First Aid®
Clinical Pattern Recognition for the USMLE® Step 1

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I am grateful to God for blessing me with so much…

I dedicate this book to:

—all the students who work so hard to seek knowledge and serve others

—our patients and teachers who inspire us to be the best we can be

—my inspirational and supportive colleagues at University of Illinois College of Medicine

—and my family and friends for their love and support

—Asra R. Khan

Contents

About the Editors

Asra R. Khan, MD

Editor-in-Chief

Asra is an Associate Professor of Clinical Medicine at the University of Illinois College of Medicine-Chicago. She earned her B.A. at the University of Chicago and was inducted into Phi Beta Kappa. She received her M.D. at The University of Chicago-Pritzker School of Medicine and completed her internal medicine residency at Northwestern University-McGaw Medical Center in Chicago. Asra has been involved in teaching residents and students since joining the University of Illinois College of Medicine-Chicago in 1998 where she currently serves as the co-Course Director of the Doctoring and Clinical Skills Course, Director of the Internal Medicine Clerkship, and Director of the Internal Medicine Sub-Internship. She was also an Associate Program Director of the internal medicine residency program. Inspired by her mission to increase student success in the USMLE Step Exams and to mentor better clinicians, she recruited and led a top-notch team of diverse and brilliant faculty, fellows, residents and students to develop this product. In addition to editing all the chapters, she created many of the algorithms, tables and cases throughout the book. It is her sincere hope that medical students will find this book useful for the USMLE Step 1, their pre-clinical years, and beyond.

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Joseph is an MD/PhD candidate in the Medical Scientist Training Program (MSTP) at the University of Illinois College of Medicine (UICOM)-Chicago who completed his PhD in Neuroscience and has since returned to medical school. He earned his bachelor's degree in biochemistry at the State University of New York (SUNY) College at Geneseo in 2014, graduating summa cum laude and being inducted into Phi Beta Kappa. He has published several peer-reviewed papers in neuroscience, clinical neurology, and medical education. He co-founded the UICOM Student Curricular Board which seeks to engage medical students as agents of change in medical education and has served as a peer tutor for USMLE Step 1 since 2016. In his spare time, he enjoys running and traveling.

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Introduction

Joseph R. Geraghty and Asra R. Khan

Congratulations! By using this book, you are one step closer to developing your skills as a future physician and in preparation for the USMLE Step 1 exam and the practice of medicine.

Why Use This Book?

- USMLE Step 1 has increasingly used clinical case-based approaches to licensing exam questions, translating into a need for medical students to rapidly recognize clinical patterns, to develop a differential diagnosis, and to use clinical reasoning and basic science skills to answer questions. Cases or vignettes provided on Step 1 are usually given in their most classic presentation. *First Aid for USMLE Step 1* is the most commonly used resource by medical students as they prepare for USMLE Step 1. Given the goals and sheer volume of material necessary to include in the book, the text often only provides a list of signs, symptoms, tests, and findings for a given condition, without providing the context that ties all of these features together. What is often missing is a discussion of the subtle similarities and differences between conditions that initially may not seem related. Further, given the need for USMLE Step 1 to test many basic science concepts, many of the conditions tested are quite rare, greatly limiting the chances that medical students will have encountered cases like these in the clinic or hospital setting during their early years of medical training.
- The *First Aid Clinical Pattern Recognition (CPR)* book presents classic "textbook" vignettes of high-yield syndromes and cases commonly tested on USMLE Step 1 and encountered in clinical practice. This resource provides context that ties different symptoms, signs, and conditions together, encouraging medical students to consider a differential diagnosis for a given chief concern, the relationships between different conditions, and more. Ultimately, this book will help medical students learn to recognize patterns and start building illness scripts for various high-yield conditions. While several books on the market provide selected cases designed to address single high-yield points about a given condition, this book goes beyond that. By partnering with the *First Aid for USMLE Step 1* book, we combine classic clinical scenarios with basic science concepts that are tested on USMLE Step 1. The chapters are organized similarly to *First Aid for USMLE Step 1*, but the vignettes are presented in a way that students would encounter in the real world and exam setting.
- This book is designed to be used in tandem with *First Aid for USMLE Step 1* throughout preclinical curricula and leading up to the USMLE Step 1 exam. In this book, we introduce general approaches to initial presenting signs and symptoms, offer guidance for evaluating these in the context of answering a USMLE Step 1 question, provide high-yield cases that highlight major buzzwords and findings, and supply detailed discussions that compare and contrast cases, as well as schematics, tables, and algorithms that will help individual learners recognize clinical patterns commonly tested on USMLE Step 1.
- The second overarching goal of this book goes beyond just USMLE Step 1 by helping medical students build a strong clinical foundation so they can excel in medical school. By acknowledging the importance of obtaining a focused history and physical examination, developing a differential diagnosis, and understanding the purpose of common tests and general treatment concepts for various conditions, students will recognize common patterns, build illness scripts, and improve their clinical reasoning skills.

How Should I Use This Book?

- Start using this book as early as possible during your preclinical education, during which you learn basic medical sciences.
- When you learn about a particular condition in a class or encounter an interesting case in the clinic, it is helpful to go back to this book to reference what a classic textbook case would look like. Did your patient have all of these findings? They may not have. Did they have a unique or unusual presentation? Annotate this into the book!
- This book will serve as your go-to resource for identifying what features of a given condition are the most commonly tested on USMLE Step 1.
- As such, this book is a great accompaniment to your clinical experiences throughout the first two years of medical training and beyond.

- Students are encouraged to use pens and highlighters of different colors to develop their own system for annotating this book. Perhaps you can annotate based on your preclinical coursework, on your clinical experiences thus far, and on material covered in other high-yield resources.
- You may also consider removing the binding of the book and inserting with individual chapters in the larger *First Aid for USMLE Step 1* book.
- Keep in mind that this is not a question book. Instead, the vignettes highlight what a classic presentation of a particular case would look like: who gets the disease; the common symptoms and physical exam findings; other conditions that may present similarly; tests that will help confirm the diagnosis (and what the typical findings will be) or help refute the other conditions; and what the standard treatment is. The discussion portion reinforces the common presentations and expands on these and on pertinent basic science principles.
- The cases build on each other. Simple, more straightforward cases are followed by less common and more complex vignettes. It is important to note that many cases will present with more than one symptom. For instance, a patient with gastroesophageal reflux disease (GERD) may present with classic heartburn symptoms, atypical chest pain, or a chronic cough. This information will be conveyed in the discussion session.

Anatomy of the Cases

CASE 1 | Actual Case or Key Features Being Highlighted	
The vignette includes classic demographics (who gets the disease), common symptoms and signs, other relevant history, and physical exam findings.	
Evaluation/Tests	This section includes important tests to confirm the diagnosis and highlights the classic findings. If the diagnosis is typically made based on history and physical exam findings, then "clinical diagnosis" is written, followed by other tests that may be done to confirm or refute alternative diagnoses.
Treatment	Standard treatment for the presented case is explained.
Discussion	This section reinforces salient features of the case, elaborates on other reasonable differential diagnoses, includes more detailed treatment options, and—most importantly—links the basic sciences relevant to USMLE Step 1.
Additional Considerations	When applicable, this section highlights other similar conditions or complications that are important to consider for Step 1 and beyond. Common symptoms, signs, evaluation, and treatment are presented in an abbreviated format.

Example Case

CASE # | Stable Angina	
A 65-year-old man with a history of hypertension, type 2 diabetes, hyperlipidemia, and tobacco use presents with intermittent chest pain for the past 2 months. He describes it as a squeezing pressure sensation in his left parasternal to mid-clavicular area with radiation down his left arm that is associated with mild shortness of breath. The symptoms occur each time he climbs more than two flights of stairs and it improves after he rests for a few minutes. His vital signs, as well as his cardiovascular, pulmonary, and abdominal exams, are normal. There is no reproducible chest wall tenderness or lower extremity edema.	
Evaluation/Tests	Clinical diagnosis. If ordered, exercise ECG would show $\geq$1 mm ST depression in more than 1 contiguous lead. A stress echo would show induced regional wall motion abnormalities consistent with ischemia.
Treatment	Treat with aspirin, statin, and antianginal medications (beta blockers, calcium channel blockers, and/or nitroglycerin). Optimize risk factors (i.e., diabetes, hypertension) and encourage lifestyle modifications (i.e., diet, exercise, smoking cessation). Patients that have persistent symptoms despite optimal medical therapy can safely be offered revascularization.
Discussion	Stable angina typically occurs when there is an obstructive atherosclerotic lesion in the coronary arteries that is over 70% occlusive. Cardiac risk factors include age (male patients >45, female patients >55), male sex, HTN, DM, dyslipidemia, family history of premature CAD (males <55, females <65), smoking, and abdominal obesity. At times, the chest pain is described as a discomfort or pressure sensation rather than pain. Additional symptoms can include dyspnea, nausea, diaphoresis, lightheadedness, dizziness, and easy fatigability. Typical angina is provoked by exertion and relieved with rest or nitroglycerin. Physical exam findings are often normal. If a patient has atypical or vague symptoms, an exercise test stress test can confirm the diagnosis.

CASE # | Stable Angina *(continued)*

Discussion	The relatively short duration of pain and association with exertion makes **acute coronary syndrome** (ACS) (unstable angina, NSTEMI, and STEMI) less likely. New onset angina, chest pain at rest, or change in previous predictable angina in a patient with known CAD or cardiac risk factors are characteristic features of ACS. Physical exam findings are often normal. **Unstable angina (UA)** occurs secondary to coronary atherosclerosis plaque rupture and subsequent thrombus formation without complete occlusion of the coronary artery. The pain associated with UA tends to be more severe and typically lasts for 15 min or more. Patients with UA should be hospitalized on a telemetry unit to be stabilized, monitored for arrhythmias, and initiated on a protocol to rule out an MI, which includes checking serial ECGs and cardiac biomarkers. ECG may show ST depression and T wave inversions, and cardiac biomarkers would be normal. Once the patient is stabilized and asymptomatic, they may either undergo stress testing or proceed to coronary angiogram if they are at high risk of ischemia.
Additional Considerations	**Vasospastic (aka Variant or Prinzmetal) angina** is a condition in which chest pain results from transient vasospasm in the coronary arteries, limiting blood flow and causing transient ischemia. The chest pain typically occurs at rest and may be triggered by drugs or substances such as triptans (e.g., sumatriptan), cocaine, cannabis, ephedrine-based products, or alcohol. It is a diagnosis of exclusion, and it is important to rule out a fixed obstructive coronary artery lesion.

What Is the Anatomy of a Typical USMLE Step 1 Question?

- Many students feel overwhelmed by the idea of taking USMLE Step 1 and addressing clinical vignettes successfully. However, there is a specific anatomy to Step 1 questions, and once you become familiar with the format and begin to recognize clinical patterns, you will feel more comfortable answering these questions.
- Many USMLE Step 1 questions are presented in the form of a short clinical vignette that can range from a few sentences to a full paragraph.

A 48-year-old man with past medical history of hypertension and type 2 diabetes mellitus is hospitalized following a significant burn injury from a fire at home. Upon arrival to the emergency room, the patient is stabilized and transferred to the burn unit, where he then recovers over the course of the next week. Ten days after admission, the patient's vital signs are recorded as follows: temperature 38.1°C, respirations 28/min, pulse 110/min, and blood pressure 148/90 mmHg. Though his burn appears to be recovering well, he is tachypneic, and lung exam is notable for crackles bilaterally and bronchial breath sounds. He is tachycardic, but the rest of his cardiac exam is normal. Sputum culture shows a motile, gram negative rod that is oxidase-positive and produces a blue-green pigment. Which of the following best describes the toxin released by this particular pathogen?

A) Stimulates nonspecific activation of T lymphocytes
B) Inactivates elongation factor 2 via ribosylation
C) Activates adenylate cyclase via ADP ribosylation of Gs protein to increase host cell cAMP
D) Inhibits adenylate cyclase via ADP ribosylation of Gi protein to decrease host cell cAMP
E) Induces actin depolymerization leading to mucosal cell death

- **IDENTIFYING STATEMENT:** These vignettes often begin with an identifying or power statement that introduces the patient, including their age, gender, significant past medical history, and chief concern that brought them into the physician's office or hospital. If you are paying careful attention to this statement alone, you may already have an idea of what the question will ask and what limited number of conditions you should have on your differential, or you may have already arrived at an accurate diagnosis. Keep in mind that certain themes and concepts tend to be tested more heavily.
- Everything matters until you are sure it doesn't. Consider why a test writer may have chosen to include certain pieces of information (i.e., geographical location, gender, age). Oftentimes, there is a reason.
- **ADDITIONAL HISTORY/COURSE OF ILLNESS:** After presenting the initial identifying statement, USMLE Step 1 vignettes will often provide additional context clues. Does this patient have underlying cardiovascular risk factors (e.g., smoking, hypertension, diabetes, hyperlipidemia) that might predispose them to myocardial infarction or stroke? Is the patient from a developing country where they may not have received proper immunizations? Did the patient recently travel or eat something associated with particular infections? These types of statements will often allow you to start narrowing down your differential diagnosis and figuring out exactly what the vignette is testing.
- **PHYSICAL EXAM FINDINGS:** Physical exam findings are often brief in USMLE Step 1 vignettes. Typically, you are presented with one sentence providing key physical exam findings, including key findings that are normal on exam. Some

physical exam maneuvers are quite specific to a particular condition, so pay attention to how things are worded. Oftentimes, test writers will not use the exact buzzword that may be most familiar to you. For example, in a pediatric patient with Tay-Sachs disease, an exam item will likely never mention "cherry red spot in the macula" on fundoscopy; however, you should be prepared to be presented with a description of this classic finding rather than the term itself. A vignette may be more likely to note, "On fundoscopy, you note a central area of reddening in the retina."

- **LABORATORY FINDINGS:** Laboratory findings are commonly presented on USMLE Step 1 questions, and you will be expected to interpret these. You are provided with a list of common laboratory values to use for reference, and it is worthwhile to spend some time familiarizing yourself with what is provided in this list and what is not. If you are given a lab value in a vignette that is not provided on this list, the vignette may indicate whether the result is normal or abnormal. However, it is important to note that not all questions will rely on your interpreting each lab value provided. Sometimes a long list of lab values is provided, which may take a long time to go through but may ultimately be less helpful than the remainder of the vignette. If presented with a long list of lab values, it may be helpful to go on to read the rest of the question and then go back to the list with an idea of which lab values are most relevant to the case. Cases dealing with hematology, oncology, or renal and endocrine systems commonly list multiple lab results, so it will be important to train yourself to work quickly through these items.
- **IMAGING:** Images are commonly provided on USMLE Step 1, including both radiological images and pathological specimens (gross anatomical specimens and histology sections). While knowing the normal appearance of a particular specimen or tissue type is helpful, it is often not needed to adequately answer the exam item. Consider that the test writer chose to provide this image for a reason and that that a principal finding is likely to be obtained from the image that would not be clear from the text alone. *First Aid for USMLE Step 1* provides a large number of radiological and pathological images, and it would be a good use of time to familiarize yourself with these key images. You may be able to determine the answer to a question just by looking at the image and not the text, while other times you may be able to rely on the text alone without the image. This works to your advantage, as there are often several context clues in a Step 1 vignette that will allow you to successfully answer an item without using all of them.
- **THE QUESTION:** Now you arrive at the actual question. Many students are often dismayed when they have read the entire vignette and are 100% certain of the diagnosis, only to have the question give the diagnosis away and then be asked a more basic science question related to the mechanism of action of a drug or molecular cause of a particular finding. For example, a microbiology case may present a sick patient who recently ate potato salad at a company picnic and is now suffering from vomiting and diarrhea. From this statement alone, you may have already narrowed down particular pathogens that may be the culprit, and you would likely arrive at a quick diagnosis with additional context clues in the vignette. When you reach the actual question, it may ask you about the mechanism of the pathogen's toxin or virulence factor instead of asking you what bug is the causative pathogen. These are the types of questions that USMLE Step 1 prefers to ask because it will require higher-order critical reasoning skills and incorporate basic science questions into clinical vignettes.
- Should you read the whole vignette first or the actual question at the end of the vignette? Up to you! Different students have different strategies for this. Some students prefer to skip the entire vignette and first read the question and scan the answer choices. These students will then return to the beginning of the vignette and, having an idea of the question, search for pertinent context clues that may support their hypothesis of what the answer may be. This works well for many students, and it is reported to help decrease the amount of time you spend on a given test item because you are not spending time interpreting irrelevant lab values or physical exam findings before knowing the question. Other students prefer to read the vignette from beginning to end, using basic science and clinical reasoning skills to build a case in their head of what the question and answers might be before directly reading them. This is more similar to how you would approach patients in the clinic, and it provides a more logical flow to addressing test items.
- **THE ANSWER CHOICES:** The number of answer choices provided in a Step 1 exam item vary, but most questions have a minimum of 5 answer choices. The best approach to this section of the exam item is to arrive at what you think the answer is after reading the question (and/or the case, as just described). Then look through the answer choices and see whether that answer is present. If it is, select it! If it is not, you may need to do some rethinking, reviewing the vignette for key words or significant findings that you may have missed. There will be a single best answer, given the nature of multiple-choice exam items, even though, in medicine, you may actually do several things in the real world. So you have to pick a single answer if a question asks you about the next step.

We hope that this book is helpful to medical students as they master the material needed to find success on the USMLE Step 1 examination and beyond. As medicine is an ever evolving discipline where new mechanisms are discovered and new treatments are developed every year, we welcome suggestions to improve the clarity, accuracy, and completeness of this work. Good luck!

1 Biochemistry

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Failure to Thrive
1. Pyruvate Dehydrogenase Complex (PDC) Deficiency
2. Hereditary Fructose Intolerance
3. Von Gierke Disease (Glycogen Storage Disorder Type 1)
4. Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency
5. Ornithine Transcarbamylase Deficiency (OTC) (Urea Cycle Disorders)

Developmental Delay or Regression
6. Tay-Sachs Disease
7. Hurler Syndrome (Mucopolysaccharidosis Type I)
8. Phenylketonuria (PKU)

Intellectual Disability
9. Prader-Willi Syndrome

Dysmorphic Features
10. Down Syndrome (Trisomy 21)

Pediatric Ophthalmologic Abnormalities
11. Classic Galactosemia
12. Retinoblastoma

Muscle Weakness
13. Duchenne Muscular Dystrophy (DMD)
14. Myotonic Dystrophy Type 1
15. Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-Like Episodes (MELAS) Syndrome
16. McArdle Disease (Glycogen Storage Disease Type V)
17. Pompe Disease (Glycogen Storage Disease Type II)

Bone and Joint Abnormalities
18. Osteogenesis Imperfecta
19. Ehlers-Danlos Syndrome (EDS)
20. Marfan Syndrome
21. Alkaptonuria
22. Gaucher Disease
23. Lesch-Nyhan Syndrome

Altered Mental Status
24. Niacin (B3) Deficiency (Pellagra)

Neuropathy
25. Vitamin B12 (Cobalamin) Deficiency
26. Vitamin B6 (Pyridoxine) Deficiency
27. Fabry Disease
28. Zellweger Syndrome

Hematologic Abnormalities
29. Vitamin C Deficiency (Scurvy)
30. Vitamin K Deficiency
31. Pyruvate Kinase Deficiency

Dermatitis or Rash
32. Vitamin A (Retinol) Deficiency
33. Xeroderma Pigmentosum (XP)

Respiratory Distress
34. Kartagener Syndrome/Primary Ciliary Dyskinesia
35. Cystic Fibrosis

Dyslipidemias
36. Familial Hyperchylomicronemia (Hyperlipidemia Type I)
37. Familial Hypercholesterolemia (Hyperlipidemia Type IIa)

Knowledge of biochemistry is essential to detecting and understanding the consequences of disordered metabolism. In general, symptoms occur due to the accumulation of substrates upstream from a defective enzyme or due to a lack of production of important substrates downstream from the deficient enzyme. It is important to understand the key regulatory steps in metabolic pathways and areas in the pathways that can be impacted by pharmaceutical agents. Biochemical pathways are interconnected; interruption in one pathway can cause other pathways to be affected, resulting in manifestations or exacerbation of a disease.

By knowing what happens when a pathway is interrupted and the intermediate metabolites that are affected, one can predict some of the typical patient presentations. For instance, lactate builds up in a defect in pyruvate dehydrogenase complex, causing metabolic acidosis. This, in turn, leads to an increased respiratory rate to compensate for the acidosis.

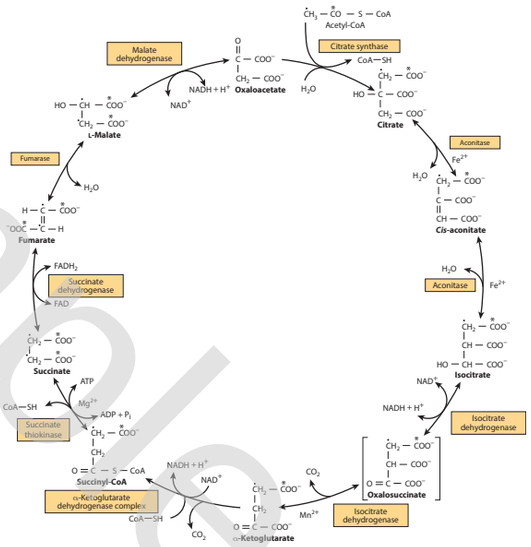
Most patients have some characteristic features in their mode of inheritance, clinical presentation, and tests that should help narrow the differential and determine if there is a biochemical reason for their symptoms. Often, patients present in early or late childhood, so a pediatric or newborn presentation should raise suspicion for biochemical or genetic disorders. As the defects presented here occur at the genetic or molecular level, these disorders frequently present with numerous symptoms, making definitive grouping into a single category more challenging. These disorders are grouped on the basis of main presenting symptoms or signs. Where possible, the text highlights other ways in which the condition may manifest.

FAILURE TO THRIVE

Inborn errors of metabolism occur in important biochemical pathways involved in the synthesis, regulation, and breakdown of important nutrients. Defects in these pathways can result in "failure to thrive," which can be described as inadequate weight gain, weight loss/deceleration, or falling consistently below the 5th percentile for growth in a child, despite meeting adequate nutritional requirements. Many of these disorders present with symptoms that include poor feeding, vomiting, irritability, or lethargy.

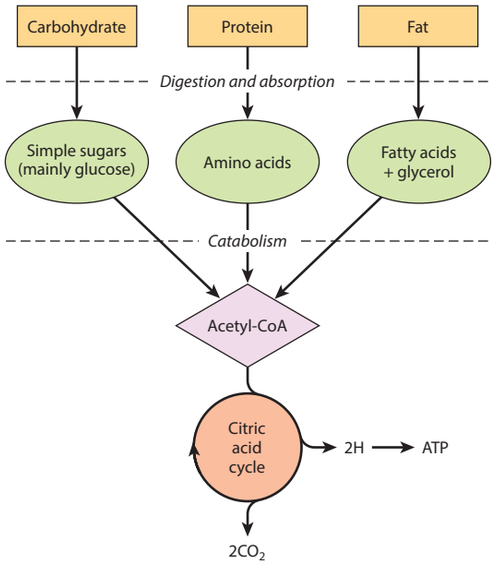
Typical pathways that, when disturbed, can lead to failure to thrive include:

- **Glucose metabolism**—Glucose provides an essential source of energy for various aerobic and anaerobic processes in all cells. Complex carbohydrates are broken down into monosaccharide forms such as glucose, which then enter glycolysis for the production of pyruvate (and 2 ATP). Pyruvate can then enter the Krebs cycle (also called the tricarboxylic acid or TCA cycle) and electron transport chain, ultimately producing a large amount of ATP to supply the energy needed to carry out cellular functions. It is important to keep in mind that the metabolism of glucose is highly regulated. Defects in key enzymes in these pathways can, therefore, have severe consequences, often resulting from a switch from aerobic to anaerobic respiration and leading to a buildup of lactic acid throughout the body.
- **Fructose metabolism**—Fructose is another monosaccharide, often obtained from the diet in the form of sucrose (glucose + fructose). Compared to the tight regulation of glucose metabolism, the metabolism of fructose and other monosaccharides (e.g., galactose) is not as well regulated. Metabolism of fructose, occurring primarily in the liver, requires phosphorylation to fructose-1-phosphate before it can be acted on by the key rate-limiting enzyme, aldolase B, to ultimately form glyceraldehyde-3-phosphate for energy production (shuttled to glycolysis or gluconeogenesis). Disruption of this pathway can, therefore, result in phosphate trapping and thus hypoglycemia. Generally, disorders of fructose metabolism are milder than those involving galactose metabolism (discussed under visual problems).



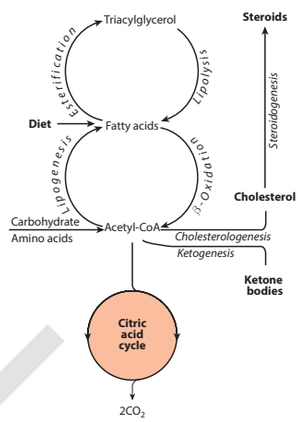
The citric acid (Krebs) cycle. Oxidation of NADH and $FADH_2$ in the respiratory chain leads to the formation of ATP via oxidative phosphorylation. In order to follow the passage of acetyl-CoA through the cycle, the two carbon atoms of the acetyl moiety are shown labeled on the carboxyl carbon (*) and on the methyl carbon (·). Reproduced with permission from Rodwell VW, Bender DA, Botham KM, et al: Harper's Illustrated Biochemistry, 31st ed. New York, NY: McGraw Hill; 2018.

- **Glycogen storage**—Glycogen storage is important because it acts as a buffer to provide glucose until gluconeogenesis is fully functional. When infants have disorders of glycogen regulation, it can present as hypoglycemia and alteration in mental status secondary to hypoglycemia. Some glycogen storage diseases only affect the liver, causing hepatomegaly with hypoglycemia. If muscle is affected, it manifests as weakness and difficulty with exercise as a result of the inability to increase glucose entry into glycolysis during exercise (also covered in myopathy section). A characteristic feature of glycogen storage disorders is a "second wind phenomenon," whereby after a period of rest, if the patient resumes exercise, increased blood flow to muscle can provide other substrates, such as glucose and free fatty acids instead of glycogen, that can lead to improvement in symptoms.



Catabolism of carbohydrate, protein, and fat. Lead to the production of acetyl-CoA, which is oxidized in the citric acid cycle, ultimately yielding ATP. Reproduced with permission from Rodwell VW, Bender DA, Botham KM, et al: Harper's Illustrated Biochemistry, 31st ed. New York, NY: McGraw Hill; 2018.

- **Fatty acid metabolism**—Fatty acids are an additional source of energy, especially in circumstances where glucose is low, such as prolonged fasting or in the onset of illness. Acetyl-CoA from the beta oxidation of fatty acids can be shuttled to the Krebs cycle and also results in formation of ketone bodies, which can be used as energy sources as well. Defects in beta oxidation inhibit the use of fatty acid for energy production. Defects cause hypoketotic hypoglycemia and elevated levels of dicarboxylic acids.

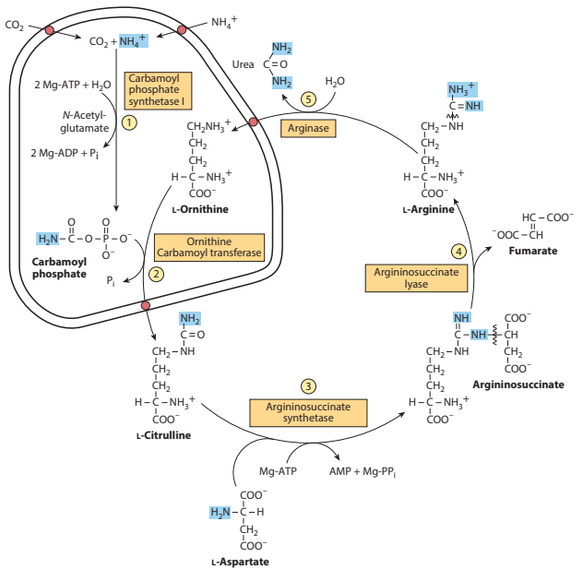


The ketone bodies are acetoacetate, 3-hydroxybutyrate, and acetone. Reproduced with permission from Rodwell VW, Bender DA, Botham KM, et al: Harper's Illustrated Biochemistry, 31st ed. New York, NY: McGraw Hill; 2018.

- **Amino acid metabolism**—When amino acids cannot be degraded, intermediates in their metabolism can build up and cause organic acidurias and metabolic acidosis. The metabolites normally produced may become limited, and important products like L-DOPA, dopamine, epinephrine, norepinephrine, and melanin are not produced. Excess amino acids can also interfere with normal amino acid transport across the blood–brain barrier and limit protein and neurotransmitter synthesis in the brain. Some of the metabolites that build up have a distinctive smell/urine color (see the following table), which is considered a hallmark of each disorder. Organic acidemias have metabolic acidosis and urine ketones, which helps differentiate them from urea cycle defects.

Smell/Color	Disease	Amino Acid
Mousy smell	Phenylketonuria	Phe
Maple syrup smell	Maple syrup urine disease	BCAA
Cabbage smell	Tyrosinemia type 1	Phe, Tyr
Rancid butter smell	Tyrosinemia type 1	Phe, Tyr
Black urine color	Alkaptonuria	Phe, Tyr

- **Urea cycle and transport of ammonia**—Excess organic acids may also interfere with the urea cycle and cause increased levels of ammonia. Urea cycle disorders cause primary hyperammonemia, and organic acidemias cause secondary hyperammonemia. Ammonia diffuses freely across the blood–brain barrier and leads to impaired cerebral function. Both of these disorders can present as altered mental status due to elevated ammonia.



The nitrogen-containing groups that contribute to the formation of urea are shaded. Reactions (1) and (2) occur in the matrix of liver mitochondria and reactions (3), (4), and (5) in liver cytosol. CO_2 (as bicarbonate), ammonium ion, ornithine, and citrulline enter the mitochondrial matrix via specific carriers (see red dots) present in the inner membrane of liver mitochondria.
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CASE 1 | Pyruvate Dehydrogenase Complex (PDC) Deficiency

A mother brings her 1-year-old boy for a well-baby checkup. She is worried because her son seems "extra tired." He doesn't seem to be getting ready to walk, sitting on his own, or babbling as much as her older children did at this age. He also has not been eating as much, and when she tries to feed him, he becomes quite fussy. She reports no history of trauma or injury. On physical exam, he is afebrile but has rapid breathing.

Evaluation/Tests	Labs show normal CBC and glucose and low serum pH. Lactate, pyruvate, and alanine levels are high. Enzyme testing reveals a deficiency in the pyruvate dehydrogenase complex (PDC).
Treatment	Cofactor supplementation with thiamine and lipoic acid stimulates the PDC and may prevent acute worsening of the syndrome. Increase intake of ketogenic nutrients (high fat, low carbohydrate, moderate protein) to promote use of fat and amino acid instead of glucose.
Discussion	Pyruvate dehydrogenase complex (PDC) is an enzyme complex that converts pyruvate to acetyl-coenzyme A (CoA), which is one of the first steps of the Krebs, or tricarboxylic acid (TCA) cycle. In PDC deficiency, this enzyme has an X-linked defect that affects the transition from glycolysis to the TCA cycle, resulting in a buildup of pyruvate. The pyruvate then gets converted into lactate and alanine. Increased lactate results in metabolic acidosis, which can lead to a compensatory respiratory alkalosis in attempts to rid the body of excess acid in the form of carbon dioxide. The buildup of these substrates and the lack of energy (from blocking the TCA and thus electron transport cycle) results in fatigue, poor feeding, and tachypnea, especially during times of illness, stress or high carbohydrate intake. Characteristic findings include neurological deficits, lactic acidosis, and increased serum alanine starting in infancy. Given the young age of the patient, suspicion should be raised for other biochemical defects like **von Gierke disease** and **medium-chain acyl-CoA dehydrogenase (MCAD) deficiency**. Many of these conditions can be ruled in or out by genetic or enzyme testing.

CASE 2 | Hereditary Fructose Intolerance

A 4-year-old boy is brought for evaluation of acute vomiting and lethargy shortly after attending a birthday party. He had several bouts of vomiting in the past, usually after consuming fruit juice. On exam, hepatomegaly and jaundice are noted.

Evaluation/Tests	Labs show low glucose, lactic acidemia, ketosis, hypophosphatemia.
Treatment	Decrease intake of fructose and sucrose (glucose + fructose).
Discussion	Hereditary fructose intolerance is an autosomal recessive disorder involving a deficiency in aldolase B, the rate-limiting enzyme in fructose metabolism. Fructose is commonly found in fruits, juice, and processed sugary foods. When consumed, it is first converted by fructokinase to fructose-1-phosphate. This phosphorylation step traps fructose-1-phosphate inside of cells. Aldolase B then acts on fructose-1-phosphate, converting it into dihydroxyacetone phosphate (DHAP) and glyceraldehyde, which can be used downstream in glycolysis or

CASE 2 | Hereditary Fructose Intolerance *(continued)*

Discussion	glycerol synthesis. Defects in aldolase B result in accumulation of fructose-1-phosphate inside of cells, leading to a decrease in available phosphate for other processes such as glycogenolysis and gluconeogenesis. This results in hypoglycemia. Symptoms develop shortly after consuming fructose-containing foods. Left untreated, it can lead to further metabolic disturbances including lactic acidemia, hypophosphatemia, and hyperuricemia. It can also progress to liver and renal damage unless fructose intake is reduced. **Essential fructosuria** is a similar disorder that is a benign, asymptomatic condition due to a defect in fructokinase. Fructose may appear in blood or urine, but it can still be used for metabolism because hexokinase (which normally phosphorylates glucose to glucose-6-phosphate) can also act on fructose. Compared to disorders of galactose metabolism (galactokinase deficiency or classic galactosemia), disorders of fructose metabolism tend to be milder. **Disorders of galactose metabolism** may present following ingestion of breast milk or other dairy products while those of fructose metabolism present after ingestion of fruit, high-fructose corn syrup, or other fructose-containing products.

CASE 3 | Von Gierke Disease (Glycogen Storage Disorder Type 1)

A 4-month-old infant is brought to the emergency room with irritability, rapid breathing, and cold-like symptoms. Parents report that episodes of fussiness occur when the baby doesn't feed for >4 hours. Exam is significant for clear rhinorrhea, pharyngeal erythema, tachypnea, with clear breath sounds. The abdomen is protuberant, and the liver edge is palpable 10 cm below the costal margin.

Evaluation/Tests	Labs show severe fasting hypoglycemia, elevated lactate, elevated pyruvate, hyperuricemia, hyperlipidemia, hypertriglyceridemia, and elevated AST and ALT.
Treatment	Frequent oral glucose or cornstarch to sustain blood sugar levels. Avoidance of fructose and galactose (to decrease glycogenesis).
Discussion	Von Gierke disease (glycogen storage disease type I) occurs when a patient has an autosomal recessive defect in the glucose-6-phosphatase enzyme. This defect prevents glucose-6-phosphate from being converted to glucose during gluconeogenesis. This failure in glycogenolysis and gluconeogenesis ultimately results in hypoglycemia. The excess glucose-6-phosphate can enter the pentose phosphate pathway (also called the hexose monophosphate or HMP shunt), causing an increase in ribose formation and purine turnover, which leads to hyperuricemia. The excess glucose-6-phosphate can also be metabolized by glycolysis, leading to increased pyruvate and thus increased lactate and alanine levels. The hypoglycemia causes physiologic epinephrine release, resulting in activation of lipoprotein lipase (LPL), which causes fatty acid release and hypertriglyceridemia. Other features include hepatomegaly and enlarged kidneys (glucose-6-phosphatase is also used in the kidneys for glycogenolysis, although to a lesser extent than the liver). **Cori disease (type III glycogen storage disease)** presents similarly to Von Gierke disease but is usually much milder. Cori disease is caused by a defect in the α-1,6-glucosidase debranching enzyme. Gluconeogenesis remains intact, so lactate levels remain normal. Patients with Cori disease also have muscle weakness and hypotonia.

CASE 4 | Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency

A 4-month-old infant is brought in for evaluation because she was not acting like herself, and her body went limp suddenly. She had a fever, poor appetite, and was vomiting and lethargic most of the day. She was diagnosed with a viral infection a few days earlier. Physical exam is significant for hypotonia and hepatomegaly.

Evaluation/Tests	Labs show hypoketotic hypoglycemia, increased medium-chain fatty acids (C6, C8, and C10), and hyperammonemia.
Treatment	Avoid fasting and place patient on a special diet.
Discussion	MCAD deficiency is the most common genetic defect in fatty acid beta oxidation and involves an autosomal recessive mutation in the medium chain acyl-CoA dehydrogenase enzyme. Following entry of fatty acyl-CoA into the mitochondrial matrix via the carnitine shuttle, fatty acids normally undergo beta oxidation via acyl-CoA dehydrogenase enzymes, eventually being converted into acetyl-CoA.

CASE 4 | Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency *(continued)*

Discussion	Acetyl-CoA is then used for ketogenesis or the TCA cycle. In MCAD, the defective medium chain acyl-CoA dehydrogenase enzyme impairs the ability to break down medium chain fatty acids (ones with 6–10 carbons) to acetyl-CoA. Infants typically develop symptoms between 3 and 24 months, as they are weaned from nighttime feedings and experience longer fasts, or in the setting of viral illness and decreased food intake. Lack of acetyl-CoA causes impairment in ketogenesis and gluconeogenesis, resulting in a characteristic hypoketotic hypoglycemia during these times. This can lead to neurologic dysfunction including weakness, lethargy, seizures, and fat accumulation in the liver that causes hepatomegaly, hyperammonemia, and liver injury.
Additional Considerations	**Maple syrup urine disease (MSUD)** is an autosomal recessive disorder involving a mutation in the branched-chain α-ketoacid dehydrogenase enzyme, which is responsible for the degradation of isoleucine, leucine, and valine. Patients may present with signs of central nervous system toxicity (seizures, hypotonia, spasms, lethargy, and intellectual disability), poor feeding, and a distinct sweet odor to the urine that smells like maple syrup or burnt sugar. Treatment includes strict dietary restriction of all three branched-chain amino acids. To differentiate between fatty acid disorders, pay attention to the particular lab findings and the length of the fatty acid chains. **Primary carnitine deficiency (PCD)** is a condition that prevents the body from using fatty acids for energy, which is needed during fasting. PCD results from an autosomal recessive mutation in the *SLC22A5* gene. Carnitine is involved in the shuttling of long-chain fatty acids into the mitochondria for subsequent beta oxidation and production of energy. PCD often appears during infancy or early childhood and can result in neurologic symptoms like weakness and confusion due to encephalopathy, dyspnea, fatigue due to cardiomyopathy, decreased ketogenesis, and low blood glucose levels (hypoketotic hypoglycemia). Although the severity varies, everyone with PCD is at risk for heart failure, liver disease, and sudden death. Symptoms are often triggered by periods of fasting, including sleeping or illness. PCD is quite similar in manifestations to medium-chain acyl-CoA dehydrogenase (MCAD) deficiency; however, labs will show reduction in total and free carnitine levels without an increase in medium-chain fatty acids. Patients with PCD are also at higher risk for rhabdomyolysis, skeletal hypotonia, and cardiomyopathy. PCD can often be mistaken for Reye syndrome, which is caused by the use of aspirin during viral infections like chicken pox or flu. An adequate history can be used to rule out Reye syndrome. Although symptoms may be similar to glycogen storage disorders, disorders of fatty metabolism typically manifest after prolonged exercise and do not improve with rest periods (no second-wind phenomenon).

CASE 5 | Ornithine Transcarbamylase Deficiency (OTC) (Urea Cycle Disorders)

A 7-day-old boy is brought in for evaluation of poor feeding, lethargy, vomiting, and irritability. Physical examination is significant for hypotonia and hepatomegaly.

Evaluation/Tests	Labs show high ammonia, low citrulline in the blood, and high orotic acid in urine.
Treatment	Limit dietary protein intake, advise high-calorie diet and essential amino acid supplements.
Discussion	Ornithine transcarbamylase (OTC) deficiency is the most common urea cycle disorder caused by an X-linked recessive complete or partial deficiency of ornithine transcarbamylase, which is needed for the breakdown and removal of nitrogen in the urea cycle. The first step of the urea cycle involves conversion of CO_2 and ammonia into carbamoyl phosphate. OTC then combines carbamoyl phosphate with ornithine to form citrulline, allowing for entry into the remainder of the urea cycle. Defects in OTC thus prevent progression through the cycle, resulting in accumulation of ammonia and decreased citrulline in the blood. Excess carbamoyl phosphate is then converted to orotic acid (part of the pyrimidine synthesis pathway). Deficiency results in hyperammonemia, which affects the CNS and stimulates increased respiration. Symptoms can vary based on the degree of enzyme deficiency and in the severe form can occur within 24 hours after birth, after a protein feed. Symptoms include poor suckling, vomiting, lethargy, irritability, and seizures. Hypotonia, hepatomegaly, and respiratory difficulties can lead to intellectual disability, developmental delay, coma, and death if untreated. **Orotic aciduria** is an autosomal recessive disorder that may present similarly to OCT deficiency but instead involves an enzyme deficiency in the *de novo* pyrimidine synthesis pathway, whereby orotic acid cannot be converted to uridine monophosphate (UMP) due to a mutation in UMP synthase. Orotic aciduria will result in orotic acid crystals in urine, megaloblastic anemia, and failure to thrive, but it lacks the hyperammonemia seen in OTC deficiency.

DEVELOPMENTAL DELAY OR REGRESSION

Many inborn errors of metabolism can present with either developmental delay or regression. While these terms are often used interchangeably, they are discrete entities. Developmental delay refers to failure of a child to meet specific milestones related to speech, motor, or cognitive development. Developmental regression is used to describe a condition in which a child who has already met normal developmental milestones then loses that function or reverts back to an earlier stage.

Developmental delay is seen in various inborn errors of metabolism such as lysosomal storage diseases, a group of inherited disorders caused by deficiencies in key lysosomal enzymes. These deficiencies result in accumulation of abnormal metabolic products that can become toxic to cells. Depending on the condition, accumulation of these abnormal products in cells (e.g., neurons) can take some time before they begin to interfere with normal physiologic processes, at which point regression may occur. Another group of disorders where developmental delay or regression may be observed is in the metabolism of amino acids. Disruption in the synthesis of essential amino acids can result in toxic accumulation of metabolites and disrupt normal cellular processes.

CASE 6 | Tay-Sachs Disease

A 10-month-old infant is brought in for evaluation of new-onset seizures and change in her ability to perform activities. This was first noticed after 6 months when she gradually lost her ability to sit and could no longer grasp objects. She became less interactive and lost interest in eating. On exam, she is underweight and her funduscopic exam reveals a central area of reddening in the retina bilaterally ("cherry-red spot"). She has exaggerated reactions to loud noises, muscle weakness, and movement problems.

Evaluation/Tests	Genetic testing reveals a deficiency in hexosaminidase A and accumulation of GM2 ganglioside.
Treatment	No cure; goal of treatment is support and comfort.
Discussion	Tay-Sachs disease is an autosomal recessive lysosomal storage disorder caused by a defect in the enzyme hexosaminidase A. This results in accumulation of GM2 ganglioside, particularly in neurons. A classic feature observed in the retina is a "cherry-red spot" in the macula. This is due to the accumulation of GM2 ganglioside within the ganglion cell layer of the retina, which is thicker within the macula. This makes the spot appear red in color, while the rest of the retina is pale. Other characteristic features include developmental regression, muscle weakness, hypotonia, seizures, blindness, macrocephaly, and abnormal startle reflexes. Lysosomal accumulation occurs predominantly in cells and organs that have the highest rates of biosynthesis or uptake of the undegradable sphingolipids and their precursors. Biopsy of affected tissue would show lysosomes with an "onion skin" morphology. The reticuloendothelial system (encompassing macrophages in lymphoid organs, liver, spleen, and more) is unaffected, so there is no hepatosplenomegaly. **Niemann-Pick disease** is an autosomal recessive lysosomal storage disorder caused by a defect in the enzyme sphingomyelinase. This results in accumulation of sphingomyelin, which can lead to cellular malfunction, particularly in the brain, spleen, liver, and lungs. Characteristic features include progressive neurodegeneration, hepatosplenomegaly, cherry-red spot on the macula, and loss of previously acquired milestones; blood smear will show lipid-laden macrophages or "foam cells." Cherry-red spots on the macula can also be seen in **central retinal artery occlusions**; however, this is typically seen in adults with underlying cardiovascular risk factors and typically presents unilaterally.

CASE 7 | Hurler Syndrome (Mucopolysaccharidosis Type I)

A 3-year-old boy is brought in for evaluation of developmental delay in milestones and hearing loss. The child is cognitively delayed for his age, as he is only able to say a few words. He has coarse facial features with a large head, flattened nasal bridge and large lips, corneal clouding, short stature for his age, hepatosplenomegaly, umbilical hernia, limited joint mobility, and cognitive impairment.

Evaluation/Tests	Enzyme assay shows a deficiency of α-L-iduronidase. There is an accumulation of glycosaminoglycans/mucopolysaccharides in urine.
Treatment	Enzyme replacement therapy and human stem cell transplantation.
Discussion	Hurler syndrome is a lysosomal storage disease under the subcategory of mucopolysaccharidoses caused by an autosomal recessive mutation in the gene encoding α-L-iduronidase. Mutation results in the accumulation of mucopolysaccharides, including heparan sulfate and dermatan sulfate. Clinical features of Hurler syndrome present in infancy or early childhood with coarsening of facial features, corneal clouding, dysostosis multiplex (skeletal anomalies), hearing loss, and neurological deterioration. Developmental delay is a key feature. The accumulation of glycosaminoglycans increases with age. At a certain point, this accumulation interferes with the normal biologic function of the tissue. This is responsible for developmental regression.

CASE 7 | Hurler Syndrome (Mucopolysaccharidosis Type I) *(continued)*

Discussion	A similar defect is seen in **Hunter syndrome**, another mucopolysaccharidosis that is X-linked recessive and that is often milder than Hurler syndrome, where patients lack corneal clouding but display aggressive behavior. Hunter syndrome is caused by a defect in iduronate-2-sulfatase.

CASE 8 | Phenylketonuria (PKU)

A 2-year-old boy is brought in for evaluation of progressive developmental delays and growth retardation over the last year. He was born at-term after an uneventful pregnancy. His parents state that he took a much longer time to hold his head up, sit, walk, and talk compared to his older siblings. His parents noted a distinct musty body odor. On physical exam, his height and weight are below the 5th percentile for age, and he has light-colored hair and eyes and eczema.

Evaluation/Tests	Cognitive testing consistent with significant delays. Phenylalanine levels are elevated, and urine is positive for phenylketones. Tyrosine and tetrahydrobiopterin levels are low. Genetic testing shows a mutation in phenylalanine hydroxylase.
Treatment	Restrict phenylalanine and increase tyrosine in the diet. Tetrahydrobiopterin cofactor supplementation.
Discussion	Phenylketonuria (PKU) is an autosomal recessive disorder involving a mutation in the enzyme phenylalanine hydroxylase (PAH), which converts phenylalanine to tyrosine. PKU can also be caused in rare instances by disorders of tetrahydrobiopterin (BH4) synthesis, which is a PAH cofactor. Deficiency of phenylalanine hydroxylase leads to toxic accumulation of phenylalanine and its metabolite phenylpyruvic acid. Newborns have no symptoms due to clearance of phenylalanine by the placenta. If left untreated, it will manifest in delayed development, microcephaly, seizures, and behavioral problems. Affected individuals are hypopigmented due to deficiency of tyrosine, which is the starting point in melanin synthesis. Patients may also have a musty body odor, which comes from phenylalanine metabolites. Newborn screening is widely practiced, allowing initiation of a phenylalanine-restricted diet before the onset of neurological damage.

INTELLECTUAL DISABILITY

Several genetic disorders can result in intellectual disability. Compared to developmental delay, intellectual disability is used to describe patients with broad impairments in cognition that limit their ability to learn at the expected level for their age and function in everyday life. It is typically associated with an intelligence quotient (IQ) less than 70 (median IQ is 100) and is diagnosed prior to the age of 18.

Here, we will cover two groups of genetic abnormalities: trinucleotide repeat expansion diseases and disorders of genomic imprinting. **Trinucleotide repeat expansion diseases** are the result of mutations in which repeats of three nucleotides result in an increase in copy number. Many of these trinucleotide repeats occur naturally; however, once their copy number exceeds a given threshold, they can cause chromosome instability and altered gene expression, which leads to manifestation of different disease types. Not all trinucleotide-repeat diseases present with intellectual disability because it is highly dependent on the particular gene involved.

Genomic imprinting is a normal phenomenon in some genes whereby epigenetic modifications (typically methylation) result in the transcriptional silencing of one gene copy from either maternal or paternal origin, leading to expression in a parent-specific fashion. The two classic disorders of genomic imprinting are Prader-Willi syndrome and Angelman syndrome. The disease phenotype of the patient depends on whether the maternal- or paternal-derived genes are silenced. When the remaining nonsilenced gene undergoes a microdeletion, the disease will occur. These diseases may also be caused by **uniparental disomy**, whereby both chromosome copies are inherited from a single parent. This can result in the silencing of both copies, resulting in disease.

CASE 9 | Prader-Willi Syndrome

A 14-year-old boy is brought to the clinic for evaluation of hypotonia and intellectual disability. His mother notes that he had feeding difficulties as an infant, but since then has developed an insatiable appetite and behavioral problems. The boy has dysmorphic facial features including almond-shaped eyes, narrow forehead, short stature, and small hands and feet, but he is also obese with a BMI of 31. Neurologic exam reveals diminished muscle tone and poor reflexes. Remainder of the exam is normal except for hypogonadism.

CASE 9 | Prader-Willi Syndrome *(continued)*

Evaluation/Tests	Genetic testing showed deletion of the paternal chromosome 15q11-13 and DNA methylation studies were positive on maternal chromosome 15q.
Treatment	Symptomatic treatment and strict supervision of food intake. Genetic counseling and growth hormone supplementation.
Discussion	Prader-Willi syndrome is a disorder of genomic imprinting. Genomic imprinting is a normal phenomenon whereby certain gene segments inherited from either the mother or father normally undergo methylation to silence that gene copy. Normally, certain segments of chromosome 15q11-13 show methylation and silencing of maternal gene copies. In addition to this normal imprinting, in Prader-Willi syndrome there is either a deletion or mutation in the corresponding paternal allele that is normally expressed. Some cases are also caused by maternal uniparental disomy (25% of cases), whereby the child receives two maternal chromosomes, which are then both silenced through genomic imprinting mechanisms. Either of these genetic alterations results in the absence of the normal paternal gene contribution to this chromosome. Clinical features of Prader-Willi syndrome at birth include hypotonia, lethargy, and feeding difficulties. Some of these features gradually resolve, but patients develop hyperphagia by early childhood, which results in (often significant) obesity. There is also intellectual disability and hypogonadism. Genetic testing is key to confirming the diagnosis and ruling out other causes.
Additional Considerations	**Fragile X syndrome (FXS)** is an X-linked dominant disorder caused by an expansion of a CGG triplet repeat in the promoter region of the *FMR1* gene. Repeat number ranges from 6 to 40 in the general population. Individuals with this syndrome have more than 200 repeats, accompanied by methylation of the promoter, which leads to silencing of the gene. FXS is the most common cause of inherited intellectual disability. Additional manifestations include developmental delay, behavioral problems (attention deficits, hyperactivity, autism spectrum disorder, etc.), dysmorphic facial features (long, narrow face, prominent forehead and chin, large head circumference, large everted ears, etc.), and macroorchidism. Patients are also at risk of developing mitral valve prolapse. **Angelman syndrome** is a disorder of genomic imprinting resulting from the absence or mutation of maternal alleles on chromosome 15. The most common gene affected is *UBE3A*. Normally, children inherit one allele from each parent, the paternally derived copy is methylated and silenced, and the maternally derived copy is expressed. In Angelman syndrome, there is a mutation or deletion in the maternal copy. Clinical features include severe intellectual disability, movement disorders, seizures, developmental delays, learning disabilities, ataxia, tremulousness, and decreased to absent speech. A distinct pattern of unprovoked episodes of laughter and smiling is observed in the disease. Similar to Angelman syndrome, **Rett syndrome** is seen almost exclusively in girls and is due to an X-linked *de novo* mutation in *MECP2*. Affected males die *in utero* or shortly after birth. Symptoms appear in early childhood and include developmental regression, ataxia, seizures, and stereotypical hand-wringing, but lack episodes of inappropriate laughter seen in Angelman syndrome.

DYSMORPHIC FEATURES

Several syndromes present with dysmorphic features, the recognition of which will help identify the underlying abnormality. Dysmorphic features are differences in normal structural development and may involve facial structures, upper or lower extremities, or other areas of the body. The presence of multiple dysmorphic features increases the likelihood of a single unifying cause such as genetic syndrome or congenital birth defect. However, sometimes it is difficult to actually resolve dysmorphic features because they may be subtle, so comparison to parents or siblings may be helpful. Further, genetic testing should be performed to confirm any suspicions.

The most pathognomonic syndromes associated with dysmorphic features are the chromosomal abnormalities resulting in inheritance of three copies of a chromosome (trisomy) rather than two. Karyotype analysis will be diagnostic, although ultrasonography and other serum tests are available. Most trisomies are not viable and will result in spontaneous miscarriage, typically within the first trimester. The only viable trisomies are trisomies 21, 18, and 13. In addition to trisomies, other chromosomal abnormalities may involve translocations, deletions, or microdeletions.

CASE 10 | Down Syndrome (Trisomy 21)

A newborn baby boy born to a 42-year-old mother is noted to have hypotonia and dysmorphic features. The child's length is low for gestational age, and he has a flat occiput with bilateral epicanthal folds. His neck is short with loose skin at the nape. Hands are short and broad with a curved fifth digit and a single palmar crease.

CASE 10 | Down Syndrome (Trisomy 21) *(continued)*

Evaluation/Tests	Chromosomal karyotype—47,XY+21
Treatment	Supportive—early childhood intervention, screening for common problems (heart and cognitive issues), work-related training.
Discussion	Down syndrome (Trisomy 21) is an autosomal trisomy involving the presence of three copies of chromosome 21. It is the most common viable chromosomal disorder and the most common cause of noninherited genetic intellectual disability (vs. inherited, which is Fragile X syndrome). Most often Down syndrome is due to maternal meiotic nondisjunction. Risk of meiotic nondisjunction increases with advanced maternal age as in this case. Rarely, cases can be due to an unbalanced Robertsonian translocation between chromosome 21 and another chromosome, usually 14. First-trimester ultrasound shows increased nuchal lucency and hypoplastic nasal bone with increased free beta-HCG. Second-trimester ultrasound shows decreased alpha-fetoprotein, increased beta-HCG, decreased estriol, and increased inhibin A. Children have weak muscle tone (hypotonia) at birth and may have congenital anomalies, especially cardiac and gastrointestinal. In childhood, duodenal atresia and congenital heart defects (e.g., atrial septal defect) predominate, along with atlantoaxial instability as the child grows. Hirschsprung disease and Brushfield spots in the iris are often present. Characteristic facial features include flat facies, prominent epicanthal eye folds and furrowed tongue. Other characteristics include short fingers and toes, curved fifth finger (clinodactyly), and a wide space between the first and second toes. Intellectual disability is common with delayed cognitive development, although this can vary. There is an increased risk of respiratory infection during childhood and a higher risk of leukemia (AML and ALL) than the general population. Adults are at risk of early-onset Alzheimer disease because the amyloid precursor protein is found on chromosome 21.
Additional Considerations	**Edwards syndrome (Trisomy 18)** is an autosomal trisomy involving the presence of three copies of chromosome 18 due to meiotic nondisjunction. This is one of the three viable trisomies; however, death usually occurs by age 1. Infants with trisomy 18 are born with multiple congenital anomalies. Most notable are low birth weight, prominent occiput, low set ears, a small jaw (micrognathia), and tightly clenched fingers. Internal organ malformations, especially congenital heart disease, are common. Serum marker screening shows decreased alpha-fetoprotein, decreased beta-HCG, decreased estriol, and decreased or normal inhibin A. Clenched fists and rocker bottom feet are often seen on ultrasonography and after birth. **Patau syndrome (Trisomy 13)** is the rarest viable autosomal trisomy involving the presence of three copies of chromosome 13 due to meiotic nondisjunction. This is one of the three viable trisomies; however, death usually occurs by age 1. Infants with Trisomy 13 are born with low birth weight and have multiple congenital anomalies, affecting the heart (congenital heart disease), brain (holoprosencephaly), and kidneys (polycystic kidney disease). Most notable are facial anomalies, including hypotelorism (eyes are closer together than normal), cleft lip and palate, microphthalmia (small eyes), and microcephaly. There may be areas of deficient or absent skin in the scalp (cutis aplasia), polydactyly and "rocker bottom feet." The first-trimester screen shows decreased free beta-HCG and decreased PAPP-A.

PEDIATRIC OPHTHALMOLOGIC ABNORMALITIES

Ophthalmologic abnormalities in a newborn should raise suspicion for genetic or biochemical abnormalities. Inborn errors of galactose metabolism commonly present with ophthalmologic abnormalities including cataracts or leukocoria (loss of red reflex) in newborns. Similar to the metabolism of fructose, galactose metabolism is not well regulated; however, symptoms tend to be more severe in disorders of galactose metabolism compared to analogous ones of fructose metabolism. This is related to the formation of galactitol, an osmotically active form of galactose which can be trapped in cells such as the lens of the eye, retina, kidneys, and Schwann cells. Genetic mutations that may give rise to visual deficits include mutation of the tumor suppressor gene *Rb*, giving rise to retinoblastoma. Identification of specific features may help narrow the differential diagnosis and focus in on the genetic or biochemical pathways involved.

CASE 11 | Classic Galactosemia

A 1-week-old girl who is breast-fed is brought in for evaluation due to poor feeding, vomiting, and lethargy. The baby also is failing to thrive. Physical exam is notable for hepatomegaly, jaundice, and presence of opacification of the lens in each eye.

CASE 11 | Classic Galactosemia *(continued)*

Evaluation/Tests	Galactose is present in the blood and urine. Blood chemistry reveals elevated liver enzymes and hypoglycemia. Feeding with a glucose solution is well tolerated, but formula causes vomiting.
Treatment	Remove lactose and galactose from the diet.
Discussion	Classic galactosemia is an autosomal recessive disorder due to the absence of the rate-limiting enzyme of galactose metabolism, galactose-1-phosphate uridyltransferase. This enzyme converts galactose-1-phosphate to glucose-1-phosphate, which can then undergo glycolysis or glycogenesis. Deficiency in this enzyme results in accumulation of two toxic substances (vs. only one seen in galactokinase deficiency): galactose (and osmotically active galactitol, which can accumulate in the lens) and galactose-1-phosphate, which can also be toxic. Symptoms of classic galactosemia begin much earlier and are more severe compared to those seen in galactokinase deficiency. Symptoms develop when an infant begins feeding (lactose is present in breast milk and formula) and include failure to thrive, jaundice, hepatomegaly, infantile cataracts, and intellectual disability. This can predispose neonates to *E. coli* sepsis. Patients with galactosemia become hypoglycemic within several hours of ingestion of galactose. Galactose is one of the degradation products of lactose (along with glucose) found in dairy products, breast milk, and many baby formulas. **Galactokinase deficiency** is an autosomal recessive disorder involving the first step in galactose metabolism, by which galactose is normally converted to galactose-1-phosphate by the enzyme galactokinase. Galactose accumulates in many tissues and can be converted by aldose reductase to the osmotically active substance galactitol. This can drive fluid accumulation in certain tissues such as the lens. Galactokinase deficiency is relatively mild, but characteristic features include galactosemia, galactosuria, infantile cataracts, failure to track objects, and failure to develop a social smile, which is normally present by 6–8 weeks of age. It can be distinguished from classic galactosemia by the fact that there is no accumulation of galactose-1-phosphate.

CASE 12 | Retinoblastoma

A 2-year-old boy is referred to the ophthalmologist because the right pupil appears white on examination. He has right-sided strabismus, leukocoria (pupil appeared white), nystagmus, a bulging of the eyeball, and decreased visual acuity.

Evaluation/Tests	Ophthalmoscopic examination under anesthesia reveals a chalky, off-white retinal mass with a soft, friable consistency. Lens appears normal. Ultrasound reveals a normal-sized globe with calcification of the mass. MRI shows no involvement of the optic nerve. Biopsy is contraindicated due to risk of tumor seeding. Molecular genetic testing reveals a mutation in the *Rb* gene.
Treatment	Local and systemic chemotherapy, cryotherapy, laser photoablation, radiotherapy, and, rarely, enucleation and genetic counseling.
Discussion	Retinoblastoma is a cancer of the retina caused by a mutation in the *Rb* tumor suppressor gene, which results in loss of heterozygosity. Loss of heterozygosity is an important concept for tumor suppressor genes and supported by the "two-hit hypothesis" whereby both alleles must be mutated or deleted before a cancer is able to develop. Normally, a patient inherits two functional copies or alleles of a tumor suppressor gene. If a patient inherits a single dysfunctional allele, the remaining allele is often sufficient to protect against neoplastic transformation. However, mutations are quite common in somatic cells, and these patients have an increased risk of acquiring a "second-hit" mutation in their remaining allele, predisposing them to the development of retinoblastoma in later childhood or adolescence. Those who inherit two defective alleles (hereditary retinoblastoma) will develop retinoblastoma much earlier in life. Both familial and *de novo* cases can occur.

Leukocoria of the left eye caused by retrolental membrane (persistent hyperplastic primary vitreous or persistent fetal vasculature).
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CASE 12 | Retinoblastoma *(continued)*

Discussion	Retinoblastoma is often detected due to the reflection of light off the tumor, which causes the pupil to appear white (leukocoria). This is sometimes noticed in photographs. Affected children are at increased risk for developing second cancers (commonly osteosarcoma, specifically in hereditary retinoblastoma) in addition to consequences of systemic chemotherapy like hearing loss with carbo-platin therapy. The *Rb* gene on chromosome 13 encodes a nuclear protein that regulates the G1 to S checkpoint of the cell cycle. Normally it is in an active, hypophosphorylated state that prevents progression to the S phase by binding to the E2F transcription factor; however, mutations result in abnormal hyperphosphorylation, resulting in release of E2F and unregulated progression through the cell cycle.

MUSCLE WEAKNESS

Muscle weakness, or myopathy, is a presenting feature of several disorders of metabolism or neurologic disorders. Approaches to a patient with myopathy can be based on the age of the patient, family history, pattern of involvement, associated signs and symptoms, and diagnostic test results.

Muscular dystrophies are genetic disorders with various forms of inheritance that result in progressive weakness and muscle atrophy due to defects in proteins important in the structure and function of muscle cells. To distinguish between different forms of muscular dystrophy, pay attention to the pattern of inheritance (X-linked, autosomal dominant, etc.) and pattern of myopathy (starts with proximal vs. distal muscles).

Mutations in mitochondrial DNA (mtDNA) are inherited from the mother and can result in a heterogenous group of disorders called mitochondrial myopathies. Although all children inherit the mutation from the affected mother, only the daughters can pass it on to their children. The difference in expression of mitochondrially inherited disease among different members of the same family (heteroplasmy) is due to involvement of different organs and the uneven distribution of normal and mutant mtDNA in different tissues. The systems that tend to be affected the most are the central nervous system, cardiac, respiratory, eye, and endocrine in addition to muscles because they contain the most metabolically active cells.

Another common cause of myopathy or hypotonia (decreased muscle tone) are inborn errors of metabolism affecting glycogen and lipid storage and transport pathways. Glycogen is an important storage source of carbohydrates; breakdown of glycogen via glycogenolysis is used to maintain blood sugar, especially during times of increased need such as exercise or stress. Failure to adequately break down glycogen and convert to glucose results in characteristic features including exertional myalgias, rhabdomyolysis, cardiorespiratory involvement, and exercise intolerance. Some patients may experience a "second wind" phenomenon whereby after a period of rest, if the patient resumes exercise, increased blood flow to muscle can provide other substrates such as glucose and free fatty acids instead of glycogen, leading to improvement in symptoms. Lipids are an additional important source of energy that can be used by the body under periods of prolonged exercise, fasting, or stress when normal glycogen stores have been depleted via conversion to ketone bodies. Patients with defective lipid metabolism are unable to produce ketone bodies so they present with hypoketotic hypoglycemia.

CASE 13 | Duchenne Muscular Dystrophy (DMD)

A 5-year-old boy is brought in for evaluation of progressive difficulty in getting up from a sitting position. His father says every time he tries to sit up, he needs to "walk up his legs with his hands." He has also been unable to keep up with his playmates for the last couple of years. On exam, there is weakness and wasting of muscles of upper legs, arms and shoulder, hypertrophy of calf muscles, waddling gait, and significant difficulty climbing stairs.

Evaluation/Tests	Serum CK is elevated. Muscle biopsy showed muscle fiber degeneration and necrosis and complete absence of dystrophin. Genetic tests were positive for a frameshift mutation in the *DMD* gene.
Treatment	There is no cure. Symptomatic treatment includes physical therapy and steroids to improve muscle strength.
Discussion	Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by a frameshift mutation in the *DMD* gene, which encodes the muscle membrane protein dystrophin. Frameshift mutations involve a deletion or insertion of a number of nucleotides not divisible by 3, therefore disrupting the reading of all downstream codons. In DMD, this leads to a complete lack of dystrophin production. Dystrophin normally

CASE 13 | Duchenne Muscular Dystrophy (DMD) *(continued)*

Discussion	helps anchor muscle fibers in cardiac and skeletal muscle. Lack of dystrophin causes myonecrosis, resulting in weakness and atrophy of the muscles commonly starting around 3–5 years of age, starting in the proximal muscles such as the pelvic girdle and then progressing superiorly. There is often associated cardiomyopathy, and there may be cognitive dysfunction. Features include waddling gait, difficulty climbing stairs, using upper extremities to stand up from a sitting position (Gower sign), and repeated falling. Calf pseudohypertrophy occurs due to replacement of muscle by fibrofatty tissue. Serum CK levels are at least 10–20 times (often 50–200 times) the upper limit of normal. Due to early onset, affected children are usually wheelchair-bound by adolescence. Death is common in the twenties, often due to dilated cardiomyopathy. **Becker muscular dystrophy (BMD)** is also an X-linked recessive muscular dystrophy; however, it results from nonframeshift deletions in the dystrophin gene, resulting in partial loss of function. BMD is therefore less severe, may present later in life (adolescence or early adulthood), progresses more slowly, and patients may survive into their forties or beyond.

CASE 14 | Myotonic Dystrophy Type 1

A 32-year-old man presents with progressive distal muscle weakness. Symptoms started when he was 20 years old. He has difficulty releasing objects after he grasps them and notes declining strength in upper and lower extremities. Family also reports memory loss and hypersomnia. His father had similar symptoms that began much later in his life. Physical exam is notable for ptosis, cloudy opacity in his lenses, and frontal balding. He has wasting in his proximal and distal muscles, prolonged muscle tension (myotonia), and testicular atrophy. No upper motor neuron defects are noted.

Evaluation/Tests	Creatinine kinase is elevated. Muscle biopsy shows a high number of nuclei and marked variation in fiber diameter with splitting fibers and adipose deposition. Genetic testing shows expansion of unstable CTG trinucleotide repeat in the *DMPK* gene on the long arm of chromosome 19.
Treatment	Supportive care with braces, scooters, or wheelchairs.
Discussion	An autosomal dominant inherited expansion of a CTG trinucleotide in the noncoding region of the DMPK gene, results in Myotonic dystrophy type 1. When this gene with expanded CTG repeats is transcribed, the abnormal RNA produced causes cellular dysfunction leading to the symptoms of myotonic dystrophy. Normal alleles include 5–35 repeats; full penetrance alleles are >50 repeats. During meiosis in germ cells, these unstable repeats can be expanded, thus increasing the number of repeats in offspring through a process known as genetic anticipation that may increase the severity of disease and lower the age of onset from generation to generation. Patients with myotonic dystrophy type 1 typically present at 20–40 years old, and men and women are equally affected (as opposed to DMD and BMD where primarily men are affected because of their X-linked inheritance patterns). Besides myotonia, affected individuals exhibit muscle weakness, wasting effect, frontal balding, cataracts, and testicular atrophy. A key feature is difficulty releasing objects after grasping them due to myotonia (delayed relaxation after muscle contraction). More distal muscles (lower legs, hands, face, etc.) are often affected first. They often develop dysphagia, generalized weakness, and respiratory failure. Cardiac conduction defects, resulting in arrhythmia, are common.

CASE 15 | Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-Like Episodes (MELAS) Syndrome

A 6-year-old girl is brought to clinic for evaluation of left-sided muscle weakness in her face, arm, and leg. Per her mother, the patient had complained of a bad headache and had convulsions the night prior to presentation. Her brother had a similar disorder and passed away a few years ago. On exam, she appears confused, is tachypneic, and aphasic, and her strength is diminished on the left side.

Evaluation/Tests	CBC and CMP are normal, and lactate level is high. ABG shows pH 7.3, PO2 72 mmHg, and PCO2 50 mmHg. MRI shows multiple small infarcts in the parietal and occipital lobes on the right side. EEG shows prominent and diffuse periodic epileptiform discharges. Genetic testing reveals a mutation in the mitochondrial DNA gene *MT-TL1*. Muscle biopsy reveals the presence of ragged red fibers.
Treatment	No specific treatment. Anticonvulsants are used to help prevent and control seizures.

CASE 15 | Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-Like Episodes (MELAS) Syndrome *(continued)*

Discussion	A mutation of mitochondrial genes (*MT-TL1* is most common) results in a maternally transmitted myopathy of variable expression (heteroplasmy) affecting energy metabolism in multiple tissues and is known as **MELAS** (Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). It often presents as stroke like episodes in childhood with focal neurologic deficits and imaging findings suggestive of infarctions. Other presenting symptoms include seizures, ataxia, myopathy and lactic acidosis with gradual loss of cognitive function. **Myoclonic epilepsy with ragged red fibers (MERRF)** is another mitochondrial myopathy caused by a mutation in the *MT-TK* gene encoding mitochondrial lysine-tRNA. It differs from MELAS in that the strokes are more generalized and myoclonic jerks are seen. Additionally, optic atrophy, hearing loss, and cardiomyopathy are commonly present. Muscle biopsy for both MELAS and MERRF show ragged red fibers on Gomori trichrome stain. mtDNA mutations associated with MERRF are diagnostic and can usually be detected in white blood cells.

CASE 16 | McArdle Disease (Glycogen Storage Disease Type V)

A 20-year-old man presents with myalgias, cramps, and easy fatigability since childhood. Symptoms are worse with moderate exercise and improve after a brief period of rest. He also notes red urine after moderate activity.

Evaluation/Tests	Blood glucose is normal. Forearm exercise test (patient performs maximal effort handgrips for one minute, then blood samples are drawn) shows inability to produce lactate (deficient glycogenolysis). Muscle biopsy–PAS staining shows increased glycogen-containing vacuoles. Genetic testing shows defect in *PYGM* gene encoding muscle glycogen phosphorylase (myophosphorylase).
Treatment	No cure, but diet and exercise strategies such as consuming sucrose before low-moderate activity can help control symptoms.
Discussion	This individual has McArdle disease (glycogen storage disease type V), an autosomal recessive deficiency of skeletal muscle glycogen phosphorylase (myophosphorylase). Glycogen phosphorylase removes glucose-1-phosphate off of branched glycogen until four glucose units remain. Defects in glycogen phosphorylase, therefore, prevent the quick liberation of glucose-1-phosphate molecules during periods of exercise or stress. Because it only involves skeletal muscle, blood glucose levels are typically unaffected (unlike in von Gierke disease). The key features are exercise intolerance, myoglobinuria with exercise, and a characteristic "second wind" phenomenon in young adults due to increased blood flow and conversion of glycogen metabolism to other sources of energy. Ischemic forearm exercise test shows no increase in pyruvate and lactate levels in venous blood from contracting ischemic forearm muscles. The lack of increase in pyruvate and lactate levels is because the muscles cannot utilize their glycogen stores. **Carnitine palmitoyltransferase (CPT) II deficiency** can present similarly and results in low carnitine levels and inability of muscles to use certain long-chain fatty acids (LCFAs) as an energy source. This results in a breakdown of muscle fibers. Labs would show decreased CPT II activity, increase in long-chain C16 and C18 plasma acylcarnitine levels, hypoketotic hypoglycemia, elevated creatine phosphokinase (CPK), and myoglobinuria.

CASE 17 | Pompe Disease (Glycogen Storage Disease Type II)

A newborn is noted to have hypotonia and a heart murmur after an uncomplicated birth. On physical exam, notable findings included macroglossia, hepatomegaly, and severe hypotonia.

Evaluation/Tests	Echocardiogram shows severe biventricular cardiac hypertrophy. Labs notable for normal glucose and increased serum lactate, AST, and ALT. Lysosomal enzyme acid-α-1,4-glucosidase activity is low.
Treatment	Treat with enzyme replacement therapy.
Discussion	Pompe disease (GSD type II) is an autosomal recessive condition involving deficiency in the lysosomal acid α-1,4-glucosidase (acid maltase) enzyme. Early-onset Pompe disease presents in the first year, typically as a floppy-baby with severe hypotonia. Unique to this form of GSD, patients present with cardiac abnormalities including cardiomegaly and hypertrophic cardiomyopathy. Other symptoms

CASE 17 | Pompe Disease (Glycogen Storage Disease Type II) *(continued)*

Discussion	include exercise intolerance, hypotonia, failure to thrive, hepatomegaly, and other systemic findings such as respiratory failure, which can lead to early death. Glycogen deposits can be observed in muscle, liver, and cardiac tissue. Later-onset Pompe disease can present with difficulty rising from a chair or climbing stairs or with morning headaches and fatigue. Pompe disease patients often have elevated lactic acid and CK levels. Glucose levels are often normal in Pompe disease, helping differentiate it from hypoglycemia in **Von Gierke disease**, in which glucose cannot be released due to deficiency of glucose-6-phosphatase.

BONE AND JOINT ABNORMALITIES

Several types of biochemical disorders present with abnormalities in bone, cartilage, and joints. One such group involves mutations in extracellular matrix proteins such as collagen or fibrillin. Given the important role of extracellular matrix proteins in forming the basement membrane underlying blood vessels, these disorders may also present with bruising and vascular damage.

Another group of disorders involves defects in metabolic pathways that lead to the accumulation of crystals that can deposit in joints and induce an inflammatory response. They typically have abnormalities in urine, behavioral disturbances, and systemic manifestations, which suggest a systemic process and helps distinguish them from other types of arthritis.

CASE 18 | Osteogenesis Imperfecta

A 13-year-old boy is referred by the school nurse to clinic for suspicion of child abuse. He has a history of recurrent fractures in the forearms and legs after minor falls, which started when he was 1 year old. These fractures healed without significant delays. Physical exam reveals blue sclera, decreased hearing, an overbite, and bowing of tibia and fibula.

Evaluation/Tests	X-rays show multiple fractures. Audiogram confirms bilateral hearing loss. Genetic testing reveals mutations in type I collagen (*COL1A1* gene).
Treatment	Supportive care, exercise, physical therapy, and surgery for fractures.
Discussion	Osteogenesis imperfecta (OI) is a genetic bone disorder often caused by mutations in genes encoding components of type I collagen (*COL1A1* and *COL1A2*). The mutation impairs triple helix formation and is commonly inherited in an autosomal dominant fashion. The basic phenotype of OI is the occurrence of brittle bones with high tendency to fracture even with minimal trauma, which occurs because type 1 collagen is the main type of collagen in osteoid. Fractures occur in locations that are not typical and can occur as early as *in utero* or at childbirth. In some instances, it is associated with short stature. Other features include blue sclera due to translucent connective tissue overlying choroidal veins, hearing loss from abnormal ossicle formation, and dentinogenesis imperfecta (weakening of the teeth). There is a wide range of variable expression, including neonatal onset with lethality early in life, to relatively mild symptoms.

CASE 19 | Ehlers-Danlos Syndrome (EDS)

A 30-year-old woman presents for evaluation of increased bruising, achy muscles and increased fatigue. As a teenager, she had recurrent dislocations of her shoulder when playing softball. On physical exam, she has a high-arched palate, hypotonia, and flat feet. She is able to place her hands flat on the floor without bending her knees. She can bend her thumb to touch her forearm. Dermatologic exam shows cigarette paper–like scars over her knees and hyperelastic skin that can be pulled about an inch without any pain.

Evaluation/Tests	Skin biopsy shows a relative increase in the elastic fibers with scant collagenous fibers showing cauliflower-like degeneration. Genetic tests and electron microscopy show collagen structure abnormalities.
Treatment	Monitor for complications and provide physical therapy.

CASE 19 | Ehlers-Danlos Syndrome (EDS) *(continued)*

Discussion	Ehlers-Danlos syndrome (EDS) has multiple forms and can be genetically heterogeneous with most forms being autosomal dominant. The classic form of EDS has mutations in the genes encoding peptides involved in forming type V collagen (*COL5A1* and *COL5A2*). There is joint hypermobility and instability, as well as soft, velvety, hyperelastic skin. There is delayed, abnormal wound healing and generalized tissue fragility. The vascular form of EDS results from a mutation in type III procollagen and has more systemic tissue fragility affecting large vessels such as aorta, muscles, and other organs. Vessel fragility in the vascular form of the disease makes them prone to rupture, and affected patients can have berry aneurysms and aortic aneurysms.

CASE 20 | Marfan Syndrome

A 13-year-old boy presents for evaluation of poor vision. On exam, he is in the >99th percentile for his height, is very thin, and has myopia. Additionally, he has disproportionately long, slender arms, legs, fingers, and toes (arachnodactyly); pectus carinatum with protruding chest; joint hypermobility (able to bend his fingers back to touch the dorsum of his hands); flat feet; and scoliosis. On cardiac auscultation, he is noted to have a high-pitched "blowing" early diastolic murmur heard best over the left sternal border.

Evaluation/Tests	Echocardiogram shows aortic root dilatation and aortic regurgitation. Detailed eye exam reveals lens dislocation. Genetic testing is positive for a mutation in the *FBN1* gene.
Treatment	Avoidance of competitive, contact sports and prophylactic surgery when aorta reaches 5 cm in diameter and valve surgery when indicated.
Discussion	Marfan syndrome is an autosomal dominant connective tissue disorder caused by a mutation in the *FBN1* gene encoding the glycoprotein fibrillin-1. Fibrillin forms a sheath around elastin, and together they form microfibrils that provide strength and flexibility to the extracellular matrix and connective tissues. Clinical features affect the bones, joints, eyes, blood vessels, and heart. The most common findings are increased height and arm span due to overgrowth of the long bones of the extremities, scoliosis, pectus deformity of the chest wall (pectus carinatum or pectus excavatum), dislocation of the lenses of the eyes, and myopia. Complications include widening and tearing of the aorta and valve deformities resulting in aortic regurgitation or mitral valve prolapse. Mitral valve prolapse can be asymptomatic or can be associated with arrhythmias and mitral regurgitation. Aneurysm of the aorta has to be monitored closely because it can cause aortic rupture if untreated. Hypoplastic iris and retinal detachment can occur, and these patients are prone to cataracts and glaucoma. Pneumothorax is another complication that can occur in these individuals. The range of manifestations is varied, and the syndrome progresses with age in most cases.

CASE 21 | Alkaptonuria

A 40-year-old man presents with pain in the low back, hips, and knees, which is significantly affecting his ability to walk. He has a history of ruptured Achilles tendon and kidney stones. He has previously passed tiny black stones in his urine and notes that his urine turns black on exposure to air. On physical exam, there is a bluish-black discoloration over the pinna and parts of his sclera, and he has restricted spine, hip, and knee mobility.

Evaluation/Tests	Urine testing reveals the presence of homogentisic acid.
Treatment	Symptomatic therapy.
Discussion	Alkaptonuria is an autosomal recessive disorder caused by a mutation in the gene encoding homogentisate oxidase. This enzyme is involved in the normal pathway of degradation of tyrosine by converting homogentisic acid (an intermediate in the breakdown of tyrosine) into maleylacetoacetic acid, which is then normally converted to fumarate to be recycled into the TCA cycle. Mutation in homogentisate oxidase results in accumulation of homogentisic acid, which can undergo oxidation and accumulate in the connective tissues of the skin, eyes, and ears. Ochronosis can occur with oxidation resulting in bluish-black discoloration of these areas and pigmented ear wax. This disease tends to be benign but can cause arthralgias due to deposition of pigment in cartilage. It can also cause cardiac valve abnormalities and formation of kidney stones. A key lab finding is the excretion of homogentisic acid in the urine, which results in black-colored urine on exposure to air.

CASE 22 | Gaucher Disease	
A 22-year-old man of Ashkenazi Jewish descent presents with fatigue, easy bruising with minor trauma, and pain over the left hip. Physical exam is significant for skin pallor, hepatosplenomegaly, and bruises over his forearms and thighs. External rotation of the left hip is limited, and there is tenderness over the hip joint.	
Evaluation/Tests	CBC shows pancytopenia. An ultrasound shows hepatosplenomegaly. X-rays show avascular necrosis of the femur, and DEXA scan is consistent with osteopenia/osteoporosis. Enzyme testing shows reduced activity of β-glucosidase (glucocerebrosidase).
Treatment	Enzyme replacement therapy with recombinant glucocerebrosidase.
Discussion	Gaucher disease is the most common lysosomal storage disease and is caused by an autosomal recessive mutation in the gene encoding the lysosomal enzyme glucocerebrosidase (β-glucosidase). This results in accumulation of glucocerebrosidase within lysosomes and can affect multiple organ systems. There are three major clinical subtypes. The most common form is characterized by bone disease (lytic lesions, osteopenia, avascular necrosis of the femur, osteoporosis), hepatosplenomegaly, pancytopenia, and lung disease. Destruction of bone occurs from the release of hydrolytic lysosomal enzymes and inflammatory mediators. Bleeding and bruising are secondary to the thrombocytopenia. Other less common forms involve a progressive neurological impairment. Biopsy typically shows Gaucher cells, which are lipid-laden macrophages resembling crumpled or crinkled tissue paper. Lipid-laden macrophages can be observed in both Gaucher and **Niemann-Pick disease**. Gaucher disease is distinguished from **Tay-Sachs** and Niemann-Pick by lack of ocular findings. It may present anytime from childhood to adulthood while these other disorders most often present in infancy or childhood.

CASE 23 | Lesch-Nyhan Syndrome	
A 3-year-old boy is brought to the office for evaluation of pain and swelling over his joints, which has been worsening over the last year. His family reports that he has had self-destructive behavior and often bites his lips and fingers over the past year. He has a pronounced limp when he walks. Range of motion of his knees and small joints of hands is reduced. He has multiple lumps on hands and feet and has swollen and deformed nose, lips, wrists, and fingers.	
Evaluation/Tests	Labs show elevated serum uric acid. Joint fluid aspiration shows negatively birefringent crystals. Enzyme testing reveals absence of hypoxanthine guanine phosphoribosyltransferase (HGPRT).
Treatment	Allopurinol or febuxostat (2nd line), symptomatic, and behavioral therapies.
Discussion	Lesch-Nyhan syndrome is caused by an X-linked recessive mutation in the gene encoding the HGPRT enzyme. Due to its pattern of inheritance, it is almost exclusively seen in men. Defects in this enzyme cause a deficiency in the purine salvage pathway, where purine metabolites such as guanine and hypoxanthine are normally recycled back to precursors for reuse in the synthesis of nucleic acids. Due to lack of purine salvage capabilities, these precursors are instead broken down into xanthine and then uric acid by the enzyme xanthine oxidase, resulting in the accumulation of these products and hyperuricemia. Hypotonia and developmental delay are the presenting symptoms seen in infancy. This is followed by progressive motor symptoms due to pyramidal and extrapyramidal system involvement. Uric acid is deposited in joints and urinary tract with infant diapers revealing sand like orange sodium urate crystals. Aggression, compulsive behavior, neurologic and renal dysfunction are other manifestations. Reduction of uric acid production via the inhibition of xanthine oxidase using allopurinol or febuxostat is the cornerstone of treatment of Lesch-Nyhan syndrome.

ALTERED MENTAL STATUS

Certain vitamin deficiencies can cause altered mental status, or a reversible form of dementia. This is important to identify in elderly patients who might otherwise be suspected of having more irreversible forms of dementia such as neurodegenerative diseases like Alzheimer disease. Altered mental status in the setting of additional skin and/or hematologic findings may indicate a vitamin deficiency or systemic process involving deposition diseases. The key to differentiating these disorders is to identify the characteristic skin and hematologic manifestations or knowing the pathways where vitamins are needed as cofactors.

CASE 24 | Niacin (B3) Deficiency (Pellagra)	
A 60-year-old man with a past medical history of chronic alcoholism presents with abdominal pain and diarrhea. He is homeless and has not eaten in a few days. On exam, he is irritable, anxious, alert, and oriented to name only. He has a reddish-brown rash over his face, chest, and arms. The skin is rough and brittle over the areas of the lesions. The abdominal exam is unremarkable.	
Evaluation/Tests	Labs show low levels of erythrocyte nicotinamide adenine dinucleotide (NAD^+), niacin plasma metabolites, and urine niacin metabolites.
Treatment	Treat with oral nicotinamide and correct other nutritional deficiencies.
Discussion	This patient is presenting with pellagra, caused by vitamin B3 (niacin) deficiency. Niacin, or nicotinic acid, is derived from tryptophan and is a component of NAD^+ and $NADP^+$. It serves as a cofactor for coenzymes in oxidation-reduction reactions and plays a crucial role in ATP synthesis, glycolysis, and metabolism of fatty and amino acids. Niacin deficiency causes pellagra, which is commonly seen in people who are chronically malnourished such as those who are homeless, abuse alcohol or drugs, or suffer from anorexia. Pellagra can also be seen in patients with Hartnup disease, malignant carcinoid, and those taking isonizaid (because this medication causes decreased B6 levels, which is a cofactor required for synthesis of B3). Pellagra is characterized by diarrhea, dementia, dermatitis, and rarely death (the four D's). The dermatitis is often reddish-brown, hyperkeratotic, and photosensitive. It often presents as a broad collar of circumferential rash along the C3/4 dermatome, called Casal necklace. The sunburn becomes darker with time instead of fading and results in hyperpigmentation of sun-exposed areas. If untreated, this can result in death.
Additional Considerations	**Thiamine (B1) deficiency** can lead to Wernicke-Korsakoff syndrome. Thiamine is a water-soluble vitamin that is a component of thiamine pyrophosphate (TPP), a cofactor for several key dehydrogenase enzyme reactions. This cofactor is used by pyruvate dehydrogenase (converts pyruvate from glycolysis to acetyl-CoA for entry into TCA cycle), alpha-ketoglutarate dehydrogenase (in TCA cycle), and transketolase (involved in HMP shunt). Thiamine deficiency can thus result in impaired ability to break down glucose to ATP. **Wernicke-Korsakoff syndrome** is an encephalopathy characterized by a triad of confusion, ataxia, and ophthalmoplegia (nystagmus and conjugate gaze palsies). It is a clinical diagnosis, and supplementation of thiamine can result in resolution of symptoms. If a patient is given glucose without thiamine, symptoms can acutely worsen, and patients can have acute onset neuropsychiatric symptoms. This is because of thiamine's key role as a cofactor that allows for progression through the TCA cycle. Without thiamine, increased glucose will be shuttled to the formation of more lactic acid, precipitating an acute worsening of the patient's symptoms. Risk factors contributing to deficiency include alcohol abuse, hyperemesis, and chronic diuretic use. Severe and chronic thiamine deficiency is known as beriberi, and it can have two forms. **Wet beriberi** affects the heart and can lead to dilated cardiomyopathy, high-output cardiac failure, and severe edema. **Dry beriberi** primarily affects the nervous system and can cause polyneuropathy, symmetric muscle wasting, and other neurologic symptoms. Over time, this can lead to Korsakoff's psychosis, which is characterized by amnesia, confabulation (fabricated or misinterpreted memories but without an intent to deceive), and personality changes. **Hartnup disease** is an autosomal recessive deficiency in neutral amino acid transporters in the gut and kidney, which results in low levels of tryptophan and pellagra-like symptoms. Niacin can also be used therapeutically to treat dyslipidemia by increasing HDL and lowering VLDL. Niacin causes a prostaglandin-dependent facial flushing on ingestion, which can be avoided by pretreatment with aspirin. In addition to facial flushing, excess niacin (podagra) can cause hyperglycemia and hyperuricemia.

NEUROPATHY

Neurons are highly active, nonreproducing cells that require a large amount of energy to satisfy their metabolic demands. As such, certain vitamin deficiencies, cellular organelle defects, and inborn errors of metabolism can present with signs and symptoms related to nervous system damage. One of the more common presenting symptoms is peripheral neuropathy due to damage of peripheral nerves. Peripheral neuropathy can present with weakness, hypotonia, tingling or burning sensations, numbness, or paresthesia. Additional dermatologic and/or hematologic findings make biochemical defects more likely compared to other causes of peripheral neuropathy.

CASE 25 | Vitamin B12 (Cobalamin) Deficiency

A 56-year-old woman presents with numbness and tingling in her hands and feet, persistent fatigue, and decreased memory. The woman has been consuming a strict vegan diet without dairy products or eggs for the past 20 years. Physical exam is notable for conjunctival pallor, loss of pinprick sensation and touch distal to the wrist and ankles, decreased vibration sense, and mild cognitive impairment.

Evaluation/Tests	CBC is normal except for Hgb of 11.0 and MCV 120, and peripheral blood smear shows hypersegmented neutrophils. Serum folate is normal, vitamin B12 levels are low, and homocysteine and methylmalonic acid levels are elevated. Serum testing for intrinsic factor antibodies is negative.
Treatment	Vitamin B12 supplementation.
Discussion	This patient is presenting with a vitamin B12 (cobalamin) deficiency. Vitamin B12 is found mainly in animal products. It is a cofactor for two essential enzymatic reactions: the remethylation of homocysteine to methionine and the conversion of methylmalonyl-CoA to succinyl-CoA. B12 deficiency can be caused by poor dietary intake (which occurs with vegan diets), malabsorption (which can occur in alcoholism), loss of intrinsic factor (as seen in pernicious anemia), gastric bypass surgery, and destruction or loss of the terminal ileum (such as in Crohn's disease), all of which result in depletion of the storage pool of vitamin B12 in the liver. It takes many years for this deficiency to develop as the liver has abundant B12 stores. In addition to its important role in DNA synthesis, vitamin B12 is a cofactor in odd-chain fatty acid metabolism through the conversion of methylmalonyl CoA to succinyl CoA. Without B12, increased methylmalonyl CoA and its precursors can disrupt lipids in plasma membranes. This can occur in cells of the nervous system, resulting in demyelination commonly affecting the dorsal columns and lateral corticospinal tract, known as subacute combined degeneration. Hematologic changes are characterized by megaloblastic anemia (large immature and dysfunctional red blood cells) and hypersegmented neutrophils. Prolonged B12 deficiency can result in irreversible nerve damage. Testing for intrinsic factor and parietal cell antibodies helps determine if pernicious anemia is the cause of the B12 deficiency. Pernicious anemia is often associated with other autoimmune diseases and atrophic gastritis.
Additional Considerations	**Folate deficiency** often coexists with other nutrient deficiencies, including B12 deficiency. It can be caused by poor nutrition or medications such as tetrahydrofolate analogs (e.g., methotrexate) and dihydrofolate reductase inhibitors (e.g., trimethoprim). Folate is normally metabolized to tetrahydrofolate (THF), a coenzyme in single carbon transfer and methylation reactions in the metabolism of nucleic or amino acids. Serum folate can decline within three weeks of decreased folate intake due to a small reserve pool in the liver. Folate deficiency results in macrocytic, megaloblastic anemia due to the diminished synthesis of purines and TMP, which inhibits the cell from making adequate amounts of DNA. Folate deficiency and vitamin B12 deficiency both cause megaloblastic anemias. However, there are several key differences between them: (1) Vitamin B12 deficiency can lead to neurologic symptoms, but folate deficiency has no neurologic symptoms; (2) vitamin B12 deficiency leads to elevated homocysteine and methylmalonic acid, whereas folate deficiency has elevated homocysteine and normal methylmalonic acid levels; and (3) vitamin B12 deficiency takes years to develop, but folate deficiencies can develop in weeks. If B12 deficiency is misdiagnosed as folate deficiency and a patient is started on folic acid, the hematologic symptoms may resolve but the neurologic symptoms will not resolve and may worsen.

CASE 26 | Vitamin B6 (Pyridoxine) Deficiency

A 43-year-old woman presents with burning pain in her legs over the past three months. She has been on treatment for latent tuberculosis with isoniazid for the last four months. On physical exam, she is irritable and has fissuring at the angles of her mouth and beefy red bald/smooth tongue. There is diminished peripheral pinprick sensation and loss of monofilament sensation in both feet.

Evaluation/Tests	Serum and urine B6 levels were low, CBC shows microcytic anemia, and a peripheral blood smear shows microcytic hypochromic red blood cells with sideroblasts.
Treatment	Pyridoxine supplementation.
Discussion	This patient is presenting with a pyridoxine (vitamin B6) deficiency. Pyridoxine is converted to pyridoxal phosphate, which is a cofactor used in transamination (synthesis of ALT and AST), decarboxylation, and glycogenolysis. It is involved in the synthesis of neurotransmitters, heme, niacin, and histamine. Common manifestations of pyridoxine deficiency include irritability, peripheral neuropathy, seizures, and sideroblastic anemia due to impaired heme synthesis and iron excess. Isoniazid, used in the treatment of tuberculosis, can induce vitamin B6 deficiency by forming an inactive derivative of pyridoxal phosphate. Deficiency is commonly seen in this setting, as well as in infants fed formulas low in B6 and in patients with alcoholism.

CASE 27 | Fabry Disease

A 20-year-old man presents with burning pain in his hands and feet, abdominal pain with alteration in bowel movements, and clusters of small red spots on his skin. He reports feeling excessively hot with dry skin and says he never sweats. His family history is significant for a maternal uncle who died at age 55 from progressive kidney damage and heart failure. On exam, he is short, has hearing loss, and has a heaving apical impulse and systolic ejection murmur over the left sternal border. Clusters of erythematous red-purple papules with a slightly keratotic surface are seen in the groin, and absence of sweat in the axilla is noted. Ophthalmic exam is notable for corneal opacities (pale gray, brownish, or yellowish streaks in the cornea of the eye).

Evaluation/Tests	Labs show low levels of α-galactosidase A enzyme, and elevated levels of ceramide trihexoside (globotriaosylceramide). Echocardiogram shows left ventricular hypertrophy.
Treatment	Enzyme replacement therapy.
Discussion	Fabry disease is a lysosomal storage disorder caused by an X-linked recessive mutation of gene encoding α-galactosidase A. Deficiency or inactivity of this enzyme leads to an accumulation of glycolipids, such as ceramide trihexoside, in lysosomes throughout the body, especially in blood vessels, the eyes, heart, kidney, and peripheral nerves. Symptoms usually appear early in life but may present in adulthood. Symptoms are exacerbated by exercise, stress, or fatigue. Patients may present with burning pain in extremities (acroparesthesias), decreased sweating (hypohidrosis), and small, dark red, nonblanching skin lesions (angiokeratomas). Major organ complications occur in the second to third decade, including kidney failure, heart irregularities, and/or progressive neurological abnormalities.

CASE 28 | Zellweger Syndrome

A newborn baby girl is evaluated for several abnormalities including hypotonia, dysmorphic features, difficulty breathing, and seizures. The pregnancy and birth were uncomplicated. On physical exam, the baby is noted to have a flattened face, high forehead, large fontanelles, hypotelorism, corneal clouding, and nystagmus. There is a broad nasal bridge with a small nose and upturned nostrils. The palate has a high arch, and she has extra folds of skin in the neck.

Evaluation/Tests	Blood testing reveals elevation of very-long-chain fatty acids (VLCFAs). Genetic testing reveals a mutation in the peroxisome biogenesis factor 1 (*PEX1*) gene.
Treatment	Poor prognosis; supportive management along with genetic counseling.
Discussion	Zellweger syndrome is caused by an autosomal recessive mutation in the *PEX1* gene involved in the biogenesis of peroxisomes. Peroxisomes play important roles in beta-oxidation of very-long-chain fatty acids (VCLFAs), catabolism of branched-chain fatty acids, and synthesis of cholesterol, bile acids, and plasmalogens—the latter of which are important membrane phospholipids, especially in white matter of the nervous system. Nervous system symptoms are common and include hypotonia, hearing loss, vision problems, and seizures. Other features include hepatosplenomegaly, respiratory failure, and progressive liver and kidney dysfunction. Testing for peroxisomal disorders can be done by chorionic villus sampling or amniocentesis in the first or second trimester.
Additional Considerations	**Refsum disease** is another disorder of peroxisomal biogenesis; however, it involves an autosomal recessive defect in the alpha-oxidation of phytanic acid, a branched-chain fatty acid typically obtained from dairy, beef, and certain types of fish. Refsum disease presents with retinitis, peripheral neuropathy, gait ataxia, scaly skin, cataracts/night blindness, and skeletal abnormalities. **Adrenoleukodystrophy** is an X-linked recessive disorder of beta-oxidation whereby very-long-chain fatty acids (VLCFAs) accumulate in the adrenal glands, white matter of the brain, and testes, which can result in adrenal crisis, coma, and death. The most common presentation is that of a degenerative neurologic disorder that begins in childhood or adolescence; progresses to severe dementia with loss of vision, hearing, speech, and gait; and results in death within a few years. ALD is characterized by high ratios of C26 to C22 VLCFA in plasma and tissues. Genetic testing (*ABCD1* gene mutation) confirms the diagnosis.

HEMATOLOGIC ABNORMALITIES

Various vitamin deficiencies and metabolic defects can give rise to hematologic abnormalities. Broadly, these abnormalities can be divided into bleeding/coagulopathies or anemias. Bleeding can occur due to conditions that lower the platelet count

(Gaucher disease), the inability of blood to clot (vitamin K deficiency), or unstable collagen (vitamin C). Biochemical disorders resulting in anemia may include:

1. Deficiency of enzymes like G6PD and delta-aminolevulinic acid synthetase;
2. Deficiency of coenzymes like vitamin B12, folate;
3. Defective proteins like in hereditary spherocytosis.

Some of these defects can result in changes in red blood cell shape and subsequent hemolysis. While a few select biochemistry-relevant cases are presented in this chapter, the remainder of anemias and coagulopathies will be discussed in the "Hematology and Oncology" chapter.

CASE 29 | Vitamin C Deficiency (Scurvy)

A 53-year-old man presents for evaluation of a new rash over his legs that has progressively worsened over the last year. He also notes fatigue, pain in his knees, and bleeding every time he brushes his teeth. His wife died a year and a half ago, and since then his diet consists primarily of microwaved rice and beans. On exam, he has friable and swollen gingiva with loss of teeth, corkscrew hair, ecchymosis, and nonblanching erythematous perifollicular petechiae over his lower extremities.

Evaluation/Tests	CBC with peripheral smear is normal; prothrombin time (PT) and partial thromboplastin time (PTT) are normal; labs are notable for low serum vitamin C levels.
Treatment	Oral vitamin C supplementation.
Discussion	Scurvy is caused by a deficiency of vitamin C (ascorbic acid). Vitamin C has many functions: It is an antioxidant and cofactor needed for hydroxylation of proline to lysine in collagen synthesis; it helps absorb iron by reducing it to the Fe^{2+} state; and it is a cofactor for dopamine beta-hydroxylase, which converts dopamine to norepinephrine. Vitamin C deficiency typically develops within 8–12 weeks of inadequate intake of fresh fruits and vegetables. Vitamin C deficiency affects blood vessels, skin, and basement membranes separating the epidermis and dermis. Patients can have poor wound healing, gum swelling, loss of teeth, corkscrew hair, petechiae and ecchymosis, and hemarthrosis. Petechial hemorrhages are common in lower extremities due to capillary fragility and gravity-dependent hydrostatic pressure. Brittle bones occur due to disruption of endochondral bone formation. Ocular manifestations can include hemorrhages, papilledema, and optic atrophy.

CASE 30 | Vitamin K Deficiency

A 3-week-old baby boy is brought to clinic for evaluation of increased sleepiness, difficulty breast-feeding, irritability, and emesis. The patient had a normal delivery; however, his parents refused vitamin K injection due to their religious beliefs. He did not have any complications with circumcision on the tenth day of his life. There is no family history of unusual illnesses or sick contacts. Physical exam reveals an irritable baby with increased heart and respiratory rate, ecchymosis over the thighs, sluggish pupils, and full fontanelles.

Evaluation/Tests	Labs show a normal CBC; coagulation studies reveal prolonged PT and aPTT, normal bleeding time, normal von Willebrand factor (vWF), and fibrinogen degradation products; CT head revealed a small intracranial bleed.
Treatment	Vitamin K injection.
Discussion	This patient is presenting with vitamin K deficiency. Vitamin K is a fat-soluble vitamin needed for the synthesis and maturation of blood clotting factors II, VII, IX, and X, and proteins C and S. It is activated by epoxide reductase to the reduced form and acts as a cofactor for gamma-carboxylation of glutamic acid residues on proteins involved in the coagulation cascade. It is present in green leafy vegetables and can also be produced by intestinal flora. Vitamin K deficiency occurs relatively quickly in the newborn because of the short half-life, limited stores of vitamin K (not in breast milk), and immature GI tracts. Neonates are given an intramuscular vitamin K injection at birth to prevent bleeding and potentially fatal intracranial hemorrhage. Vitamin K deficiency can also occur because of prolonged use of broad-spectrum antibiotics, destroying gut microorganisms. Warfarin inhibits vitamin K–dependent synthesis of clotting proteins. Correction of coagulopathy and supplementation of vitamin K are the treatment. Patients with DIC or sepsis typically will have other signs or symptoms consistent with infection, such as fever or elevated WBC count. The first step in treating prolonged PT and aPTT is to give vitamin K to make sure prolonged times are not due to nutritional deficiencies. If PT and aPTT are not corrected with vitamin K, then it is important to search for other causes of abnormal coagulation studies.

CASE 31 | Pyruvate Kinase Deficiency	
A 16-year-old boy presents with fatigue and yellow color of the skin and sclera. His mother states he had insufficient weight gain as a child. Physical exam is notable for yellowing of the white of the eyes (scleral icterus), jaundice, and splenomegaly.	
Evaluation/Tests	CBC shows low hemoglobin, normal MCV, and reticulocytosis. Peripheral blood smear reveals spiculated red blood cells (echinocytes or "burr cells"). Labs are notable for increased levels of unconjugated bilirubin and a negative Coombs test.
Treatment	People with severe anemia may need blood transfusions.
Discussion	Pyruvate kinase deficiency is an autosomal recessive disorder resulting from a defect in pyruvate kinase. Pyruvate kinase is one of several key enzymes in glycolysis as it catalyzes the last step by converting phosphoenolpyruvate (PEP) to pyruvate. RBCs rely almost exclusively on glycolysis for ATP production due to lack of mitochondria, so they are the most significantly affected by this deficiency. Decreased ATP from this deficiency, therefore, has a significant effect on RBCs. Normally, Na^+/K^+ ATP pumps help RBCs maintain their unique shape by regulating water content inside the cell. With decreased ATP, this pump cannot function, and thus the RBC becomes rigid and abnormally shaped, resulting in spicule formation and extravascular hemolysis. While RBCs are most heavily affected, pyruvate kinase is also used by all cells throughout the body. Without efficient glycolysis, cells will rely on fatty acid oxidation, producing ketones and upregulating gluconeogenesis. Acute infections or stressors may therefore increase these processes, resulting in hemolysis.

DERMATITIS OR RASH

Dermatologic abnormalities are common in vitamin deficiencies and specific genetic abnormalities affecting DNA repair pathways. Vitamin deficiencies may present with rash or dermatitis, but typically are associated with additional systemic features. Dermatitis may be limited to a specific location (e.g., the angle of the mouth) or may be more widespread. Mutations in DNA repair pathways limit the ability of cells to repair spontaneously or induce mutations. Given the exposure of skin to the environment, it is particularly susceptible to accumulation of mutations such as from UV radiation in sunlight.

CASE 32 | Vitamin A (Retinol) Deficiency	
A 32-year-old man presents with a progressive rash over his face, arms, and legs and difficulty seeing at night. He underwent a Roux-en-Y gastric bypass surgery, a type of weight-loss surgery that involves creating a small pouch from the stomach and connecting the newly created pouch directly to the small intestine, several months ago. He has dry eyes, a triangular spot on the bulbar conjunctiva, and dry skin with hyperkeratotic papules over face, shoulders, buttocks, and extremities.	
Evaluation/Tests	Vitamin A levels are decreased.
Treatment	Treat with vitamin A as retinol or retinyl esters supplementation.
Discussion	Vitamin A is an essential part of vision pigments and is needed for the growth, maintenance, and differentiation of epithelial cells. Retinoic acid binds to receptor proteins and regulates retinoid-specific RNA synthesis. This controls the expression of the gene for keratin and rhodopsin, the visual pigments in rods and cones. Deficiency can occur in the setting of fat malabsorption (e.g., following gastric bypass as seen in this case), alcoholism, or protein-energy malnutrition. Night blindness is one of the earliest symptoms of vitamin A deficiency, which can progress and be irreversible. Xerophthalmia, inability to produce tears, and white foamy spots on conjunctiva due to sloughing (bitot spots) are characteristic features; if untreated, they can lead to corneal ulceration and blindness. The skin manifestation, called phrynoderma, is characterized by dry, hyperkeratotic papules symmetrically distributed over the face, extensor surface of shoulders, and extremities. Additionally, retinol and retinal are needed for spermatogenesis in men, so deficiency in vitamin A can result in fertility problems. Acute toxicity due to excess vitamin A causes nausea vomiting and blurred vision. Chronic toxicity can result in alopecia, dry skin, liver toxicity, and pseudotumor cerebri. Oral isotretinoin, commonly used to treat acne, requires two forms of contraception because it is teratogenic and can cause cleft palate and cardiac abnormalities. *All*-trans retinoic acid (ATRA) is used to treat acute promyelocytic leukemia (APL) because it forces APL cells to differentiate and lose proliferation capacity.

CASE 33 | Xeroderma Pigmentosum (XP)

A 14-year-old girl is referred to a dermatologist for evaluation of recurrent blistering sunburns since childhood. The sunburns occur even when she has only been outside for a few minutes. She also has increased light sensitivity and itching of her eyes. Physical exam reveals dry, parchment-like skin, skin atrophy, and telangiectasias with several freckles in the sun-exposed areas. There is inflammation of the conjunctiva with some clouding of the cornea.

Evaluation/Tests	Molecular testing for mutations in the xeroderma pigmentosum genes involved in nucleotide excision repair was positive.
Treatment	Treat complications.
Discussion	Xeroderma pigmentosum (XP) is a genetically heterogeneous disorder caused by mutations in various genes involved in DNA nucleotide excision repair. This type of DNA repair is important in repairing DNA pyrimidine dimer mutations, which form upon exposure to ultraviolet (UV) light. XP is characterized by increased sensitivity to the damaging effects of UV light and typically affects the skin, eyes, and nervous system. Blistering burns on sun-exposed skin after minimal exposure is characteristic. Characteristic long-term features include dry parchment-like skin, a mixture of increased and decreased skin pigmentation (poikiloderma), skin thinning, and telangiectasias. Actinic keratosis and skin cancer are common complications. Eye involvement consists of increased light sensitivity, dry eye, inflammation of the cornea, resulting in opacification and vascularization that leads to blindness. Some patients may display neurologic symptoms. Cancers occur at a higher rate, including those of the skin, oral cavity, glioblastoma, and astrocytomas. Prevention and rigorous UV protection is critical. **Porphyria cutanea tarda** and albinism may also present with photosensitivity. Porphyria cutanea tarda typically manifests in adulthood, is associated with hepatitis C, is exacerbated by alcohol consumption or other oxidative stressors, and commonly involves hyperpigmentation of the skin. **Albinism** can be distinguished from XP by the lack of any pigmentation (hypopigmentation) due to decreased production of melanin.

RESPIRATORY DISTRESS

Several genetic defects can impair normal function of the respiratory tract in the clearance of mucous and potential pathogens. Important in this role is the mucociliary elevator maintained by the ciliated pseudostratified columnar epithelia and mucous-secreting Goblet cells lining the respiratory tract. Formation and excretion of mucous are a tightly regulated process involving the exchange of ions and fluids across the respiratory epithelia. Inherited mutations that disrupt the normal function of any of these important cells can lead to recurrent respiratory or sinus infections and respiratory distress.

CASE 34 | Kartagener Syndrome/Primary Ciliary Dyskinesia

A 22-year-old man presents for evaluation of infertility. On review of systems, he mentions that he has had recurrent sinus infections and productive cough with thick sputum all his life. He also notes thick nasal discharge and a decreased sense of smell. On physical exam, his nasal mucosa is not visible due to thick nasal secretions, and bilateral sinus tenderness is present. The apical impulse is on the right fifth intercostal space, and hepatic dullness is percussed on the left side.

Evaluation/Tests	Chest X-ray shows dextrocardia and a gastric fundus on the right with elevated left hemidiaphragm. CT sinuses shows mucosal thickening. Biopsy of sinus cavities or airway shows ciliary abnormalities. Semen analysis shows immotile spermatozoa.
Treatment	Airway clearance therapy to help loosen thick mucus. Antibiotics to treat respiratory, sinus, or ear infections.
Discussion	Kartagener syndrome is a form of primary ciliary dyskinesia that is caused by autosomal recessive mutations that affect the proteins involved in the dynein arm of cilia. Defects in ciliary movement lead to frequent middle ear, sinus, and lung infections, conductive hearing loss and infertility. In women, there is an increased risk of ectopic pregnancy. Headache, anosmia, and corneal abnormalities can also occur. It is also characterized by situs inversus (mirror image reversal of internal organs including dextrocardia).

CASE 35 | Cystic Fibrosis

An 8-month-old male infant who recently migrated from a remote fishing town in Iceland presents with a cough productive of dark brown, thick sputum. His past medical history is significant for pneumonia 1 month ago and an admission to a hospital days after birth because he was unable to have a bowel movement. On exam, the patient is fussy, underweight, and grunting and tachypneic. His temperature is 38.5°C, respirations are 40/min, pulse is 120/min, and pulse oximetry on room air shows an oxygen saturation of 89%. He has decreased breath sounds, crackles, and dullness to percussion in the left lower lung field.

CASE 35 | Cystic Fibrosis *(continued)*

DDx	Cystic fibrosis, pneumonia, primary immunodeficiency, respiratory syncytial virus, asthma, bronchiolitis.
Evaluation/Tests	Chest X-ray shows consolidation in the left lower lung field. Sweat chloride testing reveals an elevated chloride concentration of 115 mmol/L. Fecal elastase is low. Nasal transepithelial potential difference is elevated. Genetic testing confirms a Phe508 deletion in the *CFTR* gene on chromosome 7.
Treatment	Treat pneumonia with antibiotics and start chest physiotherapy.
Discussion	This patient has cystic fibrosis (CF), an autosomal recessive disorder involving a defect in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on chromosome 7. One of the more common mutations is a deletion of the amino acid, phenylalanine, at codon 508. *CFTR* encodes an ATP-gated chloride channel involved in the secretion of chloride in the lungs and GI tract and the reabsorption of chloride in sweat glands. The abnormal chloride regulation also leads to abnormal water regulation, which can lead to thick secretions. In the lungs, patients can have abnormally thick mucus. Clearance is disrupted and increases risk of recurrent infection. In the GI tract, thickened secretions can lead to pancreatic insufficiency (steatorrhea, fat-soluble vitamin deficiencies). Additional complications include biliary cirrhosis, liver disease, infertility, nasal polyps, digital clubbing, and meconium ileus in newborns. Screening involves searching for mutations in the *CFTR* gene. The diagnostic test of choice is the chloride sweat test, which will reveal an elevated chloride concentration in the sweat. Confirmation is typically done with genetic testing. Recent advances in CF therapy include lumacaftor, which helps correct misfolding of the CFTR protein, and ivacaftor, which helps promote opening of chloride channels. However, these are only effective in CF patients with homozygous Phe508 mutation. Otherwise, treatment is mostly supportive and aimed at limiting or preventing complications. A history of unexplained, recurrent infections in a child should also raise suspicion for **primary immunodeficiencies** (e.g., severe combined immunodeficiency syndrome). Unlike CF, the pathology in primary immunodeficiencies can often be explained by specific infections (e.g., sinus or GI infections) and will show decreased white blood cell count on CBC.

DYSLIPIDEMIAS

Dyslipidemias are a class of diseases related to the transport and uptake of lipids throughout the body. Acquired lipid disorders are very common in adulthood and result mainly from lifestyle habits such as poor diet, lack of exercise, and excessive alcohol intake. Here, we will focus on inherited dyslipidemias, which involve genetic defects in key enzymes or proteins involved in the transport and uptake of dietary and endogenous lipids. Typical features of inherited dyslipidemias include:

1. Severe hypercholesterolemia and/or hypertriglyceridemia, often appearing at a younger age than typically expected;
2. Family history of dyslipidemias;
3. Dermatologic manifestations related to lipid deposits in the skin or tendons (as well as the eye);
4. Increased risk of premature coronary heart disease, peripheral arterial disease, and stroke due to accelerated atherosclerosis;
5. GI manifestations including pancreatitis (related to severe hypertriglyceridemia) and hepatic steatosis.

The dyslipidemia disorders may look very similar to one another. Pay close attention to the pathogenesis and specific clinical presentations to help differentiate among them.

CASE 36 | Familial Hyperchylomicronemia (Hyperlipidemia Type I)

A 30-year-old woman was admitted to the ICU a week ago for severe pancreatitis. Her labs showed significant hypertriglyceridemia. Plasmapheresis was performed to rapidly reduce triglyceride (TG) and chylomicron levels in her blood, and her symptoms resolved. On further investigation, numerous family members also suffer from recurrent pancreatitis, but not myocardial infarctions. On physical exam, the patient has eruptive xanthomas on her back (lipid deposits in the skin and subcutaneous tissue) and milky appearance of retinal veins and arteries (lipemia retinalis).

Evaluation/Tests	Triglycerides and chylomicrons are elevated. When blood is drawn, it has a creamy layer in the vial.
Treatment	Lifestyle modification, cholesterol-lowering drugs including fibrates and/or statin.

CASE 36 | Familial Hyperchylomicronemia (Hyperlipidemia Type I) *(continued)*

Discussion	Familial hyperchylomicronemia is a type of familial dyslipidemia caused by an autosomal recessive defect in lipoprotein lipase (LPL) or apolipoprotein C-II (Apo CII), which results in reduced clearance of chylomicrons from the plasma. LPL is found on the surface of vascular endothelial cells and degrades TGs in circulating chylomicrons to release free fatty acids. The free fatty acids are then taken up by adipocytes for storage. Apo CII is a cofactor for LPL that helps catalyze this cleavage. A defect in either of these causes triglycerides and chylomicrons to accumulate in the plasma. Patients have eruptive xanthomas (lipid deposits in the skin and subcutaneous tissue), severely elevated triglycerides, hepatosplenomegaly, lipemia retinalis, and they may develop abdominal pain due to acute pancreatitis. Total cholesterol levels may also be elevated. **Familial hypertriglyceridemia** (hyperlipidemia type IV) is caused by an autosomal dominant defect in apolipoprotein A V (Apo AV), which results in hepatic overproduction of very-low-density lipoproteins (VLDLs). VLDLs are secreted by the liver and deliver hepatic TGs to peripheral tissues. Compared to other lipoproteins such as LDL and HDL, VLDLs contain the highest amount of TGs. In familial hypertriglyceridemia, elevation in VLDLs causes a severe hypertriglyceridemia and chylomicron levels are normal. This condition can also cause acute pancreatitis and is often related to insulin resistance so is seen more often in diabetics and obese patients.

CASE 37 | Familial Hypercholesterolemia (Hyperlipidemia Type IIa)

An 18-year-old man presents for a yearly physical exam, but he is very concerned about his strong family history of early heart attacks and high levels of "bad" cholesterol. Physical exam is significant for yellowish deposits on his Achilles tendon and a light-colored ring around the edge of the cornea.

Evaluation/Tests	A lipid panel shows high levels of total cholesterol and LDL but normal triglyceride levels.
Treatment	Statins.
Discussion	Familial hypercholesterolemia is caused by an autosomal dominant defect in LDL receptors or in Apo B-100. Apo B-100 is an apolipoprotein found in lipoproteins originating from the liver and helps bind to LDL receptors found on peripheral cells. The LDL receptor on peripheral cells allows for peripheral cholesterol uptake. Most patients with hyperlipidemia are asymptomatic and are often diagnosed after a routine lipid profile; however, there is commonly accelerated atherosclerosis with premature coronary artery and peripheral vascular disease. Patients also typically have tendon xanthomas (especially in the Achilles tendon), corneal arcus, and xanthelasmas on the eyelids. There are two types of familial hypercholesterolemia: IIa involves elevated LDL and cholesterol, while IIb also has elevated VLDLs. **Familial dysbetalipoproteinemia** (hyperlipidemia type III) involves an autosomal recessive defect in apolipoprotein E (ApoE). ApoE helps mediate the uptake of remnants of chylomicrons, VLDL, IDL, and HDL back into the liver. A defect in ApoE results in accumulation of these remnants, especially chylomicrons and VLDLs, in the serum. Clinical features include premature atherosclerosis leading to coronary artery and peripheral vascular disease; palmar xanthomas, which are yellowish plaques or nodules that deposit on the palm and elsewhere; and tuberoeruptive xanthomas. Symptoms are generally more severe when there is a secondary genetic or environmental factor that causes an increase in lipids such as obesity, hypothyroidism, and diabetes. Lipid panel shows elevated chylomicron and VLDL remnants. Treat with fibrates and/or statins.

2

Immunology

Mahesh C. Patel, MD

Primary Immunodeficiencies

1. X-linked (Bruton) Agammaglobulinemia
2. Thymic Aplasia (DiGeorge Syndrome)
3. Chronic Granulomatous Disease
4. Terminal Complement Deficiency (C5–C9)
5. Hyper-IgM Syndrome

Hypersensitivity Reactions

6. Type I Hypersensitivity—Anaphylaxis
7. Type II Hypersensitivity—Hemolytic Disease of the Newborn
8. Type III Hypersensitivity—Serum Sickness
9. Type IV Hypersensitivity—Tuberculin (PPD) Skin Test

Blood Transfusion Reactions

10. Anaphylactic Blood Transfusion Reaction

Transplant Rejection

11. Acute Transplant Rejection
12. Graft-Versus-Host Disease (GVHD)

PRIMARY IMMUNODEFICIENCIES

Primary immunodeficiency diseases are a group of disorders that most commonly result from inherited defects that impair the immune system. Although over 300 of these disorders have been described, most are rarely encountered by the practicing clinician. They appear fairly commonly on board exams, however, because they are relatively distinctive diseases in which the pathophysiology is relatively well understood. The vast majority of these immunodeficiencies present in the first year of life or early childhood, but a few milder ones are diagnosed in later childhood or adulthood. The typical presentation is that of recurrent and/or chronic infections, sometimes with opportunistic organisms. These disorders can be most easily classified by the main component of the immune system that is absent, deficient, or defective, which can broadly be categorized into primary problems of the innate or adaptive immune system. Problems with the innate immune system include neutrophil/phagocyte and complement protein deficiencies. Problems with the adaptive immune system include B-cell, T-cell, or mixed-cell deficiencies.

Primary Immunodeficiency Disorders Grouped by Component Deficiency/Absence

Phagocyte/Neutrophil	Complement	B-Cell	T-Cell	B- and T-Cell
- Leukocyte adhesion deficiency (type 1) - Chronic granulomatous disease (CGD) - Chédiak-Higashi syndrome	- C1 esterase inhibitor deficiency - Terminal complement deficiency (C5–C9 deficiency)	- IgA deficiency - X-linked (Bruton) agammaglobulinemia - Common variable immunodeficiency (CVID)	- Thymic aplasia (DiGeorge syndrome) - Autosomal dominant hyper-IgE syndrome (Job syndrome) - IL-12 receptor deficiency - Chronic mucocutaneous candidiasis	- Severe combined immunodeficiency (SCID) - Wiskott-Aldrich syndrome - Ataxia-telangiectasia - Hyper-IgM syndrome

In addition to problems with chronic and opportunistic infections, patients with immunodeficiency may present with failure to thrive, chronic diarrhea, mucosal abnormalities, lymphadenopathy, and skin abnormalities.

Understanding the functions of phagocytes and complement, B-cells, and T-cells is important prior to learning about these immunodeficiencies.

Several immune cells have the ability to phagocytose pathogens and cellular debris. These include neutrophils, macrophages, and dendritic cells. Neutrophils, in particular, often serve as the "first responders" to infection, tissue damage, or inflammation. Deficiencies in phagocytic cells such as neutrophils constitute approximately 10% of primary immunodeficiencies. Phagocytic cell deficiencies typically arise early in a child's life and are characterized by a wide range of infections (from mild skin infections to sepsis) due to fungi, parasites, and bacteria. In particular, children with these deficiencies are prone to infections with *Staphylococcus* spp., *Serratia*, *Nocardia*, *Pseudomonas aeruginosa, Burkholderia cepacia*, *Candida* spp., *Aspergillus*, and *Mucor*. They are not at increased risk from viral infections as viruses exist largely within intact host cells and therefore are not as easily recognized by phagocyte pattern recognition receptors.

In addition to cellular components of the innate immune system, several secreted proteins are instrumental in coordinating the immune response. Examples of secreted proteins include chemokines, cytokines, and complement proteins. Deficiencies in complement proteins are observed to constitute approximately 5% of primary immunodeficiencies. Complement deficiencies are typically diagnosed after a patient has recurrent, severe infections with encapsulated bacteria such as *N. meningitidis, H. influenzae,* and *S. pneumoniae.* Complement proteins play an important role in the binding to and subsequent opsonization of pathogens, particularly encapsulated bacteria.

The two major cell types of the adaptive immune system include B- and T-lymphocytes. B-cell defects make up approximately 65% of all primary immunodeficiencies and therefore represent the most common form of primary immunodeficiency. B-cell defects often do not present in the first 6 months of life as maternal antibodies are still present. The most common of the B-cell defects is immunoglobulin A (IgA) deficiency. Pure B-cell defects lead to recurrent and severe sinopulmonary infections and otitis media with encapsulated organisms such as *S. pneumoniae* and *H. influenzae.* Patients are often infected with **extracellular** bacteria. B-cell deficient patients are also more prone to infection with enteroviruses and giardiasis and may present with chronic diarrhea and malabsorption.

T-cell defects make up approximately 5% of the primary immunodeficiencies. Most patients are affected in the first 6 months of life. Various viruses, protozoa, fungi, mycobacteria, and **intracellular** bacteria infect patients with T-cell defects. In particular, T-cell deficient patients are more prone to fungal and viral infections as T-lymphocytes play a large role in the detection of infected host cells. Similar to patients with AIDS, these patients are predisposed to opportunistic infections such as *Pneumocystis jiroveci*, *Cryptococcus*, cytomegalovirus (CMV), JC virus, *Mycobacterium* spp., and *Candida* spp. They are also prone to chronic infection with respiratory and GI viruses.

Combined B- and T-cell defects have features of both of the preceding defects and make up approximately 15% of all primary immunodeficiencies.

Key Findings and Primary Immunodeficiency Differential Diagnosis

Primary Immunodeficiencies with Key Associated Findings	Diagnoses
Boy (X-linked)	Bruton agammaglobulinemia, SCID (commonly), hyper-IgM, Wiskott-Aldrich, CGD
Absent B-cells in peripheral blood; *BTK* (a tyrosine kinase gene) defect	Bruton agammaglobulinemia
Severe pyogenic infections early in life; additionally, patient develops opportunistic infections with organisms such as *Pneumocystis* and CMV. Normal or increased IgM with low IgG, IgA, and IgE; no germinal centers; defective *CD40L* on Th-cells	Hyper-IgM syndrome
Infections with catalase positive organisms (e.g., *Staph aureus*, *Nocardia*, *Aspergillus*, etc.) Abnormal dihydrorhodamine test; negative nitroblue tetrazolium dye reduction test	CGD
Triad of thrombocytopenia, eczema, and recurrent pyogenic infections	Wiskott-Aldrich syndrome
"Global" immunodeficiency (recurrent viral, bacterial, fungal, and protozoal infections) Defective IL-2 receptor	SCID
Sinopulmonary infections, lymphoma in a patient >2 years old Decreased plasma cells and subsequent decreased immunoglobulins; **normal B-cell number**	CVID
Asymptomatic *or* autoimmune, atopy, anaphylaxis to IgA-containing products Giardia infection	IgA deficiency
Tetany due to hypocalcemia, recurrent viral or fungal infections Absent thymus and parathyroids; congenital heart and great vessel defects Decreased PTH, calcium, T-cells; no thymic shadow on CXR	Thymic aplasia (DiGeorge)
Disseminated mycobacterial infections Poor interferon-γ function	IL-12 receptor deficiency
FATED: coarse **F**acies, cold **A**bscesses, retained primary **T**eeth, increased Ig**E**, and **D**ermatologic problems (e.g., eczema)	Hyper-IgE syndrome (Job syndrome)
Noninvasive *Candida* infections of the skin and mucous membranes	Chronic mucocutaneous Candidiasis
Difficulty with balance and walking, delayed onset of walking, cutaneous telangiectasias, recurrent infections particularly sinopulmonary infections, malignancy at a young age Cerebellar ataxia, ocular and cutaneous telangiectasias, growth retardation, immune deficiency, radiation sensitivity, increased rates of malignancy	Ataxia-telangiectasia
Recurrent skin infections *without* pus; impaired wound healing; **delayed umbilical cord separation**	Leukocyte adhesion deficiency (type 1)
Albinism, peripheral neuropathy, recurrent pyogenic infections with *Staph* and *Strep* Giant granules in granulocytes and platelets	Chédiak-Higashi syndrome
Hereditary angioedema	C1 esterase inhibitor deficiency
Increased IgE levels; increased eosinophils	Hyper-IgE syndrome (Job syndrome)
C5–C9 deficiency	Recurrent *Neisseria* infections

CASE 1 | X-linked (Bruton) Agammaglobulinemia

A 2-year-old boy is brought to clinic for evaluation of fever and right ear pain over the past 2 days. Review of his medical records reveals frequent visits for otitis media and several episodes of pneumococcal pneumonia over the last 18 months. In addition, his maternal uncle had many infections as a child, one of which ultimately led to his death. The patient's temperature is 39.2°C, pulse is 138/min, respirations are 26/min, and blood pressure is 100/52 mmHg. Bulging of the right tympanic membrane with obscured landmarks is present. Examination of the oropharynx reveals very small tonsils. No skin lesions are noted.

Evaluation/Tests	Clinical diagnosis. Labs reveal low immunoglobulin levels. A mutation is seen in the Bruton tyrosine kinase (*BTK*) gene. Absence of B-cells in peripheral blood.
Treatment	Treat with immune globulin replacement therapy at regular intervals.
Discussion	This patient with recurrent sinopulmonary infections most likely has a B-cell defect. His exam shows lymphoid hypoplasia (e.g., small tonsils, absent lymph nodes), a common finding in X-linked agammaglobulinemia. These patients lack germinal centers in their lymph nodes and do not have B-cells in their peripheral blood. Defects in the *BTK* gene lead to failure of B-cell development. Inheritance is X-linked recessive. Immunoglobulins of all classes are decreased. Patients are prone to recurrent bacterial, enteroviral, and giardia infections, which start after 6 months of age when maternal immunoglobulins have decreased. These patients should not receive live vaccines. **Common variable immunodeficiency (CVID)** involves a defect in B-cell maturation and differentiation. Patients with CVID subsequently have decreased plasma cells and decreased immunoglobulins of all classes. CVID presents *after* patients are 2 years old, which is later than X-linked agammaglobulinemia. CVID may not be diagnosed until after puberty, and patients are at increased risk for autoimmune disease, lymphoma, sinopulmonary infections, and bronchiectasis. In this case, the patient has already demonstrated recurrent infections before age 2 with a pattern of inheritance that suggests an X-linked condition, which makes X-linked agammaglobulinemia more likely.

CASE 2 | Thymic Aplasia (DiGeorge Syndrome)

A newborn girl is observed by a nurse to have a seizure. The girl's mother reports poor feeding and a "bluish" appearance to the skin, especially when the child becomes agitated. The patient's temperature is 37.3°C, pulse is 160/min, respirations are 42/min, and blood pressure is 90/52 mmHg. She appears sleepy and has mild cyanosis of the lips, and a harsh systolic murmur is heard at the left upper sternal border.

Evaluation/Tests	T-cells, parathyroid hormone, and serum calcium levels are decreased. Phosphorus is high. Thymic shadow is absent on chest X-ray. Genetic testing reveals a 22q11 deletion.
Treatment	Treat infections and calcium and vitamin D deficiency. Surgical correction of cardiac defects and possible thymic or hematopoietic cell transplantation.
Discussion	DiGeorge syndrome is the most likely diagnosis in this newborn with seizure due to hypocalcemia (secondary to absent parathyroids), episodes of cyanosis, a harsh murmur (likely due to tetralogy of Fallot), and no thymic shadow on CXR. DiGeorge syndrome results from failure of development of the third and fourth pharyngeal pouches, which leads to absent thymus and parathyroid glands. Patients with DiGeorge syndrome can present with seizures or tetany due to hypocalcemia, conotruncal abnormalities of the heart, and recurrent viral and fungal infections due to T-cell deficiency. DiGeorge syndrome is caused by a chromosomal deletion at 22q11.2. Other features include abnormal facies (small chin, overfolded ear helices) and cleft palate. **Severe combined immunodeficiency (SCID)** often presents in early infancy as this is a combined immunodeficiency with involvement of all lymphocytes (T- and B-cells). SCID can be X-linked due to a defective IL-2R gamma chain or autosomal recessive due to an adenosine deaminase deficiency. Patients may present with failure to thrive, chronic diarrhea, thrush, and recurrent infections from viruses, bacteria, fungi, and protozoa. Findings include the absence of a thymic shadow on chest X-ray, lack of germinal centers on lymph node biopsy, and absent T-cells and decreased T-cell receptor excision circles (TRECs). While SCID also presents with an absent thymic shadow and recurrent infections, the conotruncal anomalies and deficient calcium and PTH present in this vignette suggest DiGeorge syndrome. DiGeorge patients will predominantly become infected with viruses and fungi, so a pattern of infections that includes bacteria and protozoa would be more indicative of SCID rather than DiGeorge.

CASE 3 | Chronic Granulomatous Disease

A 5-year-old boy is brought to his primary care doctor for evaluation of multiple abscesses on his buttocks. On review of the medical records, it's noted that the child has had previous infections with *Aspergillus* and *Nocardia* and was treated for a *S. aureus* lung abscess last year. Patient's temperature is 38.6°C, pulse is 138/min, respirations are 26/min, and blood pressure is 92/54 mmHg. He has a 5-cm-round, painful, fluctuant bump on his right buttocks that is draining purulent material. The abscess drainage is positive for gram positive cocci in clusters.

Evaluation/Tests	The dihydrorhodamine test demonstrates decreased green fluorescence. Nitroblue tetrazolium dye reduction test does not turn blue.
Treatment	Treat acute infections.
Discussion	This patient is presenting with chronic granulomatous disease (CGD). Important clues include recurrent infections with *S. aureus* and less typical organisms such as *Aspergillus* and *Nocardia* (catalase positive organisms). Patients with CGD are prone to infection with catalase positive organisms due to a defect in NADPH oxidase, which produces the reactive oxygen species superoxide (precursor to H_2O_2) in the respiratory burst in neutrophils. Catalase negative organisms will produce their own H_2O_2 that CGD patients' cells can utilize to generate the hypochlorite needed to kill pathogens. Catalase positive organisms, however, use catalase to neutralize their own H_2O_2, so the neutrophils cannot use this to overcome their inability to produce H_2O_2 and thus cannot produce hypochlorite. Patients with CGD have normal responses to viral infections. CGD is most commonly X-linked recessive, so vignettes may include a history of men in the family with similar patterns of infection. Patients with **leukocyte adhesion deficiency (type 1)** (LAD-1) have an absence of neutrophils (pus) at sites of infection. This disease results from an autosomal recessive defect in LFA-1 integrin protein on phagocytes, so adhesion to the vascular wall cannot occur properly, causing transmigration and chemotaxis to be impaired. Consequently, neutrophils cannot adhere fully to the vessel wall, detect the chemical attractants necessary to find the site of infection, or cross the interstitium to reach the site of infection. Patients with LAD-1 have an elevated neutrophil count but will lack neutrophils at sites of infection. They will therefore be less likely to have pus formation at infection sites. These patients often present with delayed separation of the umbilical cord, absent pus, impaired wound healing, and recurrent skin and mucosal bacterial infections. Individuals with the autosomal recessive disease **Chédiak-Higashi syndrome** have microtubule dysfunction due to a defect in the lysosomal trafficking regulator gene (*LYST*). This causes impairment in phagosome-lysosome fusion, giant granules in granulocytes and platelets, and an increased risk of bacterial infections with *Staphylococci* and *Streptococci* and defects in primary hemostasis. Patients with Chédiak-Higashi also have pancytopenia, albinism, and peripheral neuropathy. In addition, they are at risk of developing hemophagocytic lymphohistiocytosis (HLH). Infections with *Aspergillus* and *Nocardia*, as in this vignette, would be uncommon.

CASE 4 | Terminal Complement Deficiency (C5–C9)

A 22-year-old woman is brought to the emergency department for evaluation of altered mental status and fever. Her friend said the patient had been complaining of a headache and neck pain for the last 12 hours and developed a strange rash. Her past medical history is notable for recurrent sexually transmitted infections with *N. gonorrhoeae*. The patient's temperature is 39.1°C, pulse is 123/min, respirations are 24/min, and blood pressure is 84/42 mmHg. She is obtunded and not responding to commands.

Evaluation/Tests	Cerebrospinal fluid cultures reveal a gram negative diplococcus suggestive of *Neisseria meningitidis*. CH50 and C5–C9 levels are decreased.
Treatment	Treat with antibiotics, and patient should be vaccinated against meningococcus.
Discussion	Terminal complement deficiency is the most likely immunodeficiency disorder in this patient presenting with recurrent *Neisseria* infections. Patients with terminal complement deficiency have recurrent *Neisseria* infections, especially with *N. meningitidis*. In particular, patients have a defect in the formation of the membrane attack complex (MAC), which is a combination of C5b, C6, C7, C8, and C9 complement components. MAC defends against gram negative bacteria through lysis and cytotoxicity. **Early complement deficiencies** (C1–C4) typically result in severe, recurrent pyogenic sinus and respiratory infections such as *Streptococcus pneumoniae* and less frequently with *Haemophilus influenzae*.

CASE 5 | Hyper-IgM Syndrome	
A 2-year-old boy is brought to clinic for evaluation of fever and a cough for 4 days. The patient has a history of recurrent episodes of acute otitis media and has been hospitalized for pneumonia in the past. The patient's temperature is 39.0°C, pulse is 140/min, respirations are 36/min, and blood pressure is 85/44 mmHg. Chest X-ray reveals diffuse, ground-glass opacities bilaterally. A lung biopsy stained with methenamine silver stain demonstrates disc-shaped yeast.	
Evaluation/Tests	IgM levels are normal. IgG, IgA, and IgE are all severely decreased.
Rx	Treat acute *Pneumocystis jirovecii* infection and continue antibiotic prophylaxis to prevent future infections. Definitive treatment is with a stem cell transplant.
Discussion	Hyper-IgM syndrome is an X-linked recessive disease most commonly due to defective CD40L on T-helper (Th) cells. In B-cell activation and class switching, the B-cell presents the antigen on MHC II to the T-cell receptor (TCR) on the Th-cell. CD40 on the B-cell then binds CD40 ligand (CD40L) on the Th-cell. Both signals are necessary for the Th-cell to secrete cytokines that induce B-cells to undergo Ig class-switching. In hyper-IgM syndrome, the second signal does not occur, so B-cells cannot undergo class switching and thus can only continue to produce IgM. This leads to low levels of IgA, IgG, and IgE, which leads to poor opsonization. This makes patients prone to recurrent pyogenic infections particularly with encapsulated organisms as well as opportunistic infections such as *Pneumocystis*, *Cryptosporidium*, and CMV. These patients also fail to make germinal centers, which is typically where class-switching and plasma cell differentiation occurs. IgM levels are normal to elevated in these patients. **SCID** also presents with recurrent infections early in life. However, the presence of normal to elevated IgM levels would be unusual in SCID. **Selective IgA deficiency** is the most common primary immunodeficiency and places patients at increased risk for mucosal infections. Most IgA-deficient patients are asymptomatic, but they are at increased risk of autoimmune disease, allergies, and anaphylaxis to IgA-containing products, such as blood products. They are also at increased risk for giardiasis. IgA levels are decreased, but other immunoglobulin levels are normal. **Wiskott-Aldrich syndrome** is due to an X-linked recessive mutation in the *WASP* gene, which prevents proper reorganization of the actin cytoskeleton. This causes defective antigen presentation and leads to defective humoral and cellular immunity. This defect also puts patients at increased risk for autoimmune diseases and cancer. Patients may present with the triad of thrombocytopenia, eczema, and recurrent infections. **Ataxia-telangiectasia** is an autosomal recessive disorder. Patients may have decreased IgA, IgG, and IgE levels, but this illness typically presents with the triad of ataxia, telangiectasia, and IgA deficiency. It is due to a defect in the ATM gene that encodes a DNA repair enzyme. Individuals are not able to repair breaks in DNA prior to cell division, which leads to the accumulation of various somatic mutations, which in turn leads to an increased risk of certain cancers, specifically lymphomas and acute leukemias.

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions occur when genetically predisposed individuals develop an overactive immune response to an innocuous/harmless antigen. The inflammation from these responses can cause serious tissue damage and disease. Hypersensitivity reactions are commonly grouped into four types: type I (acute, IgE antibody–mediated), type II (cytotoxic, IgG antibody–mediated), type III (immune complex–mediated), and type IV (delayed, T-cell-mediated). Understanding the underlying immunology associated with these reactions is very important for testing.

Examples of Hypersensitivity Reactions

Type I	Type II	Type III	Type IV
Systemic anaphylaxis Angioedema Urticaria Asthma Allergic rhinitis	Autoimmune hemolytic anemia Acute thrombocytopenic purpura Goodpasture's disease Graves' disease Myasthenia gravis Pemphigus vulgaris Hemolytic disease of the newborn Rheumatic fever Hyperacute transplant rejection	Systemic lupus erythematous Cryoglobulinemia Poststreptococcal glomerulonephritis Serum sickness Polyarteritis nodosa Arthus reaction	Type I diabetes mellitus Steven-Johnson syndrome/toxic epidermal necrolysis/erythema multiforme Drug rash, eosinophilia, systemic symptoms (DRESS) Contact dermatitis Graft vs. host disease PPD test

- Type I hypersensitivity reactions are the classic IgE-mediated, allergic reactions that occurs secondary to preformed antibodies and occurs very quickly (within minutes) after exposure to an antigen. Fever is typically **absent**, and the severity of reaction ranges from urticaria (hives) to systemic anaphylaxis (hypotension and angioedema).
- Type II hypersensitivity reactions are caused by IgG antibodies against cellular antigens. Clinical examples include autoimmune hemolytic anemia, and autoimmune diseases such as Graves' disease (autoimmune cause of hyperthyroidism).
- Type III reactions involve the deposition of immune complexes (antigen–antibody complexes) and can cause diseases such as poststreptococcal glomerulonephritis.
- Type IV reactions are T-cell-mediated and present in a more delayed fashion (as it takes time to activate sensitized T-cells). Contact dermatitis and drug reactions such as Steven-Johnson syndrome are examples.

Key Findings and Hypersensitivity Reaction Differential Diagnosis

Hypersensitivity Reactions and Key Associated Findings	Diagnosis
Immediate development of symptoms: urticaria (raised, erythematous, papules and plaques that are pruritic), wheezing, flushing, hypotension, angioedema (swelling of lips/mouth/tongue/throat), anaphylaxis History of allergies, asthma (atopy)	Type I
Febrile reaction after blood transfusion (without anaphylaxis)	Type II
Neutropenia (agranulocytosis) in patient being treated for hyperthyroidism	Type II (propylthiouracil adverse effect)
Young, male smoker with hematuria and acute kidney injury (AKI)	Type II (Goodpasture syndrome)
Progressively worsening ptosis through the course of a day	Type II (myasthenia gravis)
Bulging eyes (exophthalmos) with weight loss, tremor, dry skin, diarrhea, fatigue	Type II (Graves' disease)
Flaccid blistering rash	Type II (Pemphigus vulgaris – flaccid bullae as opposed to the tense bullae of bullous pemphigoid)
Sore throat and fever followed by hematuria and AKI days to weeks later	Type III (poststreptococcal glomerulonephritis)
Fever, rash, lymphadenopathy, arthralgia, proteinuria about 5 days after starting a new drug	Type III (serum sickness reaction)
Poor dentition and fever followed by AKI injury and hematuria	Type III (glomerulonephritis secondary to subacute bacterial endocarditis)
Malar rash (erythema on face sparing nasolabial folds)	Type III (systemic lupus erythematosus)
Exposure to forested area/outdoors followed by rash several days later	Type IV (contact dermatitis)
Fever, rash, eosinophilia with hepatic and/or renal injury after starting a new drug several days to weeks ago	Type IV (DRESS)
Severe, blistering/desquamating rash involving the mucous membranes (mouth/lips, etc.) after starting a drug	Type IV (Steven-Johnson syndrome)
"Target" rash after starting new drug	Type IV (erythema multiforme)

CASE 6 | Type I Hypersensitivity—Anaphylaxis

An 18-year-old woman with asthma and seasonal allergies is given amoxicillin for an ear infection. Within 30 minutes of taking the medication, she develops lightheadedness, hives, facial swelling, and nausea and presents for evaluation. She has never had this reaction before. She took amoxicillin once before as a child. On exam, the patient's temperature is 37.0°C, pulse is 118/min, respirations are 22/min, and blood pressure is 80/45 mmHg. She is flushed, in acute distress, and has notable swelling of the lips and face (angioedema). She has audible wheezing and a diffuse raised, erythematous rash that is pruritic (urticaria).

Evaluation/Tests	Clinical diagnosis. However, there can be elevated serum tryptase, an inflammatory mediator released from mast cells.

CASE 6 | Type I Hypersensitivity—Anaphylaxis *(continued)*

Treatment	Administer intramuscular epinephrine immediately. H1 and H2 blockers can be given as adjunctive therapy. Albuterol and prednisone can help treat bronchospasm and delayed anaphylaxis.
Discussion	The patient has classic symptoms of anaphylaxis with hypotension, angioedema, bronchospasm, and urticaria. Anaphylaxis is the most severe form of **type I hypersensitivity reaction**. Any patient who has an episode of anaphylaxis should be provided with an epinephrine injector for home use so they can initiate therapy if an attack develops. Type I hypersensitivity reactions occur due to free antigens that cross-link IgE on mast cells and basophils. This causes an immediate release of histamine, which causes vasodilation at postcapillary venules. The delayed phase results from mast cells and basophils releasing cytokines that cause cellular inflammation. This hypersensitivity reaction develops rapidly after initial exposure to the antigen because the body preforms antibodies against it, so anaphylaxis occurs on the second exposure but not the first (as in this patient). **Delayed drug reactions (type IV)** can present with rash, but the other symptoms are typically lacking. Also, the patient clearly had a very immediate onset of symptoms, which makes anaphylaxis and type I hypersensitivity more likely. **Serum sickness (type III)** would also present with urticaria, but it would be accompanied by fever, arthralgias, and lymphadenopathy, which are not present in this patient. It would also occur 5–10 days after antigen exposure rather than within 30 minutes.

CASE 7 | Type II Hypersensitivity—Hemolytic Disease of the Newborn

A 26-year-old pregnant woman with limited prenatal care comes to the doctor because she is in labor. She has been pregnant once before and carried the baby to term without complications. The baby is born via spontaneous vaginal delivery. His APGAR scores are 8 and 9, but he appears jaundiced. The mother's blood type is O–, and the baby's type and screen are pending.

Evaluations/Tests	The infant's blood type is found to be B+. Hyperbilirubinemia is confirmed.
Treatment	The infant should be treated with phototherapy.
Discussion	**Hemolytic disease of the newborn is a type II hypersensitivity reaction** that results from maternal IgG that crosses the placenta. This can occur in one of two situations: (1) An Rh– mother who has previously been exposed to Rh+ blood, such as during a previous pregnancy, develops anti-D IgG antibodies, which can cross the placenta in subsequent pregnancies. (2) A mother with type O blood with anti-A or anti-B IgG antibodies that cross the placenta and can affect the first and later pregnancies. In both cases, the neonate can present with jaundice in the first 24 hours and anemia in the most severe cases. This occurs because IgG antibodies can cross the placenta and bind to antigens on the erythrocyte surface, causing opsonization of the red blood cells. This leads to activation of complement as well as natural killer cell–mediated cytotoxicity, lysing erythrocytes and releasing their contents into the bloodstream. Other examples of type II hypersensitivity include autoimmune hemolytic anemia and acute hemolytic transfusion reactions, both of which have a similar mechanism of action. In myasthenia gravis and Graves' disease, IgG antibodies bind to cell surface receptors and block their function. Type II hypersensitivity also includes diseases in which antibodies bind to cell surfaces and cause complement activation and inflammation, such as in Goodpasture syndrome and rheumatic fever. While **Gilbert syndrome** and **Crigler-Najjar syndrome** can both cause jaundice, they would be less likely to present this early. Additionally, the incompatible blood types between the mother and the infant make hemolytic disease of the newborn more likely.

CASE 8 | Type III Hypersensitivity—Serum Sickness

A 65-year-old man with coronary artery disease presents to the emergency department with acute onset of severe, substernal chest pain. An ECG demonstrates ST-segment elevations in leads V1–V4, and his troponins are elevated. The patient undergoes percutaneous coronary intervention and is started on abciximab. Ten days later, the patient presents with joint pains, fever, and a pruritic rash. On exam, the patient's temperature is 38.6°C, pulse is 110/min, respirations are 18/min, and blood pressure is 132/82 mmHg. The patient is noted to have urticaria on his arms, torso, and back.

Evaluation/Tests	Clinical diagnosis. Urinalysis shows proteinuria, and serum C3 level is decreased.
Treatment	Stop abciximab and use a different antiplatelet agent.

CASE 8 | Type III Hypersensitivity—Serum Sickness *(continued)*

Discussion	This patient is experiencing **serum sickness**, a **type III hypersensitivity reaction**. Serum sickness results from antibodies that form against foreign proteins. As in other type III hypersensitivity reactions, these antibodies form immune complexes, which are deposited into membranes. Immune complexes fix complement thus activating this cascade and releasing C5a, which attracts neutrophils. This reaction generates inflammation and damages surrounding tissues. Serum sickness is typically caused by drugs, such as chimeric monoclonal antibodies, acting as haptens that activate this response. The **Arthus reaction** is another form of type III hypersensitivity that can occur in response to drug administration. In individuals who have IgG against a particular antigen, intradermal administration of a drug with that antigen will cause immune complex formation in the skin and underlying small blood vessels, which leads to complement activation and neutrophil recruitment. This causes small vessel fibrinoid necrosis with neutrophil infiltration. The affected area will have edema, erythema, and even necrosis. This rare reaction is often associated with vaccine boosters. While urticaria would be typical of an **atopic reaction** to a medication, proteinuria and arthralgias would be unlikely.

CASE 9 | Type IV Hypersensitivity—Tuberculin (PPD) Skin Test

A 24-year-old nursing student receives his annual PPD skin test to screen for tuberculosis infection. Approximately 72 hours later, he develops an area of induration at the injection site measuring 16 mm.

Evaluation/Tests	For the general population, the cutoff for a positive PPD skin test (performed 48–72 hours after injection) is an area of induration at least 15 mm in transverse diameter. For health care workers, the cutoff is a minimum of 10 mm. For AIDS and transplant patients, who are expected to have a decreased immune response to tuberculin, the cutoff is a minimum of 5 mm.
Treatment	A positive test would be followed with a chest X-ray to rule out active tuberculosis. Treat latent tuberculosis (if CXR is negative) with isoniazid or rifampin.
Discussion	The **tuberculin skin test is an example of type IV hypersensitivity** induced by intradermal injection of the purified protein derivative (PPD) tuberculin from *Mycobacterium tuberculosis*. Type IV hypersensitivity reactions are T-cell-mediated reactions and thus do not involve antibodies, which differentiates type IV from the other forms of hypersensitivity reactions. Type IV hypersensitivity reactions occur through (1) direct cytotoxicity via CD8+ T-cells against targeted cells and (2) delayed-type hypersensitivity via sensitized CD4+ T-cells that release cytokines in response to an antigen. In patients with prior tuberculosis exposure, upon reexposure to similar antigens with the PPD skin test, antigen-presenting cells within the skin will reintroduce the antigen to memory T-cells, resulting in a rapid and strong secondary immune response. These memory T-cells, most of which are CD4+, can release chemokines and cytokines, which then coordinate a robust immune response. One such cytokine is interferon-γ (IFN-γ), which stimulates macrophages within the skin to phagocytose the injected protein. Macrophages can further secrete tumor necrosis factor-α (TNF-α), a potent activator of endothelium that drives further immune cell influx into tissue. Swelling and phagocytic cell infiltration near the site of injection results in induration. The PPD test will be positive in situations of current or past exposure and negative in patients without exposure. False positives may be seen in patients with a previous BCG vaccination or nontuberculosis mycobacterial infection. False negatives can be seen in patients with HIV infection (especially if their CD4+ cell counts are low) or in sarcoidosis. Another test for *M. tuberculosis* infection includes the IFN-γ release assay (IGRA), a blood-based test that exposes blood samples to TB antigens or controls and measures release of IFN-γ. IGRA does not require a follow-up visit and is not affected by BCG vaccination status.

BLOOD TRANSFUSION REACTIONS

Blood transfusion reactions are potentially serious complications that can occur within minutes to hours of initiating a transfusion. When facing a question that sounds like a potential blood transfusion reaction, the time course is important to consider when trying to determine the etiology of the reaction. Additionally, which symptoms predominate can help suggest a specific diagnosis. While several reactions can include fever, the accompanying symptoms will help determine which type of transfusion reaction is occurring and thus help narrow down the etiology.

CASE 10 | Anaphylactic Blood Transfusion Reaction

A 36-year-old previously healthy woman loses a significant amount of blood during a vaginal delivery. Bleeding is controlled and transfusion of packed red blood cells is initiated. Fifteen minutes after the transfusion is started, the patient reports itching and develops a rash on her arm through which she is receiving the transfusion. Within minutes, the rash spreads over her entire body, and she reports difficulty breathing. The patient's temperature is 37.9°C, pulse is 116/min, respirations are 24/min, and blood pressure is 82/44 mmHg. Wheezes are heard in bilateral lung fields.

Evaluation/Tests	Clinical diagnosis. Urinalysis and CBC are within normal limits.
Treatment	Treat with epinephrine and antihistamines. Albuterol and prednisone can help decrease the delayed phase of anaphylaxis. Vasopressors may be needed for hypotension.
Discussion	Anaphylactic blood transfusion reactions are type I hypersensitivity reactions against proteins in the plasma of administered blood products. This can occur in patients with IgA deficiency who produce anti-IgA antibodies upon receipt of IgA in a transfusion. As patients with selective IgA deficiency are typically asymptomatic, they may not know that they have this condition. Patients present as quickly as 15 minutes from the initiation of their transfusion and experience pruritus, urticaria, wheezing, hypotension, and shock. Epinephrine acts quickly while albuterol and prednisone help prevent the delayed phase of anaphylaxis that results from mast cell and basophil degranulation and release of other cytokines that further potentiate the inflammatory response. While the other transfusion reactions should be considered, the rapid onset of symptoms in this case makes anaphylaxis the most likely diagnosis. It can be further distinguished from other reactions with the presence of urticaria and pruritus, which suggest a type I hypersensitivity reaction. **Febrile nonhemolytic transfusion reactions (FNHTRs)** present with fever and chills approximately 1–6 hours after receiving a transfusion. These patients do not have hemolysis or hemodynamic instability. FNHTRs are a type II hypersensitivity reaction with host antibodies to donor human leukocyte antigens (HLA) and WBCs. Host antibodies bind to donor HLA, causing a cytotoxic response to donor white blood cells. Donor cells can then release cytokines, which causes an inflammatory response, including fever, chills, flushing, and/or headache. These cytokines are created and accumulate during the storage of blood products. FNHTR is the most common of the transfusion reactions and is not life-threatening. Management is symptomatic. **Acute hemolytic transfusion reactions (AHTR)** are type II hypersensitivity reactions in response to foreign antigens on erythrocytes. This typically occurs in response to ABO blood type incompatibility. For instance, if a patient with blood type A receives type B blood, the anti-B IgM antibodies in the patient's blood will react to the B antigens on the surface of donor RBCs. This leads to complement activation and formation of MAC on the RBC surface. Complement-mediated lysis causes cellular destruction and intravascular hemolysis, which causes an increase in unconjugated (indirect) bilirubin, decreased hemoglobin, and decreased haptoglobin since haptoglobin binds free hemoglobin from lysed cells. The additional cytokines from complement activation cause fever, tachypnea, tachycardia, and hypotension, which should be treated urgently with aggressive IV fluid resuscitation. These reactions are rare because patients are typically typed and screened so that they can receive properly matched blood products. AHTR could present with hypotension and tachypnea, but the patient in this vignette does not have signs of hemolysis, such as flank pain and jaundice. **Transfusion-related acute lung injury (TRALI)** is an adverse blood transfusion reaction due to donor antileukocyte antibodies attacking recipient pulmonary endothelial cells and neutrophils. Donor antibodies bind to antigens on intravascular neutrophils, which causes the release of cytokines and thus further neutrophil activation. Since the neutrophils are intravascular, their activation also causes endothelial damage, which leads to vascular leakage and pulmonary edema. The release of cytokines also causes vasodilation of pulmonary vasculature and further inflammatory pulmonary edema. This occurs within 6 hours of the transfusion. Patients with TRALI present with respiratory distress and pulmonary infiltrates due to noncardiogenic pulmonary edema. Chest X-ray would demonstrate inflammatory, noncardiogenic pulmonary edema. TRALI patients typically do not have urticaria and pruritus. Anaphylaxis would also occur more quickly than TRALI and would present with wheezing rather than the crackles of pulmonary edema.

TRANSPLANT REJECTION

Transplant grafts can be divided into autografts (the graft is from the patient), syngeneic grafts (from a clone or identical twin), allografts (from another human that is not an identical twin), and xenografts (from another species). Graft rejection is a common and potentially dangerous complication of transplants. Pretransplant workup and post-transplant immunosuppression

are aimed at preventing transplant rejection, but even optimal preparation and postoperative immunosuppression cannot always prevent this complication. When determining which type of transplant rejection is occurring, the time course and key features of the rejection are important factors to consider. Some opportunistic infections in transplant recipients include CMV, BK virus, *Candida* spp., and *Aspergillus*.

CASE 11 | Acute Transplant Rejection

A 54-year-old woman who received a kidney transplant 2 months ago presents for follow-up of her transplanted kidney. She is doing fairly well but has experienced malaise over the past week. The patient has been compliant with her immunosuppressant therapy. Her vital signs are within normal limits, and her physical exam is unremarkable. Her labs show a creatinine of 2.1, which is increased from a level of 1.2 at her last visit.

Evaluation/Tests	Kidney biopsy demonstrates vasculitis of renal vessels and a dense, lymphocytic, interstitial infiltrate.
Treatment	The patient's immunosuppressants should be increased in an effort to reverse the acute rejection.
Discussion	Acute transplant rejection most commonly occurs within 6 months of organ transplantation. It is the most common failure of transplantation and is prevented through immunosuppression. Acute transplant rejection can occur in one of two ways: (1) Cellular—In a type IV hypersensitivity reaction, CD8+ T-cells are activated against donor MHC's, which causes a vasculitis in the graft vessels with interstitial mononuclear cell infiltration. (2) Humoral—The recipient develops antibodies against the donor tissue, which leads to a type II hypersensitivity and subsequent necrotizing vasculitis. Complement activation also leads to release of chemokines for neutrophils, so a neutrophilic infiltrate may be seen on biopsy (in contrast to mononuclear cells seen in the cellular type). Symptoms depend on the organ that was transplanted, but patients may be asymptomatic. **Hyperacute transplant rejection** is a type II hypersensitivity reaction in which recipient preformed antibodies react to antigens on vascular endothelial cells in the grafted organ. The formation of antibody–antigen complexes leads to the activation of complement and adhesion of immune cells to the vascular wall. Endothelial damage activates the coagulation cascade and causes widespread thrombosis of the grafted organ vessels. As blood supply to the donor organ becomes compromised, the organ undergoes ischemia and subsequent necrosis, rapidly rendering the graft nonviable. Hyperacute transplant rejection occurs within minutes and will likely be seen before the patient leaves the operating room. Pretransplant screens aim to match organ recipients and organ donors such that the recipient would not have antibodies to antigens in the donated organ. Treatment of hyperacute rejection involves removal of the graft. **Chronic transplant rejection** occurs over months to years and is irreversible. The time course and histological findings can help differentiate between chronic and acute transplant rejection. While both may happen after a few months, acute transplant rejection will have a lymphocytic or neutrophilic vasculitis on biopsy. In contrast, chronic transplant rejection will have biopsy findings consistent with arteriosclerosis, parenchymal atrophy, and interstitial fibrosis rather than vasculitis. Inflammatory cells are an uncommon finding in chronic transplant rejection biopsies. Chronic transplant rejection manifests in various ways depending on the affected organ—vanishing bile duct syndrome in the liver, chronic graft nephropathy in the kidney, bronchiolitis obliterans in the lungs, and atherosclerosis in the heart. **GVHD** is less common in kidney transplants and would have more disseminated findings.

CASE 12 | Graft-Versus-Host Disease (GVHD)

A 68-year-old man who received a bone marrow transplant for multiple myeloma 1 month ago presents with a rash, nausea, and diarrhea for the past week. He has been compliant with his immunosuppressive therapy. The rash started on his neck and arms but has spread to his entire body. His diarrhea is watery and has been increasing in volume. On exam, the patient has a maculopapular rash covering his whole body. His sclerae are icteric. His abdomen is soft but diffusely tender to palpation, and hepatosplenomegaly is noted.

Evaluation/Tests	Clinical diagnosis. Histologic confirmation by biopsy of affected site (e.g., skin, GI tract, etc.). Direct bilirubin and alkaline phosphatase levels are elevated.
Treatment	Systemic glucocorticoids. Topical corticosteroids can be used with mild GVHD involving only the skin, with additional immunosuppression in steroid-refractory cases.

CASE 12 | Graft-Versus-Host Disease (GVHD) *(continued)*

Discussion	Graft-versus-host disease (GVHD) is typically a complication of allogeneic bone marrow transplants. In GVHD, a type IV hypersensitivity reaction occurs in which donor T-cells proliferate in the immunosuppressed recipient and attack host cells. Because the donor cells are multiplying in the host, they are not localized to the graft and thus cause systemic disease. The most commonly involved organs are the skin (maculopapular rash), GI (nausea, diarrhea), and liver (destruction of bile ducts, increased bilirubin and alkaline phosphatase). These disseminated findings help differentiate GVHD from other types of transplant rejection. GVHD can occur at any point, but the classic acute form typically occurs within the first 100 days after transplantation. Chronic GVHD typically presents much later. **Infectious** causes of **diarrhea** may also cause rash (e.g., *Salmonella typhi*), but the findings of hepatosplenomegaly and hepatic dysfunction are less likely.