 months. Symptoms include scaly skin, nausea, diarrhea, headache, papilledema, and hepatosplenomegaly, which may lead to eventual cirrhosis.

A 48-year-old man presents to your office complaining of generalized weakness and increased pain on his left side as well as in his right thigh. His medical history includes a Billroth type II gastrectomy more than 1 year ago. Physical examination reveals muscle strength of 4 out of 5 in all extremities as well as pain on palpation of the fifth and sixth ribs on his left side. You order several routine lab tests and x-ray films of the chest and right femur. The x-ray films reveal several healed rib fractures as well as diffuse radiolucency with thinning of the cortical bone of his femur. You begin to suspect that this patient may be suffering from a vitamin deficiency that is likely related to his gastrectomy.

Vitamin D Deficiency

Etiology	Causes include malnutrition, fat malabsorption syndromes, decreased exposure to the sun, liver disease, and chronic renal failure.
Function and Supply	Vitamin D can be either **absorbed intestinally** or **synthesized in the skin** by ultraviolet radiation and then hydroxylated by either the liver or the kidney to form potent metabolites, $25[OH]D_3$ or **$1,25[OH]_2D_3$**, respectively. Vitamin D is involved in stimulating the synthesis of a calcium-binding protein found in the intestine and thus is involved in **increasing intestinal calcium absorption**. Vitamin D also acts in conjunction with PTH to stimulate osteoblast activity, leading to **bone demineralization** and calcium release into the blood, and **calcium reabsorption by the distal tubules of the kidney**.
Clinical Manifestation	**Rickets**: Seen in young children; **skeletal deformities** (resulting from disruption of mineralization at epiphyseal plates); **shortened stature**; pigeon breast (resulting from sternum protrusion); **rachitic rosary** (costochondral junction thickening); late closing of fontanelles; **craniotabes** (thinning of occipital and parietal bones).
	Osteomalacia: Seen in adults; **diffuse bone pain**; muscle weakness; pathologic fractures; hypocalcemia; radiographs demonstrate diffuse radiolucency with thinning of cortical bone.
Treatment	Vitamin D supplementation; adequate sunlight exposure.
Notes	Clinical manifestations of **vitamin D toxicity** include hypercalcemia, calcification of soft tissues, kidney stones, and bone demineralization. Vitamin D toxicity can also be seen in sarcoidosis, in which abnormal cells convert vitamin D into active metabolites.

A 72-year-old woman presents to your clinic for follow-up of her ulcerative colitis. She also suffers from diabetes, and she tells you that she recently had a foot ulcer, which is being treated with broad-spectrum antibiotics. On physical examination, you notice that she has several bruises on her arms and legs, which she attributes to clumsiness. You order routine lab tests, which reveal a prolonged PT and PTT. You suspect that these abnormal lab values are due to her current medical conditions, and they will likely be corrected rapidly with treatment.

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Vitamin K Deficiency

Etiology	Caused by **fat malabsorption syndromes** and use of broad-spectrum **antibiotics**, which serve to suppress bowel bacterial flora, thereby decreasing the synthesis of vitamin K.
Function and Supply	Vitamin K is supplied to the body through diet and endogenous synthesis by intestinal bacteria. Vitamin K acts as a cofactor for glutamate carboxylase, which catalyzes the **post-translational γ-carboxylation of glutamic acid residues on clotting factors II, VII, IX, and X** and thereby results in superior activation of the coagulation cascade.
Clinical Manifestations	May be asymptomatic in mild cases or may present with bleeding from mucous membranes, impaired blood clotting, and increased bruising.
	Lab findings: **Prolonged PT and PTT**; normal bleeding time and thrombin time.
Treatment	Vitamin K supplementation.
Notes	Infants are always given a dose of vitamin K at birth because they are born with a mild vitamin K deficiency, resulting from poor diffusion of vitamin K across the placenta as well as decreased intestinal flora and subsequent decreased vitamin K synthesis.
	Vitamin E is believed to act as an antioxidant, reacting with free radicals and thereby protecting cellular membranes from damage. Deficiency occurs in fat malabsorption syndromes and abetalipoproteinemia. Vitamin E deficiency manifests clinically with vision disturbances, hemolytic anemia (because of the increased fragility of RBC membranes), neurologic dysfunction (ataxic gait, areflexia, decreased proprioception), and myopathies.

A 56-year-old man is brought to the emergency room by several concerned family members, who report that the patient has been increasingly confused lately. The family tells you that the patient has been forgetful over the past month, but has become even more confused in the last week and has been inventing stories about people and places unknown to the family. Medical history is significant for a 30-year history of alcohol abuse, although a current breathalyzer test reads 0. A neurologic examination reveals that the patient is oriented only to name and that he has significant nystagmus, decreased sensation to pinprick from the knees down bilaterally, and an ataxic gait. As you prepare to admit this patient to the hospital for further evaluation, you suspect that he will need a thorough cardiac workup as well as neurologic care.

8

Vitamin B$_1$ (Thiamine) Deficiency

Etiology	Most commonly associated with **alcoholism**, which leads to thiamine deficiency through poor dietary nutrition and impaired absorption of thiamine. Thiamine deficiency is also associated with malnutrition, malabsorption syndromes, and dialysis treatment.
Function	Thiamine acts as a **precursor molecule for TPP**, which is a coenzyme for enzymes involved in carbohydrate and amino acid metabolism. These enzymes include pyruvate dehydrogenase (glycolysis), α-ketoglutarate dehydrogenase (citric acid cycle), transketolase (pentose phosphate pathway), and branched-chain keto acid dehydrogenase (amino acid metabolism). TPP has also been implicated in **nerve conduction**.
Clinical Manifestations	Early disease presents with muscle cramps, poor appetite, and peripheral motor and sensory neuropathy (**dry beriberi**). More advanced disease may present with **wet beriberi** (dilated cardiomyopathy resulting in **high-output heart failure** and pulmonary edema) or **Wernicke-Korsakoff syndrome**, which is a combination of **Wernicke encephalopathy** (characterized by the triad of **confusion**, **ataxia**, and **ophthalmoplegia**) and **Korsakoff syndrome** (**amnesia and confabulation**).
Treatment and Prognosis	Thiamine supplementation. About half of patients will only have partial or no resolution of their symptoms with treatment.
Notes	

A 21-year-old homeless man presents to your clinic complaining of generalized weakness. He reports that he has only been eating 3 to 4 days per week, when he is able to attend meals at a local soup kitchen. You notice that he has cracked skin at the corners of his lips, and further physical examination reveals vascularization of his corneas. Although you suspect that this patient likely has other medical problems related to poor nutrition, you believe that these physical findings are due to a deficiency in the precursor for enzymes involved in oxidation-reduction reactions of the cell.

Vitamin B$_2$ (Riboflavin) Deficiency

Etiology	Usually caused by dietary deficiency or other conditions associated with malnutrition, such as alcoholism.
Function	Riboflavin is the **precursor for the coenzymes FAD** and **FAMN**, both of which act as electron acceptors in a variety of oxidation-reduction reactions (especially in the citric acid cycle and the electron transport chain).
Clinical Manifestations	Usually occurs in conjunction with other B vitamin deficiencies. Symptoms of riboflavin deficiency include dermatitis, glossitis, **corneal vascularization**, **angular cheilitis** (cracking at corners of lips), weakness, and anemia.
Treatment	Vitamin B$_2$ supplementation.
Notes	**Vitamin B$_5$** (**pantothenic acid**) is a constituent of **CoA** and **fatty acid synthase**. Deficiency is rarely seen, but when it does occur (usually in conjunction with other B vitamin deficiencies), it may present with dermatitis, hair loss, and GI upset.

An 87-year-old woman is brought to the emergency room from her nursing home for increased weakness. By report, she has been increasingly depressed and has recently admitted to secretly throwing out her food trays. You are able to establish a good rapport with this patient, and she tells you that she has not eaten a healthy meal in more than 2 months. She also reports that, over the past 3 weeks, she has developed a watery, nonbloody diarrhea and is having difficulty remembering things. When her physical examination reveals several dark, scaly patches on her face, neck, and dorsum of both hands, you begin to suspect that this patient's presentation is related, in part, to a nutritional deficiency.

8

Vitamin B$_3$ (Niacin) Deficiency

Etiology	Causes include dietary inadequacy, alcoholism, Hartnup disease (results in deficiency of tryptophan), isoniazid treatment, and carcinoid syndrome.
Function and Supply	Niacin is supplied to the body through dietary ingestion or by endogenous synthesis from the amino acid tryptophan. Niacin serves as a **precursor for coenzymes NAD** and **NADP**, both of which act as electron acceptors in a variety of oxidation-reduction reactions, especially in the citric acid cycle and the electron transport chain.
Clinical Manifestations	Symptoms of mild deficiency include poor appetite with weight loss, weakness, and glossitis. More advanced deficiency results in **pellagra**, which consists of the triad of **dermatitis** (usually on sun-exposed areas), **dementia**, and **diarrhea**.
Treatment	Niacin supplementation.
Notes	High doses of niacin supplementation have been found to reduce LDL and VLDL levels and to increase HDL levels and thus can be used to treat hypercholesterolemia and hypertriglyceridemia. Side effects of high-dose niacin include peripheral flushing (caused by vasodilation) and GI upset.

A 28-year-old woman presents to the emergency room after having a generalized tonic-clonic seizure. She has no history of a seizure disorder, but she is currently receiving isoniazid prophylaxis after having a positive PPD test with no sign of active tuberculosis. Physical examination is significant for a mild peripheral neuropathy, manifesting as decreased sensation to light touch and pinprick in all distal extremities. When her blood tests reveal a sideroblastic anemia, you begin to suspect that her symptoms are related to her isoniazid treatment.

8

Vitamin B$_6$ (Pyridoxine) Deficiency

Etiology	Caused by dietary malnutrition, alcoholism, pregnancy, certain metabolic diseases (eg, homocystinuria), or certain pharmacologic agents (**isoniazid**, penicillamine, oral contraceptives) that interfere with pyridoxine metabolism or act as competitive inhibitors at pyridoxine-binding sites.
Function	Vitamin B$_6$ is a **precursor forpyridoxal phosphate**, which is a coenzyme that acts as a **carrier of amine groups during the transamination reaction** in amino acid breakdown, as a **cofactor for cystathionine synthase** during methionine metabolism, and as a cofactor during other decarboxylation and trans-sulfuration reactions. Pyridoxal phosphate is also involved in the **synthesis of heme**.
Clinical Manifestations	Mild deficiency results in personality disturbances (irritability, depression), dermatitis, and glossitis. More severe deficiency manifests as a **peripheral neuropathy**, **seizures**, and a sideroblastic anemia.
Treatment	Vitamin B$_6$ supplementation.
Notes	Vitamin B$_6$ toxicity can occur in patients receiving large doses of vitamin B$_6$ over a long time. It generally manifests as a sensory neuropathy, which can be irreversible.

A 24-year-old man presents to your office complaining of a gradual onset of diarrhea, generalized weakness, and a feeling of numbness in both legs over the past week. He has no significant medical history, although on social history he does tell you that he eats sushi five to six times a week. On physical examination, you note that he has impaired proprioception and vibratory sensation in both lower extremities, a smooth red tongue, and an ataxic gait. Laboratory testing reveals megaloblastic anemia but a negative Schilling test. You decide to test a stool sample to look for a parasitic infection, but in the meantime you begin the patient on empiric praziquantel as well as a specific nutritional supplementation.

Vitamin B$_{12}$ (Cobalamin) Deficiency

Etiology	Causes include dietary deficiency (usually seen only in **vegans**), pancreatic insufficiency, decreased production of intrinsic factor (eg, **pernicious anemia** or gastrectomy), decreased ileal absorption of vitamin B$_{12}$ (eg, Crohn disease, *Diphyllobothrium latum* infection, sprue, or surgical resection of small intestine), or blind loop syndrome (leading to bacterial overgrowth and resulting competition for vitamin B$_{12}$).
Function and Supply	When ingested, vitamin B$_{12}$ becomes bound to intrinsic factor, a protein secreted by the parietal cells of the gastric mucosa. The vitamin B$_{12}$-intrinsic factor complex is then absorbed in the distal ileum, and the vitamin B$_{12}$ is stored in the liver. In methionine metabolism, vitamin B$_{12}$ serves as a **cofactor in the conversion of homocysteine to methionine**. In the metabolism of propionyl CoA, a final product of fatty acid β-oxidation, vitamin B$_{12}$ serves as a **cofactor in the conversion of methylmalonyl CoA to succinyl CoA**.
Clinical Manifestations	**Neurologic abnormalities** (ataxia, impaired proprioception, and vibratory sensation); glossitis; diarrhea; symptoms of autoimmune gastritis (if vitamin B$_{12}$ deficiency is caused by pernicious anemia).
	Lab findings: **Megaloblastic anemia** (with hypersegmented neutrophils on peripheral blood smear); **decreased serum vitamin B$_{12}$.** Possibly anti-intrinsic factor antibodies and abnormal Schilling test (tests for decreased absorption of vitamin B$_{12}$) if vitamin B$_{12}$ deficiency is caused by pernicious anemia.
Treatment	Vitamin B$_{12}$ supplementation.
Notes	

A 17-year-old adolescent boy presents to your evening clinic complaining of generalized weakness. He tells you that he had run away from home a year ago and has been living on the streets. On further questioning, he tells you that he has not been eating well because of his financial constraints. Physical examination reveals multiple purpura over his body, gingival swelling with bleeding gums, and several cuts that look poorly healed. When laboratory tests demonstrate anemia, you suspect that this patient's condition is likely related to a nutritional deficiency and recommend that he take supplements that the clinic can provide to treat his illness.

8

Vitamin C (Ascorbic Acid) Deficiency

Etiology and Epidemiology	Usually caused by dietary inadequacy. More often seen in the elderly, alcoholics, the homeless, or patients with chronic illnesses such as cancer or chronic renal failure.
Function	Vitamin C acts as a cofactor for several different oxidation-reduction reactions, including the **hydroxylation of proline and lysine in the synthesis of collagen** leading to decreased osteoid matrix synthesis, metabolism of tyrosine, conversion of dopamine to norepinephrine, and synthesis of carnitine. Vitamin C also has antioxidant properties and **facilitates iron absorption in the intestine** by keeping iron in a reduced state (Fe^{2+}), which is more amenable to absorption.
Clinical Manifestations	Manifests as **scurvy**: subperiosteal hemorrhage; **bleeding into joint spaces**; purpura and petechiae; **bleeding from gums**; osteoporosis; gingival swelling; fatigue; weakness; **anemia**; **impaired wound healing**.
Treatment	Vitamin C supplementation.
Notes	

A 25-year-old woman presents to your genetics clinic for a workup of elevated cholesterol levels, which were discovered during a routine physical. While you prepare to order several tests to check for genetic abnormalities that might explain her elevated cholesterol levels, she reveals that she has also been suffering from generalized muscle cramping, scaly skin, hair loss, and chronic diarrhea over the past month. When you probe further and learn that she has been on a fad diet for the past year that requires consumption of 25 raw eggs a day, you begin to suspect that her health problems are related to a nutritional deficiency and you suggest that she discontinue her fad diet.

8

Biotin Deficiency

Etiology	Associated with long-term antibiotic use, increased ingestion of raw egg whites (which contain avidin, a protein that interferes with biotin digestion), and long-term parenteral nutrition.
Function and Supply	Biotin can be ingested in the diet and is also synthesized in the bowel by intestinal flora. Biotin acts as a **cofactor** for three different carboxylase enzymes: **pyruvate carboxylase** (converts pyruvate to oxaloacetate during gluconeogenesis), **propionyl CoA carboxylase** (involved in breakdown of propionyl CoA, a product of β-oxidation in fatty acid metabolism, to methylmalonyl CoA), and **acetyl CoA carboxylase** (converts acetyl CoA to malonyl CoA in fatty acid synthesis).
Clinical Manifestations	Deficiency is **rarely seen**, but symptoms include alopecia, **dermatitis**, **GI upset**, muscle pain with paresthesias, and elevated cholesterol levels.
Treatment	Biotin supplementation for patients requiring parenteral nutrition or long-term antibiotic use.

Notes

A 32-year-old woman presents to your neurology clinic for follow-up of her newly diagnosed seizure disorder. She has been taking phenytoin for the last 6 months, which has been quite effective in controlling her seizures. During the appointment, she tells you that she has been feeling more tired than usual and that she has recently developed some watery diarrhea. On physical examination, you notice that she is rather pale, has a smooth red tongue, and is tachycardic. When laboratory testing reveals a megaloblastic anemia, you suspect that the phenytoin is responsible for the nutritional deficiency that is causing her symptoms.

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Etiology	Caused by **inadequate dietary intake** (especially seen in alcoholics), medications that decrease folate absorption in the intestine (eg, sulfasalazine, phenytoin, TMP-SMX), sprue, methotrexate use (inhibits conversion of folic acid to active form), or conditions in which folic acid requirements are increased (eg, pregnancy or chronic hemolytic anemia).
Function	The reduced form of folic acid (**tetrahydrofolate**) acts as a cofactor for many **one-carbon transfer** reactions in nucleotide synthesis (especially the conversion of dUMP to dTMP in the **synthesis of thymidylate**), in methionine synthesis (especially the **conversion of homocysteine to methionine**), and in the conversion of serine to glycine and vice versa.
Clinical Manifestations	Glossitis and diarrhea; neural tube defects can result from maternal folate deficiency. *Lab findings:* **Megaloblastic anemia** (with hypersegmented neutrophils on peripheral blood smear).
Treatment	Folic acid supplementation.
Notes	

A 75-year-old man presents to your clinic complaining of worsening shortness of breath with exertion and fatigue over the past month. On further questioning, he reveals that his stools have become darker ("like tar") over the past month. When a rectal examination reveals stool positive for occult blood and blood tests reveal a microcytic hypochromic anemia, you refer him to a gastroenterologist immediately for an endoscopy and possible colonoscopy. You tell the patient that you suspect that his symptoms of fatigue and dyspnea with exertion are partially related to a mineral deficiency caused by his GI blood loss.

Etiology	Caused by dietary inadequacy, decreased absorption of iron from GI tract (eg, antacids can interfere with iron absorption; vitamin C deficiency), **blood loss** (eg, **menstrual or GI tract**), increased need for iron (eg, pregnancy or breastfeeding), or hemoglobinuria (usually associated with hemolysis).
Function	Iron is a key component of **heme molecules**, such as hemoglobin and myoglobin, and thereby plays a role in oxygen transport through the blood. Iron is also a constituent of the **cytochrome molecules** (complexes III and IV and cytochrome c) **of the electron transport chain**.
Clinical Manifestations	**Fatigue**; **pallor**; tachycardia and dyspnea during exercise; smooth tongue; brittle nails; development of pica (craving for odd foods such as ice or dirt).
	Lab findings: **Microcytic**, **hypochromic anemia**; **decreased serum iron**; **decreased serum ferritin** (storage form of iron); **increased TIBC**.
Treatment	Iron supplementation; treatment of underlying cause.
Notes	Iron toxicity can occur in people taking excessive amounts of iron. Excess iron may promote the formation of reactive free radicals, which may lead to the oxidation of LDL and thereby promote the development of cardiovascular disease.

A 63-year-old man presents to your office for a follow-up visit regarding his chronic renal insufficiency. He tells you that he has been suffering from wrist spasms recently, has felt increasing pain in his lumbar spine, and that his urine output has decreased significantly. During physical examination, you notice that he has carpal spasms 2 minutes after you inflate the blood pressure cuff. You begin to suspect that his renal function has worsened since you saw him last and that he may have developed a mineral deficiency as a result, which would account for his symptoms.

8

Calcium Deficiency

Etiology	Causes include **malnutrition**, alcoholism, vitamin D deficiency, increased loss of calcium (**renal failure**; loop diuretic use), and **endocrinologic disease** (hypoparathyroidism; pseudohypoparathyroidism; medullary thyroid carcinoma with resulting calcitonin release).
Function	Calcium circulates in the body in a free ionized form or bound to protein (usually albumin). Ionized calcium is necessary for **normal muscle contraction and nerve function**. Calcium is also a **major component of the skeletal system** and teeth and is involved in **facilitating the coagulation cascade** (activation of several clotting factors is calcium dependent).
Clinical Manifestations	**Muscular cramps**, **tetany**, paresthesias, or other signs of neuromuscular irritability; **prolonged QT interval** on ECG, which may lead to ventricular arrhythmias; **Trousseau sign** (carpal spasm 2 minutes after inflation of blood pressure cuff above systolic blood pressure); **Chvostek sign** (twitching of the facial muscles on superficial tapping of the facial nerve); **bone pain** with pathologic fractures.
Treatment	Calcium supplementation; vitamin D supplementation.
Notes	**Hypercalcemia** is most commonly caused by hyperparathyroidism or malignancy (multiple myeloma; lung, ovary, or kidney neoplasm). Other causes include sarcoidosis, milk-alkali syndrome (increased calcium ingestion), vitamin D toxicity, and Paget disease of bone. Symptoms include constipation, polyuria, ventricular arrhythmias, and coma. Hypercalcemia can be treated with intravenous saline and furosemide to enhance renal calcium excretion.

A 45-year-old alcoholic man presents to the emergency room complaining of painful muscle spasms in his arms and legs. He has had a long history of alcohol abuse and reports having poor nutritional intake. His ECG shows ventricular arrhythmias, and laboratory testing reveals several electrolyte abnormalities. You immediately begin fluid and electrolyte repletion because you suspect that his presentation is likely due to a mineral deficiency.

Other Mineral Deficiencies

Iodine Deficiency	*Function:* Necessary for **thyroid hormone synthesis**.
	Clinical manifestations: **Hypothyroidism** manifesting as **cretinism** (mental retardation, stunted growth) in children and **myxedema** (periorbital edema, thick facial features) in adults.
Magnesium Deficiency	*Function:* Binds to ATP to facilitate many ATP-dependent reactions.
	Clinical manifestations: Increased excitability at neuromuscular junction leading to muscular spasms and **tetany**; seizures; confusion; **ventricular arrhythmias**; decreased PTH release resulting in **hypocalcemia**; hypokalemia.
Phosphorus Deficiency	*Function:* Constituent of nucleic acids, cell membranes, and bone matrix.
	Clinical manifestations: Rare but may include bone pain with skeletal malformations or fractures, hemolytic anemia, platelet dysfunction, and encephalopathy.
Zinc Deficiency	*Function:* Cofactor for many metalloenzymes.
	Clinical manifestations: Dermatitis; increased susceptibility to infection; stunted growth; altered mental status.
Notes	

A 58-year-old man presents to the emergency room after being found lying on the sidewalk on a busy city street. After you rouse the patient, you find that he is unable to provide any medical history, although you are struck by his slurred speech and ataxic gait. You order laboratory tests, which reveal an elevated serum ethanol level and hypoglycemia. You suspect that this patient's hypoglycemia is related to impaired gluconeogenesis caused by ethanol ingestion.

Etiology	Caused by ethanol ingestion.
Pathophysiology	Ethanol is converted to acetaldehyde by *alcohol dehydrogenase*, which is an enzyme that operates via zero-order kinetics. Hence, large amounts of ethanol can take significant time to metabolize given the fixed rate of oxidation by *alcohol dehydrogenase*. Acetaldehyde is then converted to acetate by *acetaldehyde dehydrogenase*. Acetaldehyde is an unstable molecule, which is prone to forming free radicals, which can be toxic to the liver (leading to cirrhosis). Acetaldehyde can also be damaging to embryological neural crest tissue and is thought to be involved in the neurologic manifestations of fetal alcohol syndrome.
Clinical Manifestations	Mild intoxication results in **altered mental status** with euphoria, ataxia, and slurred speech. More severe intoxication can lead to respiratory depression, bradycardia, hypotension, and coma. If significant amounts of ethanol are ingested during pregnancy, **fetal alcohol syndrome** (as defined by growth deficiency, characteristic facies with a smooth philtrum, developmental delay, and neurologic impairments) can result.
	Lab findings: Hypoglycemia; elevated serum ethanol levels.
Treatment	Fluid resuscitation; airway protection if necessary.
Notes	Alcoholics are at risk for **hypoglycemia** when they ingest ethanol. The increased ratio of $NADH/NAD^+$, which results from the metabolism of ethanol, causes pyruvate and oxaloacetate to be reduced to lactate and malate, respectively. Because pyruvate and oxaloacetate are intermediates in gluconeogenesis, gluconeogenesis is impaired and hypoglycemia can result in people with poor glycogen stores (ie, people who are malnourished, such as alcoholics).

GENERAL CONCEPTS

DNA and RNA structure
Genetic code
Techniques of biotechnology
DNA replication
Cell cycle
Transcription and mRNA processing
Transfer RNA
Translation
Autosomal dominant inheritance
Autosomal recessive inheritance
X-linked recessive inheritance
Mitochondrial inheritance
Meiotic nondisjunction and chromosomal disorders
Definitions of genetic concepts
Types of mutations
Hardy-Weinberg population genetics

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DISEASES

Chromosomal Disorders
Down syndrome
Edwards and Patau syndromes
Prader-Willi and Angelman syndromes
Klinefelter syndrome
Turner syndrome
Fragile X syndrome
Cri Du Chat syndrome

Genetic Disorders of the Hematologic System
Factor V Leiden
Fanconi anemia
Hemophilia A and B
Hereditary spherocytosis
Glucose-6-phosphate dehydrogenase deficiency
Sickle cell anemia
Thalassemias
von Willebrand disease
Glanzmann thrombasthenia and Bernard-Soulier syndrome

Genetic Disorders of the Cardiovascular System
Familial hypertrophic cardiomyopathy
Noonan syndrome
Hereditary hemorrhagic telangiectasia
von Hippel-Lindau disease

Genetic Disorders of the Respiratory System
Cystic fibrosis
Kartagener syndrome

Genetic Disorders of the GI System
α_1-Antitrypsin deficiency
Congenital hyperbilirubinemias
Primary hemochromatosis
Multiple polyposis syndromes
Wilson disease

Genetic Disorders of the Renal System
Alport syndrome
Autosomal dominant and autosomal recessive polycystic kidney disease

Genetic Disorders of the Endocrinologic System
Multiple endocrine neoplasia syndromes
Pseudohypoparathyroidism

Genetic Disorders of the Nervous System
Ataxia-telangiectasia
Friedreich ataxia
Huntington disease
Neurofibromatosis 1
Tuberous sclerosis
Charcot-Marie-Tooth disease

Genetic Disorders of the Eye
Leber hereditary optic neuropathy
Retinoblastoma

Genetic Disorders of the Musculoskeletal System
Achondroplasia
Duchenne muscular dystrophy
Ehlers-Danlos syndrome
Marfan syndrome
Mitochondrial myopathies
Myotonic dystrophy
Osteogenesis imperfecta

Genetic Disorders of the Skin
Albinism
Xeroderma pigmentosum

Genetic Disorders of the Immune System
Bruton agammaglobulinemia
Wiskott-Aldrich syndrome
Chronic granulomatous disease of childhood
Hyper IgM syndrome
DiGeorge syndrome
Chediak-Higashi syndrome
Mediterranean familial fever

Genetic Disorders of the Cell Cycle
Bloom syndrome
Li-Fraumeni syndrome

THE STRUCTURE OF DNA AND RNA

DNA STRUCTURE

- DNA is composed of deoxyribonucleotides.
- The nitrogenous bases that compose the deoxyribonucleotides include adenine, cytosine, thymine, and guanine.
- The deoxyribonucleotides are linked together by **3′-5′ phosphodiester bonds**.
- DNA is a **double-stranded helix**.
- Each strand has a 5′ end (with a phosphate group) and a 3′ end (with a hydroxyl group).
- The strands are **antiparallel**, meaning that one strand runs in a 5′ to 3′ direction, while the other strand runs in a 3′ to 5′ direction.
- The strands are **complimentary**, meaning that the base adenine always interacts with a thymine (A-T) on the opposite strand via two hydrogen bonds and cytosine always interacts with guanine (C-G) via three hydrogen bonds on the opposite strand.
- The shape of the helix is stabilized by hydrogen bonding and hydrophobic interactions between bases.

RNA STRUCTURE

- RNA is composed of **ribonucleotides**.
- The nitrogenous bases that compose the ribonucleotides include adenine, cytosine, uracil, and guanine.
- The ribonucleotides are linked together **by 3′-5′ phosphodiester bonds**.
- RNA is a **single-stranded helix**.
- The strand has a 5′ end (with a phosphate group) and a 3′ end (with a hydroxyl group).
- There are three types of RNA.
  - ► **rRNA** (ribosomal): Involved in protein synthesis.
  - ► **tRNA** (transfer): Involved in translation.
  - ► **mRNA** (messenger): Involved in transcription.

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PRINCIPLES OF THE GENETIC CODE

- The genetic code consists of 64 different codons, each of which codes for 1 of the 20 amino acids.
- A codon consists of a triplet of nucleotide bases.
- The genetic code has several characteristics:
  - ► It is **degenerate** if some amino acids are coded for by more than one codon.
  - ► It is **unambiguous** if each codon codes for only one amino acid.
  - ► It is **universal** if all organisms use this code, with a few exceptions, such as yeast, mitochondria, and *Mycoplasma*.
  - ► It is **contiguous** if codons do not overlap and there are no spaces between codons.

TECHNIQUES OF BIOTECHNOLOGY

- **RFLP analysis:**
  - ► Each individual's DNA contains variations known as polymorphisms.
  - ► Restriction endonucleases cleave DNA at specific sequences called restriction sites, thereby producing DNA fragments.
  - ► Polymorphisms cause the restriction endonucleases to produce DNA fragments of different lengths in different individuals.
  - ► These differently sized fragments result in a DNA "fingerprint" that is specific to an individual.
- **Polymerase chain reaction:**
  - ► Produces large numbers of replicated portions of DNA.
- **DNA analysis:**
  - ► *Gel electrophoresis:* Sorts DNA fragments by size.
  - ► *Northern blotting:* Uses DNA probes to detect RNA fragments.
  - ► *Southern blotting:* Uses DNA probes to detect DNA fragments.
  - ► *Western blotting:* Uses antibodies to detect proteins.
  - ► *Southwestern blotting:* Uses DNA probes to bind proteins in order to understand DNA-protein interaction.
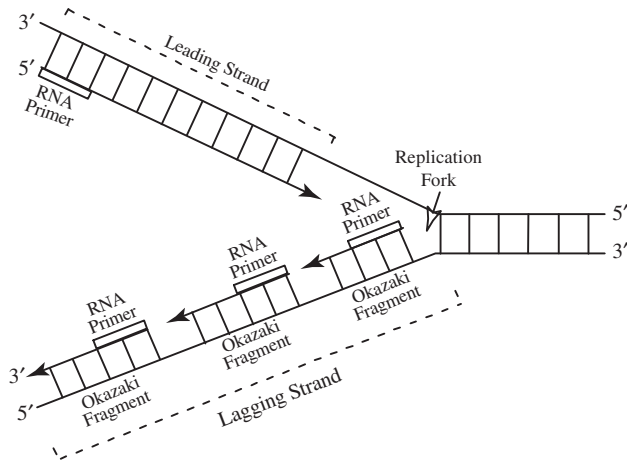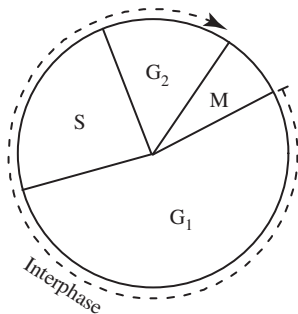
DNA REPLICATION

THE ENZYMES OF DNA REPLICATION

- *Helicases:* Unwind the DNA helix at the start of replication.
- *SSB proteins:* Bind to the single strands of unwound DNA to prevent reformation of the DNA helix during replication.
- *Primase:* Synthesizes the RNA primer needed for the initiation of DNA chain synthesis.
- *DNAP III:* Elongates DNA strand by adding deoxyribonucleotides to the 3′ end of the chain. Synthesis can only occur in the 5′ to 3′ direction because of DNAP III.
- *DNAP I:* Replaces RNA primer with the appropriate deoxynucleotides.
- *DNA topoisomerase I:* Relaxes the DNA helix during replication through creation of a nick in one of the DNA strands.
- *DNA topoisomerase II:* Relieves the strain on the DNA helix during replication by forming supercoils in the helix through the creation of nicks in both strands of DNA.
- *DNA ligase:* Forms a 3′-5′ phosphodiester bond between adjacent fragments of DNA.

THE PROCESS OF DNA REPLICATION

- The helix is unwound by *helicase* to form a pair of replication forks.
- The unwound helix is stabilized by *SSB proteins and DNA topoisomerases*.
- *Primase* forms RNA primers (10 bases), which serve to initiate synthesis of both the leading and lagging strand.
- The leading strand is synthesized continuously in the 5′ to 3′ direction by *DNAP III*.
- The lagging strand is synthesized discontinuously in the 5′ to 3′ direction through the formation of Okazaki fragments.
- *DNAP I* removes the RNA primers and replaces the existing gap with the appropriate deoxynucleotides.
- *DNA ligase* seals the breaks between the Okazaki fragments as well as around the primers to form continuous strands.

DNA REPAIR

- **Proofreading:** *DNAP I and III* "proofread" during synthesis. If an error is detected, the erroneous base is removed via 3′ to 5′ exonuclease activity of *DNAP I* and *III* and replaced with the correct base.
- **Excision repair:** Removes pyrimidine dimers formed by UV rays or other mutated bases and replaces them.

- **Interphase:**
  - ► The period of time that precedes mitosis.
  - ► Consists of three subphases: G_1, S, and G_2.
- **G1 phase:**
  - ► Period of time that precedes chromosomal replication.
  - ► During this phase, cellular growth occurs (synthesis of lipids and proteins).
  - ► Usually lasts 12 hours, but in some cells (nerve or muscle cells) G_1 can last much longer such that the cell appears to have been halted in the cycle. These cells are said to be in the G_0 phase.
- **S phase:**
  - ► Period of time after G_1 phase.
  - ► During this phase, chromosomal replication occurs and mitochondria and centrioles divide.
  - ► Usually lasts 6-8 hours.
- **G_2 phase:**
  - ► Period of time after S phase.
  - ► During this phase, cellular growth continues in the now tetraploid cell.
  - ► Usually lasts 3-4 hours.
- **Mitosis:**
  - ► Period of time after the G_2 phase of interphase.
  - ► During this phase, cellular division occurs.

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THE PROCESS OF TRANSCRIPTION

- In the nucleus, *RNAP II* binds to a promoter sequence of the DNA.
- *RNAP II* binding is facilitated by the binding of transcription factors to specific promoter sequences (eg, TATA box, CAAT box).
- The DNA helix unwinds to form a "transcription bubble."
- *RNAP II* moves along one strand of DNA (the "sense" strand), adding ribonucleotides to the growing strand of mRNA in a 5′ to 3′ direction.
- When *RNAP II* reaches the end of the gene, the process is terminated through poorly understood mechanisms and the mRNA is released.
- Transcription can be enhanced or inhibited via binding of transcription factors to regulatory regions located either upstream or downstream of the gene.

mRNA PROCESSING

- **5′ Capping:**
  - ► A 7-methylguanine molecule is added to the 5′ end of the mRNA via a 5′-5′ triphosphate linkage.
  - ► The "cap" acts to protect the mRNA chain from degradation.
- **Addition of poly A tail:**
  - ► A nucleotide sequence consisting of between 20 and 250 adenine molecules is added to the 3′ end of the mRNA by the enzyme *poly A polymerase*.
  - ► The poly A tail is believed to stabilize the mRNA.
- **Splicing:**
  - ► The mRNA molecule consists of exons (coding sequences) and introns (intervening sequences of nucleotides that do not code for protein).
  - ► Small nuclear RNAs bind to the beginning and end of introns and facilitate their excision.
  - ► The remaining exons are then ligated together to form the mature mRNA.
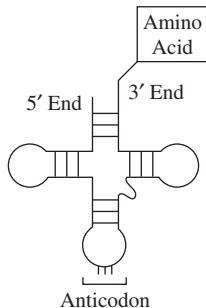
- **Structure of tRNA:**
  - ► Three structural loops are formed via hydrogen bonding.
  - ► The 3′ end serves as the amino acid attachment site.
  - ► The center loop encompasses the **anticodon**.
    - ► The anticodon is a three-base nucleotide sequence that binds to the mRNA codon. This interaction between codon and anticodon specifies the next amino acid to be added during protein synthesis.
    - ► **"Wobble" theory:** The tRNAs have the ability to recognize more than one codon for their specific amino acid because nontraditional base pairing can occur between the tRNA anticodon and the mRNA codon.
- **The role of *aminoacyl-tRNA synthetases*:**
  - ► Responsible for attaching amino acids to the 3′ end of their respective tRNA.
  - ► These enzymes catalyze a two-step reaction that requires one molecule of ATP.
  - ► There are multiple *aminoacyl-tRNA synthetases* because each enzyme corresponds to a specific amino-acyl tRNA.
- **Function of tRNA:**
  - ► The tRNA is responsible for delivering amino acids to the ribosome in the sequence indicated by the mRNA.

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THE RIBOSOME
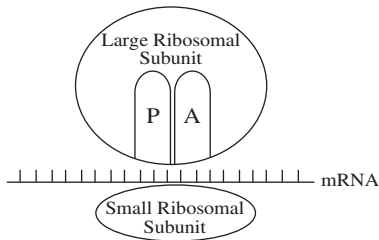
- **Structure:**
  - ► Two subunits composed of protein and rRNA.
  - ► **A site:** Binds tRNA containing the next amino acid to be added to the growing peptide chain.
  - ► **P site:** Binds tRNA containing growing peptide chain.
- **Location:**
  - ► Located in the cytosol, either freely floating or associated with the endoplasmic reticulum.
- **Function:**
  - ► Serves to synthesize proteins.

THE PROCESS OF TRANSLATION

- **Initiation:**
  - ► The start codon, AUG, is recognized by an initiator tRNA.
  - ► The initiator tRNA, which carries methionine, enters the P site of the ribosome.
- **Elongation:**
  - ► The tRNA with the anticodon that corresponds with the next downstream codon enters the A site.
  - ► *Peptidyl transferase*, an enzymatic component of the large ribosomal subunit, catalyzes the addition of the A-site amino acid to the carboxyl end of the P-site peptide chain. The elongated peptide chain is now present at the A site.
  - ► The P-site tRNA (now devoid of any amino acid or peptide chain) is released into the cytosol to be recharged with another amino acid.
  - ► The ribosome moves three nucleotides downstream in the 5′ to 3′ direction on the mRNA, thereby moving the tRNA with the peptide chain from the A site to the P site and allowing the next mRNA codon to enter the A site.
  - ► The elongation process repeats until a stop codon enters the A site.
- **Termination:**
  - ► When a stop codon (UAA, UAG, UGA, UAA) enters the A site, a release factor causes the release of the peptide chain from the tRNA in the P site.
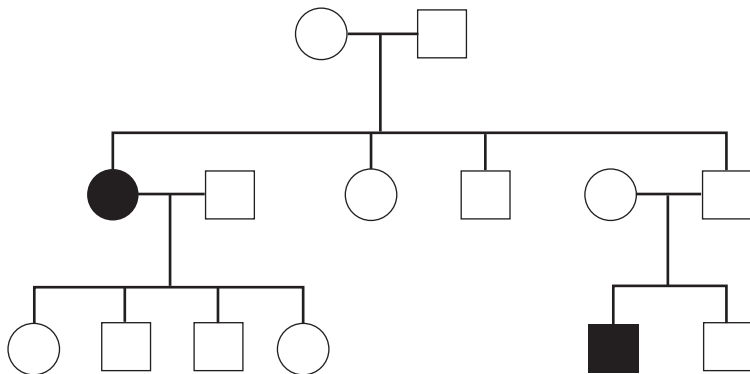
FEATURES OF AUTOSOMAL DOMINANT INHERITANCE

- Affected children usually have affected parents, which tends to result in the absence of skipped generations.
- There is a 50% chance of a child inheriting the gene from an affected parent.
- There is no carrier state.
- Males and females are equally likely to transmit the phenotype and to be affected.
- Many autosomal dominant diseases arise via new mutations.

ORGAN-BASED AUTOSOMAL DOMINANT DISEASES

- Achondroplasia
- Autosomal dominant polycystic kidney disease
- Charcot-Marie-Tooth disease (most forms)
- Crigler-Najjar syndrome type II
- Ehlers-Danlos syndrome (certain forms)
- Familial hypertrophic cardiomyopathy
- Gilbert syndrome
- Hereditary hemorrhagic telangiectasia
- Hereditary spherocytosis
- Huntington disease
- Li-Fraumeni syndrome
- Marfan syndrome
- MEN syndromes
- Multiple polyposis syndromes
- Myotonic dystrophy
- Noonan syndrome
- Osteogenesis imperfecta
- Neurofibromatosis
- Retinoblastoma
- Tuberous sclerosis
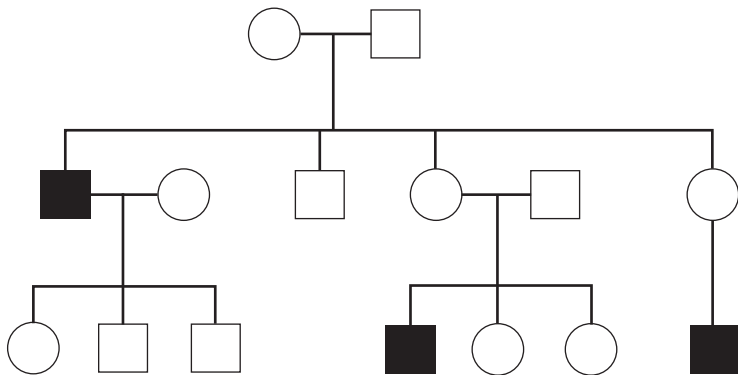- von Hippel-Lindau syndrome
- von Willebrand disease

FEATURES OF AUTOSOMAL RECESSIVE INHERITANCE

- Affected children may have unaffected parents, which tends to result in skipped generations.
- There is a 25% chance of a child developing the phenotype by inheriting the gene from two carrier parents.
- The appearance of autosomal recessive phenotypes is seen more commonly with in-breeding.
- Males and females are equally likely to transmit the phenotype and to be affected.
- Many autosomal recessive diseases do not arise via new mutations.

ORGAN-BASED AUTOSOMAL RECESSIVE DISEASES

- Albinism
- α_1-Antitrypsin deficiency
- Ataxia-telangiectasia
- Autosomal recessive polycystic kidney disease
- Bernard-Soulier syndrome
- Bloom syndrome
- Chédiak-Higashi syndrome
- Crigler-Najjar syndrome type I
- Cystic fibrosis
- Dubin-Johnson syndrome
- Ehlers-Danlos syndrome (certain forms)
- Familial Mediterranean fever
- Fanconi anemia
- Friedreich ataxia
- Glanzmann thrombasthenia
- Hemochromatosis
- Kartagener syndrome
- Pseudohypoparathyroidism
- Rotor syndrome
- Severe combined immune deficiency
- Sickle cell anemia
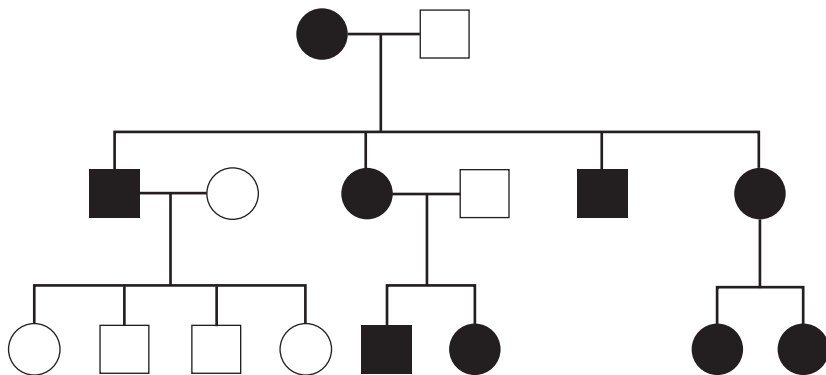- Thalassemia
- Wilson disease
- Xeroderma pigmentosum

FEATURES OF X-LINKED RECESSIVE INHERITANCE

- Affected children may have unaffected parents, which tends to result in skipped generations.
- There is a 50% chance of a male child developing the phenotype by inheriting the gene from a carrier female parent.
- Only females will transmit the phenotype (ie, there is no male-to-male transmission), although males can transmit the gene, thereby leading to carrier states in female offspring.
- Males, with only one X chromosome, are more commonly affected than females because only one altered copy of the gene is required to cause disease.

ORGAN-BASED X-LINKED RECESSIVE DISEASES

- Alport syndrome (X-linked dominant disease)
- Bruton agammaglobulinemia
- Chronic granulomatous disease of childhood
- Duchenne muscular dystrophy
- Ehlers-Danlos syndrome (certain forms)
- Glucose-6-phosphatase deficiency
- Fragile X syndrome
- Hemophilia A
- Hemophilia B
- Hyper IgM syndrome
- Ocular albinism
- Wiskott-Aldrich syndrome

FEATURES OF MITOCHONDRIAL INHERITANCE

- There is a 100% chance of all offspring developing the phenotype by inheriting the gene from an affected female parent.
- Only females will transmit the phenotype (ie, there is no male transmission of the disease).
- Males and females are equally affected by the disease.

ORGAN-BASED MITOCHONDRIAL DISEASES

- Leber hereditary optic neuropathy
- Mitochondrial myopathies (MERRF, MELAS)

Etiology of Trisomy and Monosomy Chromosomal Disorders
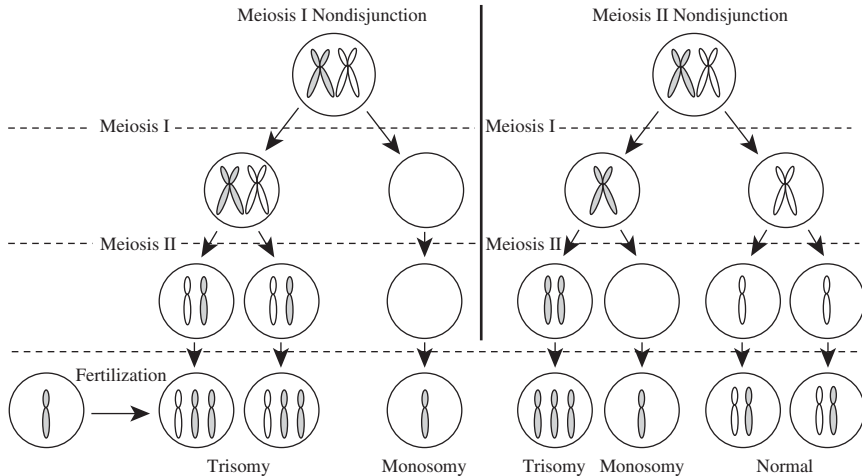
FEATURES OF CHROMOSOMAL DISORDERS

- Chromosomal abnormalities can fall under two categories: structural abnormalities (eg, deletions or rearrangements) or abnormalities of chromosomal number.
- Abnormalities of chromosomal number generally arise from meiotic nondisjunction (failure of chromosome pairs to separate during cell division) or through anaphase lag (loss of chromosome during cell division).
- Definitions of terms regarding chromosomal disruption:
  - ▶ **Aneuploidy:** Chromosome number that is not a multiple of 23.
  - ▶ **Polyploidy:** Chromosome number that is 3 or 4 times the haploid number of 23.
  - ▶ **Deletion:** Loss of part of chromosome.
  - ▶ **Translocation:** Exchange of chromosome parts between nonhomologous chromosomes.
  - ▶ **Balanced translocation:** No genetic material lost; clinically asymptomatic.
  - ▶ **Robertsonian translocation:** Joining of long arms of two acrocentric chromosomes with loss of short arms.
- **Inversion:** Reunion of separated portion of chromosome back into an inverted position.

CHROMOSOMAL DISORDERS

- Angelman syndrome
- Cri du chat syndrome
- DiGeorge syndrome
- Down syndrome
- Edward syndrome
- Klinefelter syndrome
- Patau syndrome
- Prader-Willi syndrome
- Turner syndrome
- XYY syndrome

DEFINITIONS OF SELECTED GENETIC CONCEPTS

- **Anticipation:** The phenomenon in which the number of codon repeats increases with each generation and results in increasingly severe disease manifestations. Examples of disorders demonstrating anticipation include Huntington disease, myotonic dystrophy, and fragile X syndrome.
- **Codominance:** The situation in which two different alleles for the same gene in a heterozygote are expressed. An example of codominance is a person with blood type AB (both A and B antigens are expressed).
- **Imprinting:** The phenomenon in which the same mutation results in different phenotypes depending on whether the mutated chromosome was of maternal or paternal origin. Examples of disorders demonstrating imprinting include Angelman and Prader-Willi syndromes.
- **Incomplete dominance:** The situation in which two different alleles for the same gene in a heterozygote produce a mixed phenotype.
- **Expressivity:** Refers to the degree to which a phenotype is clinically expressed. Variable expressivity refers to the notion that different patients with the same genotype may have different phenotypes.

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DEFINITIONS OF SELECTED GENETIC CONCEPTS

- **Linkage disequilibrium:** The propensity for certain groupings of alleles for different genes to be inherited together.
- **LOD score:** A calculation used by geneticists to determine whether two gene loci are linked. The qualitative formula of the LOD score is LOD = $\log_{10}$ (chance that the genes are linked/chance that the genes are unlinked). If the LOD score is ≥ 3, then the gene loci are linked.
- **Mosaicism:** Refers to the idea that individual cells may have two different chromosomal karyotypes. This usually occurs as a result of mitotic nondisjunction.
- **Penetrance:** The likelihood that a genotype will produce any phenotype at all. Incomplete penetrance refers to the idea that some people with a certain genotype will demonstrate a phenotype, whereas others with the same genotype will demonstrate no phenotype at all.
- **Pleiotropy:** The situation in which one gene has multiple different effects on several organ systems.

TYPES OF MUTATIONS

- **Amorphic mutation:** Results in complete loss of gene product function.
- **Antimorphic mutation:** Results in the production of a mutated protein that acts to inhibit a normally expressed protein.
- **Frameshift mutation:** The addition or removal of nucleotides to a gene sequence that results in an alteration of the reading frame of the protein synthesis machinery.
- **Hypomorphic mutation:** Results in the loss of only a portion of gene product function.

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TYPES OF MUTATIONS

- **Hypermorphic mutation:** Results in the increased activity of gene product function.
- **Missense mutation:** Caused by a point mutation (mutation of one nucleotide base pair) that results in a change in the gene sequence.
- **Neomorphic mutation:** Results in the addition of new abilities to a gene product's function.
- **Nonsense mutation:** Caused by a base pair mutation that results in the formation of a stop codon. Reading of the gene sequence is usually terminated early, and this leads to the synthesis of a worthless gene product.

THE CONCEPTS

Definition

Assuming certain conditions, the Hardy-Weinberg equilibrium proposes that allelic frequency of a population will stay stable over time.

Conditions of the Hardy-Weinberg population:

- The population must be large.
- Mating must be random, with no selection for certain genotypes.
- There must be no emigration or immigration.
- There may be no mutations.
- There may be no incestuous mating.

THE EQUATIONS

There is a gene with two alleles, A and a.

$$p + q = 1 \qquad \text{(Eq. 1)}$$

- p = frequency of A allele
- q = frequency of a allele

$$p^2 + 2pq + q^2 = 1 \qquad \text{(Eq. 2)}$$

- p^2 = frequency of AA genotype
- $2pq$ = frequency of Aa genotype
- q^2 = frequency of aa genotype

For X-linked recessive traits, the frequency of disease in males is equal to the frequency of the recessive allele because males only have one X chromosome.

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SAMPLE PROBLEMS INVOLVING HARDY-WEINBERG EQUILIBRIUM

QUESTION

Sickle cell anemia, an autosomal recessive disease, occurs in 1 of every 400 African-American births. What is the frequency of carriers of the sickle cell gene in this population?

ANSWER

Carriers (or heterozygotes) are represented by 2pq, so we need to solve for p and q.

We are told that q^2 is equal to 1/400 or 0.0025. Thus, q = 0.05

We know that p + q = 1, so p = 1 – q. In this case, p = 1 – 0.05 = 0.95.

We then solve for 2pq, which is equal to 2(0.95)(0.05) or 0.095. So 95 of every 1000 African-Americans carry the sickle cell gene.

QUESTION

Fragile X syndrome, an X-linked recessive disease, occurs in 1 of every 2000 males. What is the frequency of female carriers of the fragile X allele?

ANSWER

Carriers are represented by 2pq, so we need to solve for p and q.

Remember that in X-linked diseases, the frequency of the disease in males is equal to the frequency of the disease allele in the population (q) because males only have one copy of the X chromosome. We are told that fragile X syndrome occurs in 1 of every 2000 males, so we know that q = 0.0005.

We know that p + q = 1, so p = 1 – q. In this case, p = 1 – 0.0005 = 0.9995.

We then solve for 2pq, which is equal to 2(0.9995)(0.0005) or 0.000995. So about 1 of every 10 000 females carry the gene for fragile X syndrome.

You deliver a baby girl to a 46-year-old woman. At the birth, you notice that the child has a flat face, wide-set eyes, epicanthal folds, and a single palmar crease across each hand. When a cardiac examination reveals a holosystolic murmur that is consistent with a ventricular septal defect, you feel relatively certain that this patient may have a chromosomal disorder and you refer her to a geneticist for further workup.

Genetic Defect	**Trisomy 21** causes **95% of cases** (usually because of meiotic nondisjunction); 4% of cases are caused by **Robertsonian translocation** of the long arm of chromosome 21 to another chromosome (usually chromosome 14 or 22); 1% of cases are caused by **mosaicism**, resulting from mitotic nondisjunction of chromosome 21 during embryogenesis.
Characteristics	**Severe mental retardation**; duodenal and esophageal atresia; short hands with **simian crease** (single palmar crease). Specific facial features include flat face; **epicanthal folds**; **wide-set eyes**; Brushfield spots (white spots on periphery of iris).
	Congenital heart defects: Endocardial cushion defects leading to ostium primum atrial septal defects, ventricular septal defects, and atrioventricular valve malformations.
Complications	Patients with Down syndrome are at increased risk for acute leukemias (especially **ALL**) and increased susceptibility to infections. These patients also develop degenerative changes in the brain, similar to **Alzheimer disease**, that occur in middle age.
Treatment and Prognosis	Surgical treatment for duodenal atresia and congenital heart defects.
	More than 80% of patients survive past age 30, but life expectancy is shortened.
Notes	The incidence of trisomy 21 **increases with maternal age** such that Down syndrome occurs in 1 in 25 births to mothers older than 45.

A baby boy, born to a 44-year-old woman, is referred to you for genetic workup by his pediatrician shortly after delivery. On initial evaluation of the patient, you immediately notice that the child has a prominent occiput, a small jaw, low-set ears, and overlapping third and fourth fingers on both hands. You immediately begin to fear that the child has a severe chromosomal disorder that is usually fatal within 1 year of birth, and you suspect that further workup will likely reveal the presence of cardiac and renal defects.

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Edwards Syndrome and Patau Syndrome

Genetic Defect	**Edwards syndrome: Most cases** are caused by **trisomy 18** (usually caused by meiotic nondisjunction). A few cases are caused by **mosaicism**, resulting from mitotic nondisjunction of chromosome 18 during embryogenesis.
	Patau syndrome: Most cases are caused by **trisomy 13** (usually caused by meiotic nondisjunction). A few cases are caused by **mosaicism**, resulting from mitotic nondisjunction of chromosome 13 during embryogenesis or **translocation** between chromosomes 13 and 14.
Characteristics	**Edwards syndrome: Severe mental retardation**; **rocker-bottom feet**; specific facial features include prominent occiput, micrognathia (small jaw), low-set ears; **congenital heart and renal defects**; overlapping third and fourth fingers.
	Patau syndrome: Severe mental retardation; microcephaly and holoprosencephaly; **cleft lip and palate** and microphthalmia (small eyes); **polydactyly**; congenital heart and renal defects; umbilical hernia; rocker-bottom feet.
Prognosis	Both disorders are usually fatal within 1 year of birth.
Notes	Incidence of both Edwards and Patau syndrome **increases with maternal age**.

A 17-year-old boy presents to your pediatrics clinic for his annual checkup. The patient is new to your clinic. His mother tells you that the child has been mentally retarded since birth and was diagnosed with type 2 diabetes more than 3 years ago, for which he takes an oral hypoglycemic medication. On further questioning, his mother also notes that she does not think that the patient has gone through puberty yet. Physical examination reveals an obese young man of short stature with hypotonia in all extremities, absence of facial, axillary, or pubic hair, and childlike external genitalia. You begin to wonder whether his mental retardation, diabetes, and hypogonadism might be part of a genetic syndrome caused by a mutation on the paternally derived chromosome 15.

9

Prader-Willi and Angelman Syndromes

Genetic Defect	Both diseases are due to an **identical deletion on chromosome 15q** and demonstrate **imprinting**, a phenomenon in which the same mutation results in different phenotypes depending on whether the mutated chromosome was of maternal or paternal origin. **Prader-Willi syndrome** develops when the deletion is on the **paternally derived** chromosome, whereas **Angelman syndrome** develops when the deletion is on the **maternally derived** chromosome.
Characteristics	**Prader-Willi syndrome: Mental retardation**; **hypogonadism**; hypotonia; **obesity** leading to diabetes. **Angelman syndrome: "Happy puppet"** with ataxic gait and inappropriate laughter; **mental retardation**; seizures.
Treatment	Treatment of symptoms with lifelong supervision.
Notes	

A 27-year-old man presents to your office for a workup for possible infertility. He tells you that he and his wife have been trying to conceive for the last 2 years but have been unsuccessful. He has no significant medical history and reports no exposure to radiation or noxious chemicals. Physical examination reveals a tall man with gynecomastic features and small atrophic testes. When laboratory results demonstrate decreased testosterone levels and increased FSH and LH levels, you begin to suspect that this patient may have a genetic disorder that would account for the couple's infertility.

9

Klinefelter Syndrome

Genetic Defect	This disorder is characterized by two or more X chromosomes with one or more Y chromosomes (most commonly **47, XXY** karyotype with a **single Barr body**) and is most commonly caused by **maternal meiotic nondisjunction**. Other causes include mosaicism or paternal meiotic nondisjunction.
Characteristics	Small **atrophic testes**; **tall stature**; lack of secondary male characteristics and **gynecomastia**. **Male infertility**, often resulting from reduced spermatogenesis. Occasionally associated with mild mental retardation. *Lab findings:* **Decreased testosterone** levels; **increased FSH and LH** levels.
Treatment	Testosterone replacement after puberty (does not treat infertility).
Notes	**XYY syndrome** results in tall males with severe acne but no other clinically significant manifestations. Of interest, studies have found an increased frequency of XYY syndrome among criminals.

A 2-week-old girl is referred to your cardiology practice for a workup of a possible congenital heart defect. Physical examination is significant for weak femoral pulses as well as a broad chest with widely spread nipples and the presence of a cystic hygroma on the neck, giving the child a "webbed-neck" appearance. Cardiac catheterization confirms your suspicions that the child has coarctation of the aorta, and you refer the patient and her family to a cardiothoracic surgeon. Given the patient's other physical findings, you also suspect that this patient may have a genetic disorder that will cause her to experience primary amenorrhea later in life. Therefore, you refer the patient to a medical genetics clinic as well.

9

Turner Syndrome

Genetic Defect	Caused by partial or complete monosomy of the X chromosome **(XO karyotype** with **no Barr body)**.
Characteristics	**Short stature** with a **broad chest** and widely spread nipples; cystic hygroma of the neck, leading to **webbed-neck** appearance; lymphedema of extremities; **coarctation of the aorta** and other congenital heart defects. Reproductive symptoms include **primary amenorrhea**, replacement of ovaries with **fibrous strands** (no ova or follicles), and infantile genitalia and breasts.
	Lab findings: **Decreased estrogen** production; **increased FSH and LH** levels.
Complications	Patients with Turner syndrome are at increased risk for diabetes mellitus, hypertension, Hashimoto thyroiditis, and osteoporosis.
Treatment and Prognosis	Estrogen replacement; growth hormone (treat short stature).
	Patients have a decreased life expectancy because of cardiovascular abnormalities.
Notes	

A 1-month-old boy presents to your pediatric clinic for a routine checkup. The child's mother notes that the child has been relatively well, although she has not been feeding as well as expected and often appears listless. On physical examination, you note that the child has a round face with microcephaly and low-set ears. While you are examining the child, she lets out a high-pitched distinctive cry. You begin to fear that the child may have a chromosomal abnormality that leads to significant cognitive deficits and you refer the patient to a geneticist.

Cri-du-Chat Syndrome

Genetic Defect	Caused by **partial deletion of chromosome 5p**.
Characteristics	Patients exhibit a high-pitched **cat-like cry** at birth, which is usually due to structural abnormalities in the larynx; patients also have **severe developmental delay and cognitive deficits** and **distinctive facial abnormalities** (round face, low-set ears, microcephaly, and a hypoplastic nasal bridge). Other complications include structural cardiac defects and difficulty swallowing, which can result in failure to thrive. *Lab findings:* Cytogenetic studies reveal a deletion of chromosome 5p.
Treatment and Prognosis	Supportive care with special attention to the developmental needs of the patient; genetic testing for any patient of childbearing age. Patients have up to a 10% annual morbidity and mortality rate, although most of these deaths occur within the first year of life.

Notes

A 14-year-old boy is brought to your pediatrics office by his parents, who have recently adopted him. The parents report that their new son is mentally retarded and that they were told that several other members of his biological family suffer from a syndrome associated with mental retardation. As you observe the patient, you note that he has a long face with large ears and a large jaw. When physical examination reveals large testicles, you begin to suspect that the patient suffers from a genetic syndrome that demonstrates the genetic concept of anticipation.

Genetic Defect	Caused by increased number of **CGG repeats** in the **FMR-1 gene** on the **X chromosome**. Fragile X syndrome, along with Huntington disease and myotonic dystrophy, demonstrates **anticipation**, a phenomenon in which the number of repeats increases with each generation and results in more severe disease manifestations.
Characteristics	Severe **mental retardation** with autistic characteristics; long face with large jaw and ears; **macroorchidism** (large testicles); connective tissue defect manifesting with hyperextensible joints and mitral valve prolapse.
Prognosis	Life span is not affected, but lifelong supervision is required.
Notes	Fragile X syndrome affects both males (1:2000) and females, although females generally have less severe clinical manifestations. Fragile X is named for its fragile gap at the end of the long arm of the X chromosome in lymphocytes grown in folate-deficient medium.

A 25-year-old woman presents to your office complaining of painful swelling in her left calf. She denies any trauma to the leg and has no significant medical history. The only medication that she takes is an oral contraceptive pill, which she has been using for 3 months. Physical examination reveals an erythematous, tender, swollen left calf with an increase in calf pain with sharp dorsiflexion of the left ankle (ie, positive Homans sign). You tell the patient that you suspect that she has a deep venous thrombosis in her left calf, and you send her to the emergency room for a lower extremity Doppler ultrasound and possible anticoagulation therapy. In addition, you inform the patient that she may need evaluation for a genetic disorder that might predispose her to a hypercoagulable state.

9

Factor V Leiden

Genetic Defect	Caused by an **autosomal dominant** mutation in the **gene for factor V** on chromosome 1.
Pathophysiology	One of the major regulators of the coagulation cascade is protein C. After binding with protein S, protein C degrades factors Va and VIIIa of the coagulation cascade, thereby resulting in cessation of coagulation. The factor V Leiden mutation results in the production of a mutated **factor V that is resistant to degradation by protein C**. Thus, cessation of coagulation is impaired and a hypercoagulable state manifests.
Clinical Manifestations	Patients with factor V Leiden are at an **increased risk for deep venous thrombosis and pulmonary embolism**. This risk is increased with pregnancy, recent surgery, cancer, and use of oral contraceptives.
Treatment	Consider anticoagulant therapy with coumadin; avoid oral contraceptive use.
Notes	

A 9-year-old boy presents to your hematology practice for evaluation of a pancytopenia discovered by the child's pediatrician. While speaking with the boy and his mother, you notice that the child has café au lait spots on his neck as well as deformed thumbs on both hands. A bone marrow biopsy reveals hypocellularity, consistent with aplastic anemia. You tell the patient's parents that his physical anomalies as well as his pancytopenia are likely part of a rare disorder that also carries an increased risk for cancer in later years.

9

Fanconi Anemia

Genetic Defect	A **rare autosomal recessive condition** resulting in the mutation of one of eight Fanconi anemia genes (termed genes FA-A through FA-H).
Pathophysiology	The exact action of the Fanconi anemia gene products is unknown; however, the prevailing theories are that the Fanconi anemia proteins are involved in DNA repair or the removal of damaging oxygen-free radicals. If these proteins are mutated, as in Fanconi anemia, there may be increased damage to sensitive cells, such as those involved in hematopoiesis and other stem cells.
Clinical Manifestations	Patients are most often **diagnosed between the ages of 3 and 14**. Physical findings include **café au lait spots on the trunk and neck** and stunted growth with resulting **short stature** and hypogonadism. Some patients may also have **skeletal anomalies** (dysplastic thumbs and radii), congenital heart, eye or kidney defects, microcephaly, and mental retardation. Complications include increased sensitivity of tissues to alkylating agents, with resulting increases in the development of cancers. *Lab findings:* **Aplastic anemia** (**pancytopenia** [develops in adolescence] with **hypocellular bone marrow** on biopsy); increased chromosome fragility.
Treatment	Stem cell transplantation is curative.
Notes	

A 4-year-old boy presents to the emergency department complaining of swelling in his left elbow joint. He and his mother deny trauma to the elbow. On further questioning, his mother tells you that the patient's older brother has a bleeding disorder. Physical examination reveals a warm swollen joint. Laboratory tests demonstrate a prolonged PTT, a normal PT, and a normal bleeding time. To provide the proper treatment for this patient's likely hemarthrosis, you order a clotting factor assay and consult a hematologist.

9

Hemophilia A and B

Genetic Defect	**Hemophilia A: X-linked recessive** disorder resulting in a **deficiency of factor VIII**.
	Hemophilia B: X-linked recessive disorder resulting in a **deficiency of factor IX**.
Pathophysiology	Deficiency of clotting factor VIII or IX interferes with the intrinsic pathway of coagulation, thereby resulting in an **ineffective coagulation response**.
Clinical Manifestations	**Bleeding** into muscles and joints (spontaneous hemarthrosis).
	Lab findings: **Prolonged PTT**, **normal PT**, **normal bleeding time**, normal thrombin time.
Treatment	Replace deficient clotting factor.

Notes

A 6-year-old girl presents to your pediatric clinic for her annual checkup. You observe that the child has developed scleral icterus since you saw her last. The patient has no significant medical history, although her father tells you that he suffers from a genetic blood disorder. Physical examination of the child reveals splenomegaly, and laboratory tests demonstrate a hemolytic anemia with an increased mean corpuscular hemoglobin concentration and an increased red blood cell osmotic fragility. You suspect that this patient's constellation of symptoms and test results are due to a defect in an erythrocytic membrane protein.

9

Hereditary Spherocytosis

Genetic Defect	Caused by an **autosomal dominant** condition that results in the production of defective erythrocytic membrane proteins (usually **spectrin**).
Pathophysiology	The membrane of the erythrocyte is supported by a protein scaffold that allows the red blood cell to maintain the biconcave shape of the erythrocyte and also to be deformable so as to fit through capillaries and splenic fenestrations. Spectrin is the major component of the scaffolding for the erythrocytic membrane. When spectrin is deficient or mutated, the erythrocyte loses the biconcave shape, resulting in a less deformable spherical shape of the cell and a decrease in surface-to-volume ratio. The spherical cells are unable to pass through the splenic fenestrations and become trapped in the spleen, where they are hemolyzed.
Clinical Manifestations	Patients may have jaundice with scleral icterus or pigment gallstones because of chronic hemolysis. Splenomegaly may also be present.
	Lab findings: **Hemolytic anemia**; **spherocytes** on peripheral blood smear; **increased MCHC**; **increased erythrocyte osmotic fragility**; reticulocytosis; normal MCV; normal hemoglobin.
Treatment	Splenectomy (eliminates site of hemolysis); folic acid supplementation.
Notes	

An 8-year-old boy presents to the urgent care clinic for evaluation. He had been seen there 2 days earlier for right ear pain and had been diagnosed with otitis media, for which he had been prescribed Bactrim. He reports that over the last 2 days, she has developed yellowing of her skin and eyes as well as significant fatigue. He denies any recent exposure to shellfish or blood products. Physical examination reveals the presence of splenomegaly and jaundice. When blood tests demonstrate the presence of a hemolytic anemia, you begin to suspect that the patient may have an X-linked genetic defect that is associated with a deficiency in an enzyme of the pentose phosphate pathway.

9

G6PD Deficiency

Genetic Defect	Caused by an **X-linked recessive** condition that results in **decreased** or absent levels of the enzyme, *glucose-6-phoshate dehydrogenase*.
Pathophysiology	*Glucose-6-phosphate dehydrogenase* is a key component of the pentose phosphate pathway and is responsible for catalyzing the conversion of glucose-6-phosphate to 6-phosphogluconate. This reaction also **generates** a molecule of **NADPH** and serves as the main source of NADPH in the red blood cell. In the red blood cell, **NADPH acts as a cofactor for glutathione**, which is a molecule that is **responsible for scavenging and removing oxidative metabolites**, such as peroxide. If NADPH is absent, then glutathione is unable to remove these dangerous molecules, which subsequently accumulate, leading to cell membrane damage and ultimately, hemolysis.
Clinical Manifestations	Patients may have jaundice or splenomegaly present during a G6PD crisis (eg, states of oxidative stress that can be brought on by infection or exposure to certain drugs or foods). Gallstones may also be present. *Lab findings:* **Hemolytic anemia** (which will be associated with increased haptoglobin levels and increased levels of indirect bilirubin); decreased G6PD enzyme activity.
Treatment	Avoidance of food or drugs (eg, fava beans, sulfa drugs, analgesics, and antimalarial drugs) that precipitate a crisis.
Notes	G6PD deficiency has been associated with protection against malaria.

An 11-year-old African-American girl presents to the emergency department complaining of severe pain in both of her legs and her back. She reports that she is currently attending summer camp and has been engaging in multiple sporting events during the past few days with her playmates. She also tells you that she has suffered from severe bouts of back and leg pain in the past and that her cousin suffers from a similar disorder. You order blood tests to check her hematocrit level and immediately begin administering intravenous fluids, oxygen, and narcotics for pain control.

9

Sickle Cell Anemia

Genetic Defect and Epidemiology	An **autosomal recessive** disorder that leads to the **production of hemoglobin S**. Hgb S arises from a mutation (substitution of valine for glutamine) in the gene coding for the β-globin chain of hemoglobin. About 8% of African-Americans carry the gene for hemoglobin S.
Pathophysiology	**Hemoglobin S polymerizes in hypoxic environments** (as caused by infection, exercise, or dehydration), causing the **RBC shape to become distorted** ("sickled") and more susceptible to hemolysis. The increased hemolysis of erythrocytes leads to elevated levels of indirect bilirubin and consequent jaundice. The sickled cells may cause microvasculature blockage, leading to painful vaso-occlusive crises in the back or limbs or to infarction of the spleen.
Clinical Manifestations	Chronic **hemolytic anemia**, which may lead to jaundice and leg ulcers; severe pain in the back or limbs **(vaso-occlusive crises)**; **autosplenectomy** resulting from repeated infarction; **aplastic crises**, which are usually provoked by parvovirus B19 infection; increased susceptibility to **infection** by encapsulated organisms (*Salmonella*).
	Lab findings: Anemia; elevated indirect bilirubin; reticulocytosis; **crescent-shaped RBCs** and **Howell-Jolly bodies** on peripheral blood smear.
Treatment	Intravenous fluids, oxygen, and pain control during vaso-occlusive crises; blood transfusion; hydroxyurea (increases hemoglobin F levels).
Notes	Patients with **hemoglobin C disease** (different mutation in β chain of hemoglobin) and **sickle cell trait** (heterozygous for the hemoglobin S gene) tend to have milder versions of sickle cell anemia. The hemoglobin S gene provides resistance to *Plasmodium falciparum* malaria.

An 8-month-old child from Italy presents to your pediatrics office with failure to thrive. During physical examination, you find that the child's spleen is enlarged, and you note that she has several bony abnormalities of her limbs and facial structure. When laboratory testing shows signs of a hemolytic anemia with the presence of target cells on peripheral smear, you fear that this child will need blood transfusions for the rest of her life in order to treat her genetic blood disorder.

Thalassemias

Genetic Defect	α-t: **Autosomal recessive** disorder resulting in the **deletion** of 1^+ of 4 genes coding for the α-**globin chain of Hgb** on chromosome 16.
	β-t: **Autosomal recessive** disorder resulting in a **point mutation in the β-globin gene of Hgb** on chromosome 11.
Pathophysiology	Normal adult Hgb is usually composed of two α chains and two β chains. In α-t, there is excess production of β chains. The **excess β chains can form Hgb H**, which leads to hemolysis. In β-t, there are excess α chains, leading to hemolysis. In β-t, there is also reduced synthesis of β chains, leading to an increase in γ and δ chains and resulting in the formation of Hgb A_2 and F.
Clinical Manifestations	α-T: Four variants exist. (1) α-t trait (three to four normal genes): asymptomatic; (2) α-t minor (two normal genes): mild anemia; (3) **hemoglobin H disease** (one normal gene): **severe hemolytic anemia**, presence of Hgb H, **splenomegaly**; (4) hydrops fetalis (no normal genes): stillborn fetus.
	β-T: Two variants exist. (1) β-t minor (heterozygosity): mild anemia; (2) **β-t major** (homozygosity): **severe hemolytic anemia**, **increased Hgb F**, **splenomegaly**, bony abnormalities, hemosiderosis (from chronic transfusions), and heart failure (from hemosiderosis).
	Lab findings for α-t and β-t: Hypochromic, **microcytic RBCs** and **target cells** on peripheral smear.
Treatment	No treatment needed for α-t trait or β-t minor; transfusions for α-t minor and hemoglobin H disease; transfusions and/or bone marrow transplantation for β-t major.
Notes	β-t is relatively more common in people of Mediterranean ancestry, whereas α-t is relatively more common in people of Southeast Asian ancestry.

A 9-year-old boy is brought to the emergency department because of uncontrollable bleeding from his nose after being hit in the face with a soccer ball. Further questioning reveals that the boy has been taking aspirin recently for a viral illness, that he has a history of prolonged bleeding, and that his mother and two cousins suffer from a bleeding disorder. Laboratory tests reveal a prolonged bleeding time, a prolonged PTT, and a normal PT. As you pack the boy's nose, you advise him and his family to avoid aspirin use because you suspect that they are affected with the most common hereditary bleeding disorder.

9

von Willebrand Disease

Genetic Defect and Epidemiology	**Autosomal dominant** disease marked by a **deficiency in vWF**. von Willebrand disease is the **most common hereditary bleeding disorder**, affecting 1% of all people.
Pathophysiology	Lack of vWF causes **impaired platelet adhesion** to the subendothelium during vascular injury, thereby resulting in deficient platelet plug formation. Because vWF also acts as a carrier protein for factor VIII, deficient vWF results in a **functional deficiency of factor VIII**, thereby impairing the intrinsic pathway of coagulation.
Clinical Manifestations	**Mucosal bleeding** (epistaxis, gingival bleeding, menorrhagia). *Lab findings:* **Prolonged PTT**; **prolonged bleeding time**; **normal PT**; normal thrombin time.
Treatment	Avoid aspirin and other anticoagulants; desmopressin or factor VIII replacement if necessary.
Notes	

A 19-year-old woman presents to your hematology clinic, having been referred by her primary care physician for long-standing fatigue. She reports that her fatigue is most severe after she menstruates and she does report that she suffers from extremely heavy bleeding during her menstrual cycle. Upon direct questioning, she also tells you that her gums often bleed when she brushes her teeth and that she has at least one nosebleed a month. Physical examination is notable for the minor bruises. Laboratory studies reveal a normal platelet count, normal prothrombin time, and normal activated partial thromboplastin time. However, she does have borderline anemia and a prolonged bleeding time. You begin to suspect that she may suffer from an autosomal recessive disorder associated with the deficiency of the glycoprotein IIb/IIIa receptor.

9

Glanzmann Thrombasthenia and Bernard-Soulier Syndrome

Genetic Defect	**GT: Autosomal recessive** disorder resulting in the **deficiency or dysfunction of glycoprotein IIb/IIIa receptor** on the platelet surface.
	BSS: Autosomal recessive disorder resulting in the **absence or deficiency of glycoprotein Ib receptor** on the platelet surface.
Pathophysiology	**GT: Glycoprotein IIb/IIIa receptor complex is responsible for binding fibrinogen to the platelet surface**. When fibrinogen is bound to the platelet, cross-linking between adjacent platelets can occur, and hence **platelet aggregation results**. When there is a defect in the glycoprotein IIb/IIIa receptor complex, platelets are unable to aggregate properly and bleeding results.
	BSS: Glycoprotein Ib receptor is responsible for binding von Willebrand factor (vWF) to the platelet surface. When vWF binds the platelet, **platelet adhesion** to the injured endothelial surface **occurs**. When there is a defect in the glycoprotein Ib receptor, platelet adhesion does not occur and bleeding results.
Clinical Manifestations	**GT: Excessive bleeding** (often manifested as dental bleeding, epistaxis or menorrhagia). *Lab findings:* Normal platelet count, prothrombin time and activated partial thromboplastin time; **prolonged bleeding time**.
	BSS: Excessive bleeding (often manifested as dental bleeding, easy bruising, epistaxis or menorrhagia). *Lab findings:* **Low platelet count**; **prolonged bleeding time**.
Treatment	**GT and BSS: Avoid antiplatelet medications**; supportive treatment of bleeding episodes (platelet/red blood cell transfusions).

Notes

A 17-year-old boy presents to the emergency room after passing out during soccer practice. He tells you that he often feels excessively short of breath during practice and occasionally even has had chest pain that resolves with rest. On taking a family history, you learn that his father died suddenly at age 30. Concerned, you send the patient for an echocardiogram, which reveals a hypertrophic heart with a functional left ventricular outflow obstruction during systole. You tell the patient and his mother that he should avoid strenuous exercise, and you refer him to a cardiologist and a geneticist for further evaluation.

9

Familial Hypertrophic Cardiomyopathy

Genetic Defect	An **autosomal dominant** disorder with variable expression that results in the mutation of a component of the cardiac sarcomere (β**-myosin heavy chain** [most common]; myosin-binding protein C; cardiac troponin T; α-tropomyosin).
Pathophysiology	Although it is not entirely understood how mutations in a component of the cardiac sarcomere can lead to disease, the affected organ is characterized by **hypertrophy of the interventricular septum and myocardium**, which results in a small banana-shaped left ventricular lumen. The reduced volume of the left ventricle gives rise to reduced filling of the heart during diastole and resulting low cardiac output, which can manifest as dyspnea and syncope. Sudden death can also occur from **left ventricular outflow obstruction**, caused by a mitral valve leaflet swinging toward the interventricular septum during systole. The hypertrophied myocardium is **susceptible to ischemia**, leading to the common complaint of angina.
Clinical Manifestations	Dyspnea; angina; syncope; palpitations; arrhythmias; **sudden death (often in young athletes)**.
	Lab findings: Haphazard arrangement of hypertrophied myocytes under microscopic examination.
Treatment	β-Blockers; avoid strenuous exercise.
Notes	

A 2-week-old girl presents to the pediatrics clinic for evaluation of swelling. The child's mother tells you that, since her birth, the baby has developed progressive swelling in her lower extremities. Furthermore, she has also noted that the child seems listless and inactive. Physical examination reveals lymphedema of the extremities as well as a harsh systolic ejection murmur at the left sternal border, consistent with pulmonic stenosis. You also note that the child has down-slanting eyes and strabismus. You begin to worry that the baby may have a congenital disorder that is related to an abnormality in a protein of the RAS signal transduction pathway.

9

Genetic Defect	An **autosomal dominant** disorder with variable expression that results from the **mutation** of one of several genes (PTPN11, SOS1, KRAS, RAF-1) of the **RAS signal transduction pathway**.
Pathophysiology	The RAS signal transduction pathway has been shown to be an important pathway in the **regulation of the cell cycle**. The proteins coded for by the affected genes are **involved in embryological cell migration, growth, and differentiation** (and in particular, development of the semilunar heart valves). Disruption in this pathway can result in abnormal fetal development.
Clinical Manifestations	Short stature; **distinctive facial features** (short webbed neck, strabismus, high nasal bridge, down-slanting eyes); hepatosplenomegaly; congenital heart defects (classically **pulmonic stenosis**); joint laxity; lymphedema; **mental retardation**; **bleeding disorders**.
Treatment	Supportive treatment; surgical treatment of cardiac abnormalities if needed; growth hormone can be considered to treat short stature.
Notes	

A 6-month-old Mormon boy in Utah is brought into your pediatrics office. His mother is concerned that the child seems to suffer from frequent spontaneous nosebleeds. While speaking with the mother, you immediately notice that the child has multiple small telangiectasias of the skin. Further examination of the child demonstrates telangiectasias on the oral and nasal mucosa as well. His nasal lesions are open and bleeding. When questioned about family history, the mother reports that the child's father also suffers from frequent nosebleeds and that he has several skin lesions similar to those seen on the child. You suspect that this child's and his father's conditions are caused by an autosomal dominant genetic disorder.

9

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Genetic Defect	**Autosomal dominant** disorder that results in mutations in TGF-β–binding proteins.
Pathophysiology	Mutations in TGF-β–binding proteins lead to abnormal development of vascular structures, which results in the localized **dilation and convolution of venules and capillaries** of the skin and mucous membranes of the oral cavity, respiratory tract, GI tract, and urinary tract.
Clinical Manifestations	Recurrent hemorrhage from skin and mucous membrane lesions.
	Complications include **GI bleeding** and **epistaxis**.
	Lab findings: Normocytic, normochromic anemia.
Treatment	Nasal packing; cautery; estrogens to control epistaxis.
Notes	Osler-Weber-Rendu disease is seen with increased frequency in Utah Mormons.

A 15-year-old girl presents to the emergency room complaining of decreased vision in both eyes. She also tells you that she has been experiencing worsening headaches over the last 2 months and that she has been tripping more when she walks. You immediately order a CT scan of her head, which demonstrates the presence of multiple cystic lesions throughout the cerebellum and brainstem consistent with hemangioblastomas. You begin to suspect that this patient has a genetic disorder, which results in the deletion of the *VHL* gene.

9

Genetic Defect	**Autosomal dominant** disorder that results in the deletion of the *VHL* gene (tumor suppressor gene) on chromosome **3p**.
Pathophysiology	The *VHL* gene encodes for a protein that is involved in inhibiting RNA synthesis. With the mutation of this gene, the ability to inhibit RNA synthesis is hindered and vascular malformations and other tumors result.
Clinical Manifestations	Initially presents with headaches, ataxia, or loss of vision. The disease is characterized by **hemangioblastomas** or cavernous hemangiomas (large vascular spaces filled with blood) of the **cerebellum**, **brainstem**, and **retina** as well as adenomas and cysts of the liver, kidneys, and pancreas.

Complications include **increased incidence of renal cell carcinoma**, pheochromocytoma, and ocular hemangioblastomas. |
| **Treatment** | Surgical removal of tumor and radiation therapy. |
| **Notes** | |

A baby boy is born to a 29-year-old woman. Although there were no complications with the birth, you become concerned when, 48 hours after birth, the child still has not passed any stool. Radiographic imaging demonstrates the presence of a meconium ileus. On further questioning, the mother also tells you that her younger sister suffers from a severe genetic pulmonary disease that also affects her pancreas. You immediately decide to test the level of chloride ions in this child's sweat because you fear that the boy may have a genetic disorder, which involves a mutation on chromosome 7.

Cystic Fibrosis

Genetic Defect	**Autosomal recessive** disorder, caused by a mutation (most common is ΔF508, but there are 230+ recognized mutations) on **chromosome 7**, which results in a **defective membrane Cl⁻ channel (CFTR)**.
Pathophysiology	The mutated Cl⁻ channel causes defective chloride and water transport in epithelial cells. This results in the **secretion and trapping of thick mucous plugs** in the lungs, liver, and pancreas. The mucous plugs obstruct various secretory ducts (bile canaliculi, bronchioles, pancreatic ducts), leading to inflammation and eventual tissue damage. In the lung, the thick mucous in combination with high concentrations of DNA (results from remnants of destroyed neutrophils, which flood the chronically inflamed lung) leads to increased viscosity of sputum.
Clinical Manifestations	**Chronic lung disease** causing productive cough, **pulmonary infections**, **bronchiectasis**, cyanosis, and a "barrel-shaped" chest; **pancreatic insufficiency** causing **steatorrhea**, malabsorption, and abdominal pain; **meconium ileus** (small bowel obstruction by mucous plugs in newborn); infertility in males.
	Complications include pneumothorax and cor pulmonale.
	Lab findings: **High Cl⁻ concentrations in sweat test**; hypoxia; **increased ratio of residual volume to TLC**.
Treatment and Prognosis	Antibiotics; bronchodilators; techniques to clear airway secretions; **lung transplantation**.
	Median age of survival is 31 years; death occurs from pulmonary complications.
Notes	Cystic fibrosis is the **most common fatal inherited disorder** in the United States; 1 in 3200 people is affected.

A 29-year-old man presents to your infertility clinic with his wife. The couple has been trying to conceive for 3 years with no success. His medical history is significant for recurrent sinusitis and several bouts of pneumonia that have required hospitalization in the past. He also tells you that his heart is on the right side. When laboratory tests reveal defective sperm motility, you begin to suspect that this patient might suffer from a rare genetic disorder.

Kartagener Syndrome

Genetic Defect	A rare **autosomal recessive** disorder that results in a **defect in dynein arms** within cilia.
Pathophysiology	Dynein arms are responsible for the ciliary movement; therefore, **defective dynein arms result in deregulated movements of cilia**. In the respiratory tract, impaired ciliary motility results in decreased clearance of bacteria, leading to increased incidence of infection in the lungs and sinuses. In the reproductive system, sperm are unable to travel effectively because of the defective motility of the sperm tail, thereby resulting in infertility. During embryogenesis, defective ciliary motion can lead to situs inversus.
Clinical Manifestations	**Bronchiectasis** as manifested with a productive cough, hemoptysis, and cyanosis; **sterility** in males; recurrent sinusitis; **situs inversus** (dextrocardia) is seen in 50% of patients.
	Imaging: Findings consistent with bronchiectasis (dilated bronchioles with "signet ring" appearance on CT scan).
	Lab findings: **Decreased FEV_1/FVC ratio.**
Treatment	Treatment of bronchiectasis with antibiotics, bronchodilators, and surgical resection.
Notes	

A 25-year-old man presents to the emergency room complaining of severe right-sided abdominal pain. He also reports that his urine has been darker over the last couple of days. His medical history is significant for emphysema, although he denies any smoking history. Physical examination of the abdomen reveals scleral icterus and tenderness in the RUQ of his abdomen. Laboratory tests reveal elevated liver enzymes and hyperbilirubinemia. His viral hepatitis serologies are negative. You admit him to the hospital for treatment of acute hepatitis and wonder whether an autosomal recessive genetic disorder might account for both his hepatitis and his emphysema.

9

α₁-Antitrypsin Deficiency

Genetic Defect	An **autosomal recessive** disorder causes a mutation on chromosome 14 at the α_1-antitrypsin gene, leading to **low levels of α_1-antitrypsin**. There are multiple different alleles for the α_1-antitrypsin gene. The most common allele combination associated with clinical α_1-antitrypsin deficiency is the **PiZZ genotype**.
Pathophysiology	α_1-Antitrypsin is a liver-synthesized protease inhibitor, which has the important role of **inhibiting neutrophil elastase**. At sites of inflammation, neutrophil elastase is released and acts to destroy pathogens as well as the affected tissue. **If α_1-antitrypsin is deficient, neutrophil elastase is uninhibited and damages delicate tissues, such as the lung** (destroys elastin in the alveolar wall), leading to emphysematous changes. α_1-Antitrypsin deficiency also results in liver damage. In the liver, the mutated α_1-antitrypsin is unable to be secreted by the hepatocyte and instead accumulates, leading to variable hepatic disease.
Clinical Manifestations	**Symptoms of emphysema:** Dyspnea; cyanosis; **"barrel-shaped" chest**; use of accessory respiratory muscles. **Hepatic disease** ranging from intermittent attacks of hepatitis to the development of cirrhosis. Patients also are at an increased risk for hepatocellular carcinoma. *Lab findings:* **Decreased FEV₁/FVC ratio; elevated LFTs.**
Treatment	Avoid cigarette smoking (worsens emphysema) and alcohol use; bronchodilators as needed; symptomatic treatment of liver disease with liver transplantation if necessary.
Notes	The frequency of this disorder is as high as 1:5000 in the US population.

A 24-year-old woman is referred to your hepatology clinic for recurrent episodes of jaundice and RUQ abdominal pain. She tells you that the painful episodes usually resolve spontaneously. According to her medical chart, LFTs during these episodes are consistent with conjugated hyper-bilirubinemia and elevations in her aminotransferases. After an ultrasound does not elucidate the cause of her symptoms, you decide to perform a liver biopsy. When the pathologist reports to you that the gross specimen of liver is darkly pigmented, you begin to suspect that this patient might suffer from a rare autosomal recessive condition that is caused by defective transport of bilirubin out of the liver.

Congenital Hyperbilirubinemias

Gilbert Syndrome	*Genetic defect:* **Autosomal dominant** condition resulting in **decreased UDPGT activity**.
	Clinical manifestations: Often asymptomatic; mild jaundice; **unconjugated hyperbilirubinemia**.
Crigler-Najjar Syndrome Types I and II	*Genetic defect:* **Autosomal recessive (type I)** or **autosomal dominant with variable penetrance (type II)** conditions resulting in **absent UDPGT activity**.
	Clinical manifestations: **Type I: Fatal** within 2 years of birth; presents early with jaundice, **kernicterus**, and **unconjugated hyperbilirubinemia**. **Type II**: nonfatal; presents with jaundice and **unconjugated hyperbilirubinemia**; kernicterus rarely occurs.
	Treatment: Plasmapheresis and phototherapy (type I); phenobarbital (type II).
Dubin-Johnson Syndrome	*Genetic defect:* **Autosomal recessive** condition resulting from defective bilirubin transport out of the liver because of a mutated canalicular membrane carrier.
	Clinical manifestations: Intermittent jaundice; RUQ and epigastric pain; **conjugated hyperbilirubinemia**; mildly elevated LFTs; **black liver** on gross pathology.
Rotor Syndrome	*Genetic defect:* **Autosomal recessive** disorder resulting in defective uptake and excretion of bilirubin by hepatocytes.
	Clinical manifestations: Usually asymptomatic; may have bouts of intermittent jaundice; **conjugated hyperbilirubinemia**.
Notes	**UDPGT** is a protein in the liver responsible for conjugating bilirubin, thus allowing for urinary excretion. If this enzyme is deficient, bilirubin will build up and damage susceptible tissues, such as the brain.

A 58-year-old immigrant from Ireland presents to your clinic complaining of weakness and generalized abdominal pain over the past couple of months. On further questioning, he tells you that he has been thirstier lately and is urinating more frequently than usual. He also comments on how tan he has become, even though he has not been out in the sun that often. On physical examination, you note mild scleral icterus, hyperpigmentation of the skin on his trunk and extremities, and hepatomegaly. Laboratory tests reveal a fasting blood glucose level of 200 mg/dL and mildly elevated LFTs. You wonder whether he may have an autosomal recessive genetic disorder that would explain his constellation of symptoms, and you decide to order iron studies to test your hypothesis.

Primary Hemochromatosis

Genetic Defect	An **autosomal recessive condition** involving a mutation on chromosome 6 that results in **excessive absorption of iron in the intestinal mucosa** (exact mechanism is unknown).
Pathophysiology	Elevated circulating levels of iron results in iron deposition in tissues, including the liver, pancreas, heart, adrenals, and skin. Iron is toxic to organs, causing DNA damage through an increase in free radical formation, thereby leading to tissue damage and fibrosis. Fibrosis in the pancreas leads to decreased insulin production and results in diabetes. Fibrosis in the liver leads to cirrhosis. Fibrosis in the adrenals leads to an increase in ACTH release from the pituitary through a loss of negative feedback. By increasing ACTH levels, MSH also increases (MSH and ACTH are from the same precursor molecule), resulting in increased melanin deposition in skin.
Clinical Manifestations	Tends to present in northern Europeans males after age 50 with the classic triad of **cirrhosis**, **diabetes**, and **skin hyperpigmentation ("bronze diabetes")**. Other symptoms include arthropathy, hepatomegaly, and cardiac disease.
	Complications include an **increased risk of hepatocellular carcinoma**.
	Lab findings: Mildly elevated LFTs; **increased serum iron**; **decreased total iron-binding capacity**; **transferrin saturation >80%**; **serum ferritin 1000 μg/L**.
Treatment	**Weekly phlebotomy** and **deferoxamine**; prevention by neonatal screening for increased transferrin saturation.
Notes	There is a strong association of primary hemochromatosis with the HLA-A3 haplotype as a result of linkage disequilibrium.

A 46-year-old woman presents to your gastroenterology office for her first routine screening colonoscopy. As you take her history, you notice that she has several melanotic macules on her hands and lips. Colonoscopy reveals multiple hamartomatous polyps scattered over the entire length of her colon. You assure the patient that these polyps are benign and that she is not at increased risk for colon cancer, but you wonder whether she may have a genetic condition that would predispose her to developing other types of GI and gynecologic cancers.

Multiple Polyposis Syndromes

Familial Adenomatous Polyposis	*Genetic defect:* **Autosomal dominant** condition caused by mutation of the *APC* gene on chromosome 5.
	Clinical manifestations: There are 500 to 2500 colonic adenomas present at puberty.
	Treatment: Prophylactic colectomy (**100% will evolve into colon cancer** if not resected).
Hereditary Nonpolyposis Colorectal Cancer	*Genetic defect:* **Autosomal dominant** condition caused by defect in DNA mismatch repair genes on chromosome 2, 3, or 7.
	Clinical manifestations: Appearance of colonic adenomas in early adulthood; increased risk for colorectal cancer and other cancers (especially endometrial cancer).
	Treatment: Surgical resection.
Peutz-Jeghers Syndrome	*Genetic defect:* **Autosomal dominant** condition caused by defect in *LKB1* (tumor suppressor gene).
	Clinical manifestations: Multiple **hamartomatous (nonneoplastic) polyps** of the colon and small intestine; **melanotic macules** in the mouth, lips, hands, and genitalia; no increased risk for colon cancer but increased risk of gastric, breast, gynecologic, pancreatic, or lung cancer.
	Treatment: Regular screening for gynecologic and GI cancers.
Gardner Syndrome and Turcot Syndrome	*Genetic defect:* **Autosomal dominant** conditions associated with defects in *APC* gene on chromosome 5.
	Clinical manifestations: **Gardner syndrome**: **Adenomatous polyps** along with **osteomas** and soft tissue tumors. **Turcot syndrome**: **Adenomatous polyps** with **CNS tumors.** Both conditions are associated with an increased risk for colorectal cancer.
	Treatment: Surgical resection.

Notes

A 12-year-old boy is brought to your pediatrics office complaining of right-sided abdominal pain over the past 2 days. On further questioning, his mother tells you that he has seemed more emotionally labile than usual and that he has occasionally made statements that are out of context with the conversation. On physical examination, you note the presence of Kayser-Fleischer rings on both corneas, tenderness in the RUQ of his abdomen, and a resting tremor of both hands. LFTs reveal the presence of mild hepatitis. You immediately order laboratory studies to test for serum ceruloplasm levels because you suspect that this boy may have a rare disorder that necessitates treatment with penicillamine.

Wilson Disease

Genetic Defect	Rare **autosomal recessive** disorder involving a mutation of chromosome 13 that results in a **defective copper-transporting membrane protein** in the liver.
Pathophysiology	Copper is absorbed in the intestine and transported to the liver, where hepatocytes conjugate the copper to an α_2-globulin to form ceruloplasmin. Ceruloplasmin can then circulate in the plasma and is eventually broken down by lysosomes and secreted into the bile for excretion. In Wilson disease, the **copper cannot be transported into the hepatocytes** for transformation into ceruloplasmin. The **increased copper then accumulates throughout the body**, especially in the parenchymal cells of the liver, kidney, brain (especially the basal ganglia), and cornea.
Clinical Manifestations	Usually presents between the ages of 10 and 30. Symptoms include **liver disease** (beginning with hepatitis and progressing to cirrhosis), hemolytic anemia, portal hypertension, psychosis, or dementia, **Kayser-Fleischer rings** (thin brown rings around the corneas on eye examination), and **choreiform movements** (extrapyramidal motor signs similar to those in Parkinson disease). Complications include **increased risk of hepatocellular carcinoma**. *Lab findings:* **Decreased serum ceruloplasmin**; hypercupriuria (copper in urine).
Treatment	**Penicillamine** (chelates copper for removal from body).
Notes	

A 15-year-old boy is brought to the pediatrician's office for his annual checkup. He reports feeling relatively healthy over the last year, although he does note that his vision and hearing seem to have deteriorated recently. On further probing, you learn that his uncle suffers from a genetic disorder characterized by deafness and kidney disease. When routine urinalysis of this patient reveals hematuria with erythrocyte casts, you begin to worry that this boy may suffer from a rare genetic disorder characterized by a mutation of type IV collagen.

Alport Syndrome

Genetic Defect	Genetic disorder with **heterogenous inheritance** (usually **X-linked dominant**, although autosomal recessive and dominant variations exist) that results in the **mutation of type IV collagen**.
Pathophysiology	**Type IV collagen** is an important component of the **cochlea**, the **anterior lens capsule of the eye**, and forms the scaffolding of the **glomerular basement membrane**. Defective type IV collagen leads to irregularities in the glomerular basement membrane and results in malfunctioning of the glomerular filtration barrier, leading to eventual sclerosis.
Clinical Manifestations	Triad of **nephritis**, **sensory deafness**, and ocular disorder (**cataracts**, lens dislocation, corneal dystrophy). Often initially presents with hematuria and erythrocyte casts during adolescence and will usually progress to renal failure by middle age.
Treatment	ACE inhibitors; renal transplantation.

Notes

A 30-year-old woman presents to your clinic for a routine physical. She reports that she has been in good health except for an occasional headache. Physical examination reveals a blood pressure of 160/96, mild costovertebral angle tenderness with palpation, and a murmur consistent with mitral valve prolapse. When her urinalysis reveals hematuria, you question your patient further regarding her family history, and she tells you that her aunt is on dialysis for kidney disease. You decide to send the patient for renal ultrasounds to confirm your suspicions, and you worry that this patient's likely genetic disorder will put her at an increased risk for berry aneurysms.

Autosomal Dominant and Autosomal Recessive Polycystic Kidney Disease

Genetic Defect	**ADPKD: Autosomal dominant** disorder caused by a mutation of *PKD* **gene** on chromosome 16 that results in a defective protein called *polycystin*, which is involved in cell-to-cell matrix interactions.
	ARPKD: Autosomal recessive disorder caused by a mutation on chromosome 6 that results in a defective protein called *polyductin*, which is present in the cilia of renal epithelial cells.
Pathophysiology	**ADPKD:** Although the exact mechanism is unknown, it is thought that defective polycystin results in abnormal cell differentiation, which may lead to cyst formation.
	ARPKD: The exact mechanism is unknown, but it is thought that polyductin may be involved in cell-to-cell signaling during renal tubular differentiation.
Clinical Manifestations	**ADPKD: Hypertension**, **hematuria**, and **palpable renal masses**. CT shows multiple large cysts in both kidneys. Associated with secondary polycythemia, polycystic liver disease, **berry aneurysms**, and mitral valve prolapse. Patients eventually progress to ESRD.
	ARPKD: Hypertension, growth failure, bilateral abdominal masses, and progressive renal failure during childhood. Congenital hepatic fibrosis develops in older children. Imaging shows multiple renal cysts at birth.
Treatment and Prognosis	**ADPKD:** No therapy can prevent renal failure, although blood pressure control and a low-protein diet may slow progression of ESRD.
	ARPKD: Treatment of hypertension; dialysis for ESRD; disease course is variable, but most patients die during childhood.
Notes	

A 25-year-old man presents to your endocrinology office for further evaluation of abnormal laboratory testing done by his primary care physician. As you read his medical chart, you find that he suffers from hypercalcemia in the setting of increased levels of parathyroid hormone, suggesting primary hyperparathyroidism. You also note that his blood pressure is 180/110, and he mentions that he often experiences pounding headaches and heart palpitations. You send for a 24-hour urine collection study, which reveals increased 24-hour urinary VMA, metanephrine, and catecholamine levels. On the basis of these findings, you begin to think that this patient will likely develop medullary carcinoma of the thyroid and that he should undergo a prophylactic thyroidectomy to avoid this malignancy.

9

Genetic Defect	**MEN I: Autosomal dominant** disorder caused by a mutation on chromosome 11 in the *MEN1* gene.
	MEN IIa and IIb: Autosomal dominant disorders caused by differing mutations on chromosome 10 in the ***RET* proto-oncogene**.
Pathophysiology	**MEN I:** Although the exact function of the protein coded for by the *MEN1* gene is unknown, mutations in the gene have been linked to tumor formation.
	MEN IIa and IIb: The ***RET* proto-oncogene** is a tyrosine kinase receptor that is involved in **cellular growth signaling**. The MEN mutations in this protein result a constitutively active receptor, thereby promoting uncontrollable growth and neoplasia.
Clinical Manifestations	**MEN I:** Triad of **parathyroid hyperplasia/adenoma**, **pituitary adenoma**, and **pancreatic islet cell tumors**, which often manifests as Zollinger-Ellison syndrome (peptic ulcers secondary to gastrinoma).
	MEN IIa: Triad of **pheochromocytoma**, **parathyroid hyperplasia**, and **medullary carcinoma of the thyroid**.
	MEN IIb: Triad of **pheochromocytoma**, **medullary carcinoma of the thyroid**, and **mucocutaneous neuromas** of the skin, eyes, and GI tract.
Treatment	Treat symptomatically; surgery when appropriate for thyroid carcinoma and pheochromocytoma; genetic screening of family members for preventive thyroidectomy in MEN IIa and IIb.
Notes	

A 5-year-old boy presents to your pediatrics office for a routine visit as a new patient. His mother tells you that the child is mentally retarded and has recently been complaining of muscle pain in his arms and legs. While speaking to the mother, you note that the child is short and obese and has very short metacarpals on his fourth and fifth fingers of both hands. Physical examination is significant for positive Trousseau and Chvostek signs. Laboratory tests reveal low serum calcium levels in the setting of elevated parathyroid hormone levels. You begin to suspect that the child suffers from a rare autosomal recessive disorder, and you prescribe calcium and vitamin D supplements to relieve the child's symptoms.

Pseudohypoparathyroidism

Genetic Defect	**Autosomal recessive** disorder, caused by a chromosome 20 mutation leading to a **faulty PTH receptor**.
Pathophysiology	PTH binds to PTH receptor, which then interacts with a G protein to activate AC and increase cAMP production in bone, kidney, and intestine. In **type 1**, there is a deficiency in $G_{s-\alpha}$, which leads to decreased coupling of PTH receptor to AC, such that activation of PTH receptor does not activate the target cell. In **type 2**, the regulation of $G_{s-\alpha}$ is altered such that the levels of cAMP produced by PTH stimulation are inadequate to activate the target cell. In both forms of the disease, the target cell is not activated and it is as though PTH is not present.
Clinical Manifestations	**Symptoms of hypocalcemia: Tetany** or other signs of neuromuscular irritability; **prolonged QT interval** on ECG; **Trousseau sign** (carpal spasm 2 min after inflation of blood pressure cuff above systolic blood pressure); **Chvostek sign** (twitching of the facial muscles on superficial tapping of the facial nerve). Patients with **type 1** also have **Albright hereditary osteodystrophy**: short stature, mental retardation, shortened fourth and fifth metacarpal and metatarsal bones, obesity. *Lab findings:* **Hypocalcemia**; **increased PTH levels**; increased serum phosphate levels.
Treatment	Calcium and vitamin D supplements.
Notes	PTH acts to increase serum calcium and decrease serum phosphate through effects on the bone (increases osteoclastic activity), the kidney (promote calcium reabsorption and formation of activated vitamin D), and the intestine (increased levels of activated vitamin D promotes increased calcium reabsorption in the gut).

A 3-year-old boy is brought to your office by his mother, who is concerned that her child's gait seems to be deteriorating. The child's medical history is significant for several sinus infections. The child's medical file does not reveal any indication that he had any difficulty walking in the past. However, as you observe the child walk now, you note that his gait is distinctly ataxic. A full neurologic examination reveals decreased DTRs in both legs. When close examination of the child's conjunctiva reveals multiple telangiectasias, you begin to suspect that this child suffers from a condition that is ultimately fatal.

9

Ataxia-Telangiectasia

Genetic Defect	An **autosomal recessive** disorder that results in a mutation on chromosome 11 in the *ATM* gene.
Pathophysiology	The gene product of the *ATM gene is involved in sensing DNA that has been damaged* by radiation and then signaling p53 to delay the cell cycle to allow for DNA repair. If the *ATM* gene is mutated, p53 is not activated and the cell cycle continues, allowing for replication of damaged DNA. This may lead to abnormal cellular development, especially in the neuro-logic, vascular, and immune systems. The **cerebellum is particularly affected** (pathologic examination reveals **loss of Purkinje and granule cells**), thereby accounting for the ataxia.
Clinical Manifestations	Presents in early childhood with neurologic symptoms (**cerebellar ataxia** with eventual wheelchair confinement; decreased DTRs; dysarthria) and **telangiectasias** of the face and conjunctiva. Some patients have **various immunodeficiencies**, leading to recurrent respira-tory infections or various endocrinologic abnormalities.
	Complications include a **predisposition to developing cancers** (breast, lymphoma, leukemia).
	Lab findings: Increased α-fetoprotein levels.
Treatment and Prognosis	Vitamin E (antioxidant) and folic acid supplementation; avoid radiation when possible. Most patients do not live past 25; many die much earlier.
Notes	

A 2-year-old girl is brought to your pediatric clinic for evaluation of a delay in walking with repetitive falling. Upon taking a history from the child's mother, you learn that the patient was slow to walk initially and now is only able to walk for several feet before falling down. Physical examination reveals absent deep tendon reflexes in legs, mild scoliosis, and an ataxic gait. When a cardiac workup reveals signs of hypertrophic cardiomyopathy, you decide to order a study to evaluate for a deficiency in the protein, frataxin.

Friedreich Ataxia

Genetic Defect	An **autosomal recessive** disorder caused by a deficiency in the protein, **frataxin**.
Pathophysiology	**Frataxin** is coded for by a gene locus on chromosome 9. Frataxin is involved in **maintaining normal mitochondrial function as well as iron homeostasis**. In Friedreich ataxia, there is a **GAA trinucleotide repeat expansion** at the gene locus for frataxin, which results in decreased expression of the gene. With decreased levels of frataxin, iron accumulates in the mitochondria and leads to decreased mitochondrial function and eventually cell death. **Neuronal tissues and cardiac tissue are particularly sensitive to frataxin deficiencies**; hence damages to the nervous system and cardiac system are prominent symptoms of Friedreich ataxia.
Clinical Manifestations	Presents in childhood with an **ataxic gait**. The patient's ataxia becomes progressive until the torso and arms are involved and the patient needs a wheelchair. Other symptoms include **dysarthria**, sensory neuropathy, absent deep tendon reflexes, kyphoscoliosis, and **cardiac disease** (particularly hypertrophic cardiomyopathy).
Treatment and Prognosis	Supportive treatment for neurologic degeneration; treatment of cardiac disease if present. Most patients become wheelchair bound within 5 years of diagnosis and die prematurely.
Notes	

A 43-year-old woman presents to the emergency room complaining of uncontrollable, jerking movements of both her arms, which has been progressing over the past 3 months. Her husband also tells you that her memory function has declined and that she seems more irritable than usual. On taking a family history, you learn that the patient's father suffered from similar symptoms, which eventually progressed to dementia. When imaging of the patient's brain reveals atrophy of the caudate nucleus with dilation of the lateral and third ventricles, you suspect that this patient has a hereditary neurologic degenerative disorder that will eventually be fatal.

Huntington Disease

Genetic Defect	**Autosomal dominant disorder** associated with **increased number of CAG repeats** in the *HD* gene on chromosome 4. Exhibits variable penetrance.
Pathophysiology	The exact function of the *HD* gene product is unknown, but researchers theorize that the protein is involved in neuronal apoptosis, which is consistent with the finding that the neurologic system is severely affected in this disease. GABAergic striatal neurons of the basal ganglia are damaged, leading to **atrophy of the caudate nucleus and putamen**. Because the caudate and putamen are part of the extrapyramidal motor system, destruction of these structures gives rise to motor abnormalities, such as those observed in Huntington disease.
Clinical Manifestations	Progressive disorder that initially manifests between the **ages of 40 and 50**; **chorea** (involuntary jerky movements); cognitive impairment; mood disturbances. Eventually progresses to **severe dementia**. *Imaging:* MRI demonstrates caudate atrophy and dilation of lateral and third ventricles.
Treatment and Prognosis	Symptomatic treatment for dyskinesia and mood disturbances. Usually fatal within 15-20 years of diagnosis.
Notes	Huntington disease, along with fragile X syndrome and myotonic dystrophy, demonstrates **anticipation**, a phenomenon in which the number of repeats increases with each generation and results in more severe disease manifestations.

A 9-year-old boy is taken to your clinic by his mother, who is concerned by the development of multiple nodules on her child's skin. The child is adopted so you are unable to ascertain his entire family history, but adoption records show that his biological father suffered from some sort of disfiguring genetic disorder. Examination reveals multiple coffee-colored macules on the boy's torso and limbs and distinctive pigmented nodules on his irises. You suspect that his condition is due to an autosomal dominant genetic disorder caused by a mutation on chromosome 17, and you refer the patient to a medical genetics clinic and a neurologist.

9

Neurofibromatosis Type 1

Genetic Defect	**Autosomal dominant** disorder that is caused by a mutation in the *NF1* gene, which is a tumor suppressor gene located on **chromosome 17**. The disease can also occur through sporadic mutations of the *NF1* gene.
Pathophysiology	*NF1* encodes for a protein (neurofibromin) that acts as a tumor suppressor gene by decreasing the activity of p21 *ras* oncogene. With mutation of *NF1*, the p21 *ras* oncogene is uninhibited and can trigger **unhindered cellular growth**, which results in the **formation of neurofibromas** (masses of spindle cells, occurring in the dermis, peripheral nerve, or large nerve trunk). Neurofibromas in the dermis or in the iris can cause hyperpigmentation of the overlying cells, leading to observation of café au lait spots and Lisch nodules, respectively.
Clinical Manifestations	Neurofibromas (may cause **neurologic symptoms**) and **gliomas of the optic nerve**; Lisch nodules **(pigmented nodules of the iris)**; café au lait spots **(cutaneous pigmented macules)**; various **skeletal abnormalities**.
	Complications include an increased risk for other tumors (Wilms tumor, meningiomas, pheochromocytomas, chronic myeloid leukemia).
Treatment	Surgery to remove neurofibromas if disfiguring or causing neurologic abnormalities.
Notes	**Neurofibromatosis 2** is an autosomal dominant disorder caused by a mutation in the *NF2* gene (also a tumor suppressor gene), located on chromosome 22. It is rarer than NF1 and presents with bilateral acoustic schwannomas, multiple meningiomas, and other neoplasms.

A 6-month-old boy is brought to the emergency room after his parents witnessed him having a seizure. The child has had multiple seizure episodes since birth. You decide to send the baby for radiographic imaging of his brain, which reveals multiple cortical tubers through the cerebral cortex. You worry that this child suffers from an autosomal dominant genetic disorder, and you order an echocardiogram to check for a cardiac rhabdomyoma and a renal ultrasonogram to check for renal angiomyolipomas.

9

Tuberous Sclerosis

Genetic Defect	**Autosomal dominant** disorder resulting from a mutation in one of several different genes, including the *TSC1* gene on chromosome 9 and the *TSC2* gene on chromosome 16.
Pathophysiology	The exact mechanism of the *TSC* genes is unknown, but they are believed to act as **tumor suppressor genes**. With the mutation of these genes, multiple different neoplasms result, including **brain hamartomas** (nodules composed of disorganized neurons in the cerebral cortex; also called cortical tubers), **cardiac rhabdomyomas**, **adenoma sebaceum** on the face (lesion consisting of malformed blood vessels), **renal angiomyolipomas**, and cysts of the bone and lung. The neurologic tumors lead to mental retardation and seizures.
Clinical Manifestations	**Seizures** and **mental retardation** in infancy; **red nodules** on face (adenoma sebaceum), which appear between the ages of 5 and 10; presence of cardiac rhabdomyoma and renal angiomyolipoma.
Treatment	Seizure control; regular surveillance for renal angiomyolipomas; genetic counseling.
Notes	

A 15-year-old boy presents to the emergency room, complaining of enlarged cord-like lumps on both of his legs. He states that these lumps have been there over the last 6 months, but have gotten progressively larger. On review of systems, he also notes a history of frequent tripping and ankle sprains. Family history is notable for a neurologic disorder in his father, paternal aunt, and two cousins, although he cannot remember the name of this disorder. Physical examination reveals multiple palpable cords in the legs, likely consistent with enlarged nerves. You also note that he has evidence of pes cavus deformity, mild scoliosis, and decreased deep tendon reflexes. You tell the patient that his symptoms are likely reflective of a relatively common inherited neuropathy and you refer him to a neurologic clinic for further treatment.

9

Genetic Defect	**A collection of diseases** resulting from a **mutation** in one of several different genes involved in **nerve myelination and function**. There are seven major types of CMT disease, each with multiple subtypes. The two **most common forms of CMT are types 1 and 2**, both of which are mostly inherited in an **autosomal dominant** fashion.
Pathophysiology	**CMT-1:** Associated with a collection of mutations involved in formation and stabilization of myelin. **Mutation** in one of several genes on chromosomes 1, 8, 10, 16, or 17 **results in abnormal myelin formation** and subsequent myelin breakdown. In response to **demyelination**, Schwann cells proliferate at an abnormal rate in an attempt to remyelinate the nerve—the repetition of this process can result in a thickened layer of myelin around the nerve, giving rise to an **"onion bulb"** appearance to the nerve.
	CMT-2: Associated with a collection of defects on chromosomes 1, 3, 7, 8, and 12, which result in **neuronal cell death and degeneration**.
Clinical Manifestations	**CMT-1: Distal muscle weakness**; sensory neuropathy; **pes cavus** deformity (high arch); decreased deep tendon reflexes; "stork leg" deformity (secondary to calf muscle atrophy); scoliosis; **enlargement of peripheral nerves** such that they are palpable (secondary to "onion bulb" thickening of nerve).
	CMT-2: Presents with predominantly sensory neuropathy, although distal muscle weakness is also present; tremor
Treatment	Supportive treatment of neuropathies; surgical therapy of joint deformities if indicated; genetic counseling.
Notes	Charcot-Marie-Tooth disease is the most common inherited neurologic disorder.

A 24-year-old man presents to the emergency room complaining of acutely decreasing vision in both eyes. Physical examination reveals decreased vision in the central fields of both eyes. You also observe a mildly ataxic gait. As you question him further regarding his personal and family history, he tells you that he has been healthy his whole life but that his older brother and sister as well as his mother became blind before the age of 35. You begin to suspect that this patient will also become blind in the near future as a result of a rare genetic disorder.

9

Genetic Defect	A **maternally inherited** disorder that is caused by a mutation in the mtDNA, encoding for components of the electron transport chain.
Pathophysiology	There are many different mutations in the mtDNA that can lead to LHON, and most involve the alteration of the electron transport capacity and ATP production of complexes I and III of the electron transport chain. It is not known how these defects lead to the optic symptoms of LHON; however, some researchers have theorized that the retinal ganglion cells become damaged by the oxidative stress or ischemia that results from defective oxidative phosphorylation.
Clinical Manifestations	Usually presents between the ages of 15 and 35 with **central vision loss** that is acute in onset and affects both eyes, eventually **leading to blindness** within 1 year. Occasionally, patients may have other neurologic signs (dystonia, decreased intelligence, ataxia, hearing loss, multiple sclerosis-like symptoms) or cardiac conduction defects.
Treatment	Supportive treatment.
Notes	

A 7-year-old girl presents to your pediatric ophthalmology clinic complaining of worsening vision and pain in her right eye. The patient's mother tells you that the girl's father has suffered from ocular neoplasms in both eyes as well as osteosarcoma. Ophthalmologic examination reveals a "cat's eye" pupillary reflex, and recent orbital MRI demonstrated an intraocular mass of the left eye. You immediately refer this patient to both an oncologist and a medical genetics clinic because you fear that this patient likely suffers from an autosomal dominant disorder that is associated with a defective tumor suppressor gene.

9

Retinoblastoma

Genetic Defect	An **autosomal dominant** condition that is caused by **homozygous deletion** in both alleles of the *Rb* gene, a tumor suppressor gene located on **chromosome 13**. The disease is transmitted as an autosomal dominant condition even though homozygosity is necessary for disease, because more than 90% of heterozygous carriers develop the disease. Sporadic cases can also occur.
Pathophysiology	When *Rb* is activated, it serves to halt the cell cycle in the G_1 phase by inhibiting E2F transcription factors. When *Rb* is mutated, the checkpoint at G_1 is lost and the cell cycle can continue unhindered into the S (replication) phase. Uninhibited progression to S phase in the face of an *Rb* gene mutation has been shown to lead to cell apoptosis in most tissues, except for retinoblasts. Instead, neoplastic changes accumulate in the retinoblast and a tumor arises.
Clinical Manifestations	Classically occurs in **young children** who present with **diminished visual acuity**, **eye pain**, strabismus, intraocular mass on fundoscopic examination, and **white "cat's eye" pupillary reflex**.
	Patients will develop bilateral retinoblastomas with a risk of metastasis to the brain, spinal cord, bone, and lymph nodes. They are also at an increased risk for other cancers (eg, osteosarcoma).
Treatment and Prognosis	Surgery (removal of tumor or eye if necessary) and radiation.
	Tumor is fatal once it has spread beyond the eye.
Notes	Retinoblastoma is the prototype of **Knudson "two-hit" hypothesis**: two mutations are required for disease. One deletion is either inherited (familial) or occurs sporadically. The second mutation results from a somatic mutation in both familial and sporadic cases.

A newborn boy is found on the steps of the police station. He is brought to the hospital for evaluation. As you examine the child, you notice that he has midface hypoplasia, short limbs, and macrocephaly. Neurologic examination reveals mild hypotonia of his limbs. You begin to suspect that the child has an autosomal dominant condition caused by a mutation in the fibroblast growth factor receptor 3 gene.

Achondroplasia

Genetic Defect	An **autosomal dominant** condition that is caused by a mutation in the *FGFR3* **gene** located on chromosome 4.
Pathophysiology	*FGFR3* is a tyrosine kinase receptor that acts to inhibit chondrocytes at the growth plate of bones, thereby leading to the decreased cartilage proliferation and subsequent decreased growth. In achondroplasia, *FGFR3* is always active; therefore, **cartilage proliferation at the growth plate is inhibited** 100% of the time. This results in **short thick bones** with narrow epiphyseal plates, consisting of disorganized chondrocytes.
Clinical Manifestations	**Dwarfism** (short limbs with normal trunk); macrocephaly with frontal bossing; midface hypoplasia; hypotonia early in life that resolves spontaneously; may have neurologic symptoms, which result from a small foramen magnum.
Treatment	Genetic counseling for parents of affected patient regarding future offspring; symptomatic treatment of neurologic complications.

Notes

A 5-year-old boy is brought to your clinic complaining of weakness in his legs. Physical examination is significant for decreased strength in his thighs as well as enlarged calves. While you are speaking with the boy's mother, you observe the boy playing with toys on the floor and notice that he uses his arms to assist himself in rising from a crouching position. When his mother tells you that her brother died at a young age from a genetic muscle disease, you suspect that this child suffers from an X-linked recessive muscular disorder and recommend that the patient be seen by a geneticist.

9

Duchenne Muscular Dystrophy

Genetic Defect	An **X-linked recessive** disorder that is caused by a deletion in the *DMD* gene on the short arm of the X chromosome, which results in an **absence of dystrophin synthesis**.
Pathophysiology	Dystrophin is believed to be involved in maintaining the membrane integrity of the muscle cell. Absence of dystrophin leads to muscle fiber destruction and muscle atrophy.
Clinical Manifestations	Presents in **males** with **onset of disease by age 5**. Manifests with **weakness in proximal muscles of extremities** (usually the **pelvis**), which progresses superiorly and eventually leads to immobilization, **pseudohypertrophy of calves** (because of replacement of atrophied muscle with fibrous and fatty tissue), and the presence of **Gowers maneuver** (use of arms to rise from crouching position).
	Lab findings: **Increased serum creatine kinase**.
Treatment and Prognosis	No treatment.
	Death via respiratory failure in adolescence because of involvement of respiratory muscles.
Notes	**Becker muscular dystrophy** is an **X-linked recessive** disorder that is also characterized by a **mutation** in the dystrophin gene, which leads to **reduced synthesis of dystrophin**. It presents similarly to Duchenne muscular dystrophy but is clinically less severe.

A 2-year-old girl is brought to your pediatrics office by her parents, who are concerned that their daughter has not started to walk. They also report that when she stands, she tends to fall easily, the trauma of which leads to large, gaping cuts. When you examine the child, you notice that she has hypermobile joints and thin, hyperextensible skin. When the girl's father tells you that he suffers from a genetic disorder involving faulty collagen synthesis, you begin to suspect that this child's delay in walking is the result of an inherited connective tissue disorder, and you refer the family to a medical genetics clinic.

9

Genetic Defect	A disorder with 10 different variants, all of which are associated with the **defective synthesis of collagen**. The **mode of inheritance** is also **variable** and includes autosomal dominant (types I-IV, VIIA-B, VIII), autosomal recessive (types VI, VIIC, X), and X-linked recessive (types V, IX).
Pathophysiology	Collagen is involved in the formation of skin, bone, tendons, vessel walls, ocular structures, and cartilage. Various forms of collagen are mutated in the different variants of EDS, and the mutations result in various defects ranging from mutations in structural components of collagen (eg, defective pro α_1 chains in collagen type III in EDS IV) to mutations in enzymes involved in posttranslational modification of collagen (defective lysyl hydroxylase in EDS type VI). The **abnormal collagen is weak** and results in weakness in the structures that it composes, thereby leading to hyperextensible joints through weak tendons, skeletal abnormalities through abnormal bone formation, and susceptibility to various organ injury through fragile skin and vessel walls.
Clinical Manifestations	Presentations vary depending on the syndrome. Common symptoms include **thin hyperextensible skin**, **hypermobile joints** complicated by dislocation, **easy bruising**, mitral valve prolapse (I), uterine or intestinal wall rupture (IV), scoliosis (VI), ocular globe fragility with resulting blindness (VI), congenital hip dislocation (VII), periodontal disease (VIII), and the development of premature osteoarthritis (I, VII).
Treatment	Vitamin C supplementation (involved in collagen synthesis); symptomatic care for osteoarthritis; routine eye examinations.
Notes	

A 13-year-old girl presents to the emergency room complaining of an acute change in the vision in her left eye. She denies any trauma to the eye. Ophthalmologic examination reveals displacement of the lens from the center of the pupil. While you are calling an ophthalmologist to the emergency room, you note that the girl is extremely tall for her age with long extremities and long fingers on both hands. You wonder whether this patient may have an autosomal dominant genetic condition that will predispose her to aortic dissection, and you decide to refer her to a medical geneticist for further evaluation.

Marfan Syndrome

Genetic Defect	An **autosomal dominant** condition caused by **mutation in the fibrillin gene** on chromosome 15. Although most mutations are hereditary, 20% are sporadic.
Pathophysiology	Fibrillin is a glycoprotein constituent of microfibrils, which are present in great quantities in the extracellular matrix of the aorta, ligaments, perichondrium, and the ocular zonules (attach lens to ciliary body). **Mutation of fibrillin leads to a defective extracellular matrix** and weakening of the involved structures, leading to hyperextensible joints, cystic medial necrosis of the aorta (results from dilation of aortic valve and weakening of media with increased risk of intimal tear and dissection), mitral valve prolapse (resulting from loss of connective tissue support of valvular leaflet), and a predisposition to lens dislocation or subluxation. These patients also suffer from bony overgrowth and other skeletal abnormalities, but the exact pathogeneses for these changes are unknown.
Clinical Manifestations	**Tall stature** with **long extremities**; **hyperextensible joints**; long tapering digits **(arachnodactyly)**; **ectopia lentis** (dislocation of lenses); aortic incompetence; **dissecting aortic aneurysm**; **mitral valve prolapse**; skeletal abnormalities (kyphosis, scoliosis); spontaneous pneumothorax.
Treatment and Prognosis	Spine brace; endocarditis prophylaxis; aortic valve replacement if necessary; β-blockers. If untreated, death is common between ages 30 and 40 from aortic dissection or CHF secondary to aortic regurgitation.
Notes	

A 19-year-old girl presents to the emergency room after suffering a generalized seizure. She tells you that she has been recently diagnosed with myoclonic epilepsy. As you continue to assess her, she tells you that she has been having muscle weakness in all of her extremities and that she often stumbles while walking. Physical examination reveals decreased muscle strength, an ataxic gait, and decreased hearing in both ears. When she tells you that all of her siblings and her mother suffer from some sort of seizure disorder, you immediately begin to suspect that she too may have a rare genetic disorder that would cause the appearance of ragged-red fibers on muscle biopsy.

Mitochondrial Myopathies (MERRF and MELAS)

Genetic Defect	**MERRF and MELAS: Maternally inherited** disorders caused by point mutations in the *tRNA* gene of mtDNA.
Pathophysiology	The *mtDNA* genes are involved in the production of the cellular apparatus of oxidative phosphorylation. Defects in any component of this cellular apparatus can lead to defective oxidative phosphorylation. Defective oxidative phosphorylation will lead to **mitochondrial proliferation** with consequent destruction of muscle fibers **("ragged-red fibers")** and can lead to neuronal damage to the spinal cord, cerebellum, and motor cortex. NADH accumulates, leading to inhibition of pyruvate dehydrogenase and thereby resulting in the **accumulation of lactate**.
Clinical Manifestations	**MERRF:** Presents during adolescence; ataxia; **myoclonic epilepsy** with seizures; **muscle weakness**; hearing loss; progressive mental status decline.
	MELAS: Presents in childhood; **strokelike episodes** with blindness and hemiparesis; vomiting; hearing loss; seizures; **lactic acidosis**.
Treatment and Prognosis	**MERRF:** Seizure control; eventually results in encephalopathy and death.
	MELAS: Symptomatic treatment; eventually results in dementia and death before age 20.
Notes	There are multiple other disorders that are characterized by mutations in mitochondrial DNA, including Kearns-Sayre syndrome (ophthalmoplegia; heart block; retinal degeneration), chronic progressive external ophthalmoplegia (myopathy; ophthalmoplegia), Leigh disease (necrotizing encephalopathy), and Barth syndrome (myoglobinuria; cardiomyopathy).

A 7-year-old girl is brought to your pediatrics office by her father, who is concerned about the child's abnormal hand grip. The father tells you that he suffers from a muscle disease. You notice that the father is bald, even though he is relatively young. Physical examination of the girl reveals delayed relaxation of her hand grip. Slit-lamp examination reveals the beginnings of bilateral cataracts. After prescribing phenytoin for symptomatic relief, you refer the girl and her father to a geneticist for further evaluation of this disorder.

9

Myotonic Dystrophy

Genetic Defect	**Autosomal dominant disorder** resulting in **increased CTG repeats** in the **myotonin protein kinase gene** on chromosome 19.
Pathophysiology	The exact function of myotonin protein kinase has not yet been elucidated. Thus, it is still unclear how dysfunction in this enzyme leads to the clinical symptoms of the disease or to the microscopic pathologic findings in muscle ("ring fiber" [cytoplasmic band within the center of the fiber]; fiber splitting and necrosis of intrafusal fibers of muscle spindles).
Clinical Manifestations	Presents between the ages of 20 and 30 but may manifest in childhood. Symptoms include **myotonia** (inability to relax contracted muscles), often presenting as muscle stiffness as well as **weakness** and wasting of distal limb and **facial muscles**.
	Also associated with **cataracts**, **testicular atrophy**, **baldness**, cardiac disease, and decreased glucose tolerance.
Treatment	Phenytoin to treat myotonia.
Notes	Myotonic dystrophy, along with fragile X syndrome and Huntington disease, demonstrates **anticipation**, a phenomenon in which the number of repeats increases with each generation and results in more severe disease manifestations.

A 2-month-old baby girl is brought to the emergency department by her parents, who are concerned that the child seems to cry whenever her right leg is moved. While speaking with the parents, you notice that the child does not seem to react much to any sudden loud noises of the emergency room. Physical examination is significant for the presence of a hypoactive and seemingly tender right leg, likely decreased hearing in both ears, and blue sclera. A radiograph of the baby's leg reveals a new fracture of the femur as well as several old healed fractures. You begin to suspect that her condition is likely related to an inherited deficiency of type I collagen.

9

Osteogenesis Imperfecta

Genetic Defect	A genetic disorder caused by mutations in the *COLIA1* and *COLIA2* genes on chromosomes 17 and 7, respectively, which results in the **deficient synthesis of type I collagen**. There are four variants of the disorder, each of which is associated with different mutations of type I collagen. Inheritance is variable, although mostly **autosomal dominant** (types I and IV; some cases of types II and III), with some autosomal recessive inheritance in types II and III.
Pathophysiology	Type I collagen comprises the bone, teeth, ears, eyes, and skin. A **deficiency of type I collagen** causes abnormal bone formation with resulting pathologic changes in the bone **(thinning of the trabeculae)** that predispose the bone to fracture. Decreased collagen in the eye leads to a transparent **sclera**, which **appears blue** caused by the underlying choroids. Patients may have **hearing loss** as well, which is due to abnormal ear bone formation.
Clinical Manifestations	The four variants of the disorder tend to manifest with skeletal fragility leading to **multiple fractures from minimal trauma**, **blue sclerae** (types I-III only), hearing loss, and dental imperfections. Type II is a particularly severe form of the disorder and is fatal within the first week of life.
Treatment	Pneumatic bracing; avoidance of trauma.
Notes	

A newborn boy is brought to your pediatrics office for his 2-week checkup. You immediately notice that the child is extremely pale with hypopigmented skin and hair. An ophthalmologic examination reveals hypopigmentation of both retinas. You tell the mother that you think her child likely has an autosomal recessive condition, which results in deficient melanin production, and you advise her to protect her son from sun exposure while referring the patient to a geneticist. You also advise the mother that her son's vision will have to be monitored closely over time.

Albinism

Genetic Defect	An **autosomal recessive** condition caused by a mutation on chromosome 11, leading to **defective tyrosinase** protein synthesis.
Pathophysiology	Tyrosinase is an enzyme involved in melanin production. It catalyzes the rate-limiting step converting tyrosine to DOPA. If tyrosinase is defective, melanin cannot be produced, thereby resulting in hypopigmentation of the skin, hair, and retina.
Clinical Manifestations	**Hypopigmentation of the skin and hair**; **ocular abnormalities** (hypopigmentation of the retina; strabismus; nystagmus; decreased visual acuity as a result of misrouting of the optic nerves from the retina to the lateral genicular nucleus).
	Complications include **increased risk for actinic keratoses and skin cancers**.
Treatment	Protection to sun exposure; regular eye examinations.
Notes	**Ocular albinism** is an X-linked recessive disorder caused by a mutated membranous glycoprotein in the melanocytes of the eye. It presents with only the ocular symptoms of albinism (hypopigmentation of the retina).

A 2-year-old boy is brought to your office by her mother, who is concerned about what happens when the child plays outside. The mother tells you that her son seems to sunburn extremely easily, even with sunblock use. Physical examination of the child is significant for decreased hearing in both ears as well as heavy freckling of his face, neck, and extensor portions of his arms. You begin to wonder whether this child has a genetic defect in his cellular DNA repair system, and you advise the mother to keep her son inside until he is evaluated by a geneticist.

Xeroderma Pigmentosum

Genetic Defect	An **autosomal recessive** disorder caused by mutations that result in a **defect in the nucleotide excision repair pathway of DNA repair**.
Pathophysiology	**Ultraviolet light causes pyrimidine dimers to form in DNA**. Pyrimidine dimer formation can lead to chromosomal abnormalities, mutation formation, DNA-strand breakage, and apoptosis. The **nucleotide excision repair system acts to eliminate the pyrimidine dimers**. When this system is defective, pyrimidine dimers build up, causing multiple DNA abnormalities in sun-exposed tissues (skin) or tissues that rely heavily on the nucleotide excision repair system (neurologic system).
Clinical Manifestations	Onset of disease is usually between the ages of 1 and 2. Symptoms include **extreme photosensitivity** with severe sunburns, freckling on sun-exposed areas, premature aging of skin, variable occurrence of **neurologic degeneration** (mental deterioration, hearing loss), and ocular abnormalities.
	Complications include a 2000-fold increase in the development of all forms of **skin cancer**.
Treatment	**Avoid sunlight**; treatment of skin cancers.
Notes	

A 10-month-old boy is brought to the emergency room by his parents, who tell you that the child is coughing and has a fever. On speaking further with the parents, you discover that this baby has had two episodes of otitis media and a bout of sinusitis over the last 4 months. Physical examination and a chest x-ray film reveal the presence of pneumonia. As you prepare to admit the child to the hospital, the mother mentions that her brother (the patient's uncle) suffers from an immune deficiency disorder. You decide to order serum studies to assess levels of B cells, T cells, and immunoglobulin levels. These tests reveal an absence of serum B cells and low levels of all classes of immunoglobulins, thereby confirming your suspicion that the child suffers from an inherited immunologic disease.

9

Bruton Agammaglobulinemia

Genetic Defect	An **X-linked recessive** disorder caused by a mutation in *Btk* gene.
Pathophysiology	*Btk* is involved in the cell-to-cell signaling that leads to the maturation of B-cell precursors. When *Btk* is mutated, B-cell precursors do not mature into B cells, leading to an absence of B cells in the serum.
Clinical Manifestations	Presents as **recurrent pyogenic bacterial infections** (otitis media; sinusitis; pneumonia) in **boys** after **6 months of age** (when levels of maternal IgG begin to decline). Cell-mediated immunity function is normal.
	Lab findings: **Low levels** of all classes of **immunoglobulins**; **absence of serum B cells**; absent or **poorly defined germinal centers** in lymph nodes and tonsils on microscopic examination.
Treatment	Pooled gamma globulin.
Notes	

A 2-year-old boy is brought to your dermatology clinic for evaluation of his eczema. The child's father states that the patient has suffered from eczema essentially his entire life. Past medical history is also significant for multiple episodes of epistaxis, three bouts of sinusitis, and two ear infections in the last year alone. Physical examination is notable for extensive eczema. When routine laboratory testing reveals the presence of thrombocytopenia, you begin to wonder if the child may suffer from a rare X-linked recessive disorder that affects the normal functioning of the cytoskeleton of T cells.

Wiskott-Aldrich Syndrome

Genetic Defect	An **X-linked recessive** disorder caused by a mutation in the Wiskott-Aldrich syndrome (WAS) gene.
Pathophysiology	The WAS gene codes for a protein (Wiskott-Aldrich syndrome protein [WASp]), which is present in hematopoietic cells. **WASp** has been shown to be **involved in the normal functioning of the actin cytoskeleton in T cells** and myeloid lineage cells. When WASp is defective, T-cell function is impaired leading to abnormal interaction of the T cell with antigens. **With abnormal T-cell function, B-cell homeostasis is altered and, together, this results in immunodeficiency as well as autoimmunity**. Thrombocytopenia results from reduced platelet survival secondary to immune mediated mechanism or faulty platelet migration.
Clinical Manifestations	Presents with triad of **recurrent pyogenic infections**, **eczema**, and **bleeding**. Complications include a predisposition to autoimmune diseases or lymphomas and leukemias.
	Lab findings: **thrombocytopenia**; decreased number and function of T cells.
Treatment	Supportive treatment with prophylactic antibiotics and platelet transfusions as needed; IV immune globulin, bone marrow transplant, and splenectomy can be considered for severe cases.
Notes	

A 7-month-old boy is brought to your immunology clinic by his mother. The child's pediatrician referred the patient to you because the child has suffered from several infections, including UTIs, meningitis, and *Staphylococcus* pneumonia, since birth. You order several laboratory tests on the child. When the nitroblue tetrazolium dye reduction test comes back negative, you tell the patient's mother that her son suffers from an inherited immune deficiency disorder that is associated with leukocyte dysfunction.

9

Genetic Defect	Caused by inherited **X-linked** or **autosomal recessive defects** in genes encoding components of **NADPH oxidase**.
Pathophysiology	Neutrophils use the myeloperoxidase-halide system to combat bacteria. The myeloperoxidase-halide system requires H_2O_2 to function. H_2O_2 is produced by bacterial metabolism and NADPH oxidase. Catalase-positive organisms (eg, *Staphylococcus*) can destroy the H_2O_2 produced by bacterial metabolism but not the H_2O_2 produced by NADPH oxidase. **Without NADPH oxidase activity**, there is no alternative source of H_2O_2, and the **myeloperoxidase-halide system is unable to kill catalase-positive bacteria**.
Clinical Manifestations	Presents in childhood with marked susceptibility to **opportunistic catalase-positive bacterial infections**, including *Escherichia coli*, **S aureus**, *Serratia*, and *Aspergillus*.
	Lab findings: **Negative nitroblue tetrazolium dye reduction test** because of absence of reactive O_2 intermediates.
Treatment	Gamma interferon; TMP-SMX prophylaxis.
Notes	

A 9-month-old boy is brought to the emergency room with a fever. The child's mother reports that the patient developed a fever to 101°F as well as an associated cough, productive of yellowish-greenish sputum. Chest X-ray confirms your suspected diagnosis of pneumonia. As you prepare to admit the patient to the hospital, you learn that the patient has had several bouts of infection in his short life, including *Staphylococcus* cellulitis and two episodes of sinusitis. When laboratory testing reveals low levels of IgA and IgG and elevated levels of IgM, you fear that this child may have a genetic disorder that predisposes him to infections.

Hyper IgM Syndrome

Genetic Defect	Primarily caused by inherited **X-linked** defect in gene encoding for **T-cell molecule**, **CD40 ligand**.
Pathophysiology	CD40 ligand is a receptor that is located on the activated T cell. When the **CD40 ligand binds to the CD40 molecule** on the surface of the B cell, several immune processes are stimulated, including immunoglobulin class switching. **If CD40 ligand is defective**, then **immunoglobulin class-switching is severely hindered**, hence resulting in elevated levels of IgM and decreased levels of IgG and IgA.
Clinical Manifestations	Presents by age 2 with **recurrent upper and lower respiratory infections** as well as cellulitis, osteomyelitis, and sepsis. Hepatosplenomegaly and lymphadenopathy are often noted. Complications include **increased rates of lymphomas**, hepatocellular carcinoma, or neuroendocrine carcinomas.
	Lab findings: **Elevated levels of IgM**; low levels of IgA and IgG; pancytopenia.
Treatment	Intravenous immunoglobulin infusion or G-CSF injections to prevent infections; bone marrow transplant for severe forms of the disease.
Notes	A rarer form of hyper-IgM syndrome is caused by a defect on chromosome 20 that codes for CD40. This disease is inherited in an autosomal recessive manner and is clinically similar to the X-linked form of hyper-IgM syndrome.

A 2-month-old girl presents to your urgent care clinic with symptoms of a viral upper respiratory tract infection. Her mother tells you that this is the third time that her daughter has developed an illness since birth. On physical examination, you notice that the girl has a small jaw as well as a positive Chvostek sign (twitching of the facial muscles with superficial tapping of the facial nerve). You decide to order several serum studies, which reveal hypocalcemia in the presence of decreased levels of parathyroid hormone as well as an absence of serum T cells. You refer the patient and her family to a geneticist to evaluate for a chromosomal abnormality and to a cardiologist to assess for possible congenital cardiac defects, which are often associated with this patient's condition.

9

DiGeorge Syndrome

Genetic Defect	A chromosomal disorder that results in a **microdeletion on chromosome 22**.
Pathophysiology	The chromosomal abnormality results in the **failure of development of the third and fourth pharyngeal pouches**. Without the fourth pharyngeal pouch, which normally gives rise to the thymus and parathyroids, the **thymus and parathyroids do not develop**, leading to **T-cell deficiency** and **hypoparathyroidism**. Disruption in the third and fourth pharyngeal arches also occurs, which causes abnormal neural crest cell migration and results in cardiac malformations.
Clinical Manifestations	T-cell deficiency manifests as **recurrentviral**, **fungal**, **and protozoal infections**. Hypoparathyroidism manifests with signs of hypocalcemia **(tetany)**. Patients will also often have congenital **cardiovascular defects** and **facial abnormalities** (cleft palate; small jaw).
Treatment	Fetal thymus transplanted to restore T-cell immunity.
Notes	**Common variable immunodeficiency** is a disorder of **variable inheritance** that results in the **inability for B cells to mature into plasma cells**, thereby leading to a deficiency in secreted immunoglobulins. It presents with recurrent pyogenic infections, decreased immunoglobulin levels in the setting of normal serum B-cell levels, and an increased incidence of B-cell neoplasms, gastric cancer, and skin cancers.

A 3-year-old girl presents to your pediatric office for establishment of care. She and her family have recently moved to the area from a rural community. The child's mother reports that the child has suffered from several bouts of cellulitis as well as sinusitis and pneumonia in the past. As you are speaking with the child's mother, you observe that the child has fair skin, extremely light blond hair, and light-colored eyes. Physical examination is further notable for hepatosplenomegaly and several ecchymoses. When routine blood work reveals the presence of neutropenia and thrombocytopenia, you decide to send the patient for genetic testing to see if the patient has a mutation for a gene associated with lysosomal transport on chromosome 1.

9

Chediak-Higashi Syndrome

Genetic Defect	An **autosomal recessive** disorder that results from a mutation in the *CHS1/LYST* gene on **chromosome 1**.
Pathophysiology	The *CHS/LYST* **gene** codes for a protein, which is responsible for the **regulation of lysosomal content transportation** to other cells, including neutrophils, neuronal cells, and melanocytes. When the **CHS/LYST protein is defective**, lysosomes do not function normally in these cells, thereby leading to **impaired cytotoxic function of neutrophils** (which results in infections) and impaired melanin transport to keratinocytes (which results in albinism).
Clinical Manifestations	Patients present in early childhood with **recurrent pyogenic infections** (particularly with *Staphylococcus* and *Streptococcus* organisms) and **oculocutaneous albinism**. Bleeding diatheses and hepatosplenomegaly are often noted. If patients survive to early adulthood, they develop **debilitating neurologic disease**, including neuropathies, ataxia, cognitive decline, and seizures.
	Lab findings: **Neutropenia**; thrombocytopenia; elevated bleeding time; **hypergammaglobulinemia**.
Treatment	Prophylactic antibiotics and G-CSF to ward off infection; steroid courses or bone marrow transplant has been used to treat severe forms of the disease.
Notes	

A 19-year-old woman presents to the emergency room, complaining of abdominal pain, muscle and joint aches, and fever. She and her family recently moved to the area from Greece and have yet to establish primary care. The patient tells you that, for the past 5 years, she has had intermittent episodes with symptoms similar to her current episode. On vital signs, the patient is febrile to 101.4°F. She has significant diffuse tenderness to abdominal palpation, and you notice a slight rub on cardiac examination. She also has a lacy, reddish rash on her lower extremities. You initiate the standard workup for abdominal pain and fever and, as you await the results, you wonder whether the patient's symptoms are related to a genetic deficiency in pyrin.

9

Genetic Defect	An **autosomal recessive** disorder that results from mutation in the *MEFV* **gene** on chromosome 16.
Pathophysiology	The *MEFV* gene is responsible for producing a protein known as **pyrin**. Although the exact function of pyrin is unknown, it is thought to be involved in the **inhibition** of IL-8 and/or chemotactic factor 5a, two **inflammatory cytotoxins**. In patients with Mediterranean familial fever, pyrin levels are decreased. When an inflammatory response is triggered, the **lack of pyrin results in excessive inflammatory activity of cytotoxins**, thereby leading to inflammation in the visceral tissues and joints.
Clinical Manifestations	Patients present with 2- to 4-day-long **episodes** of **fever**, **abdominal pain** (from peritoneal inflammation), **chest pain** (from pleural and pericardial inflammation), muscle and **joint pain** (from synovial inflammation), and rashes on the lower extremities.
Treatment	**Colchicine** (to treat inflammation); steroids or etanercept for more severe attacks.
Notes	As the name suggests, this disorder is more common in patients of Mediterranean descent.

A 22-year-old man presents to your oncology office for further evaluation of a large mass in his left femur. The patient had noticed pain in his left thigh over the last several months, and this symptom prompted his primary care provider to order a CT scan, which subsequently demonstrated a suspicious mass in the femur, concerning for osteosarcoma. Upon taking a detailed history from the patient, you learn that his mother is currently undergoing treatment for breast cancer, his older sister died of leukemia, and that he has two maternal uncles with adrenal carcinomas. Given the significant family history of malignancy, you decide to send this patient for genetic testing to see if he has a mutation in a specific tumor-suppressive gene.

9

Li-Fraumeni Syndrome

Genetic Defect	An **autosomal dominant** disorder that results from mutation in the **tumor-suppressive gene *p53*** on chromosome 17.
Pathophysiology	The *p53* gene is responsible for multiple regulatory processes of the cell cycle and DNA repair. While the mechanisms of p53 are complex, in short, the *p53* gene product senses DNA damage and then activates expression of DNA repair proteins as well as proteins that halt the cell cycle at the G1 phase while repairing takes place. If the DNA damage is too extensive, p53 can also trigger cell death. If the *p53* gene is mutated, the above stop mechanisms are ineffective and cells with damaged DNA continue to proliferate leading to tumor formation.
Clinical Manifestations	Patients with Li-Fraumeni syndrome are at a significantly **increased risk of cancers** (in particular sarcomas, osteosarcoma, breast cancer, leukemia, brain tumors, and adrenal carcinoma) at an early age.
Treatment	Treatment of cancers with chemotherapy/radiation; genetic testing.
Notes	

A 3-year-old girl presents to your pediatrics office for evaluation of a facial rash. The child's mother states that the child developed this rash over the last year and that it has become more prominent over the last several months. As you review the child's medical chart, you note that she is well below the expected growth curve for her age and that she has already suffered from a bout of bronchitis and gastroenteritis during her short life. On physical examination, you note that the child has a small jaw and bird-like facies in addition to a butterfly-like rash over the nasal bridge and bilateral cheeks. You also note scleral telangiectasias as well as other telangiectasias on the child's limbs. Based on the constellation of symptoms and physical findings, you worry that the child may suffer from a genetic disorder that will lead her to have an increased susceptibility to developing malignancy later in life.

9

Bloom Syndrome

Genetic Defect	An **autosomal recessive** disorder that results from mutation in the *BLM* gene on chromosome 15.
Pathophysiology	The *BLM* gene codes for a protein that is part of the *DNA helicase* family. *DNA helicase* is involved in unwinding the DNA helix as well as stabilizing the DNA strands during replication. If *DNA helicase* is faulty, **DNA replication is defective** and an inordinate number of mutations occur during DNA replication.
Clinical Manifestations	Physical characteristics include **short stature**, **butterfly-shaped rash on cheeks**, distinctive facial features (narrow face with bird-like facies; small mandible), and **telangiectasias** of the skin and eyes. Patients also suffer from hypogonadism, **immunodeficiency** (manifests as recurrent respiratory and gastrointestinal infections), and **increased susceptibility to malignancy**.
	Lab findings: decreased levels of IgA and IgM.
Treatment	Avoid sun exposure; treatment of cancers with chemotherapy/radiation; genetic testing.
Notes	

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