CASE 2

A 36-year-old chemist with a 15-year history of bipolar disorder is rushed to the emergency department by his wife, who found him lying unconscious in the living room of their home. The patient's wife reports that he is prescribed lithium but does not regularly take it. The man's skin is bright red, and he is breathing rapidly. Upon presentation, his breath smells like bitter almonds.

What is the most likely diagnosis?
This man has ingested cyanide (the "bitter almond" breath is pathognomonic). During a manic episode, patients with bipolar disorder are more likely to use illegal drugs and engage in self-injurious behavior so a toxicology screen is mandatory. Other causes of unconsciousness, including dehydration, metabolic acidosis, and diabetic ketoacidosis, should be investigated.

What biochemical process is disrupted in this condition?
Cyanide is a direct inhibitor of one step in the electron transport chain (Figure 2-2). Cyanide inhibits cytochrome oxidase.

![Diagram of electron transport chain](image)

**FIGURE 2-2.** Cyanide inhibition of oxidative phosphorylation in the electron transport chain. ADP = adenosine diphosphate; ATP = adenosine triphosphate; FAD = oxidized flavin adenine dinucleotide; FADH₂ = reduced flavin adenine dinucleotide; NAD⁺ = oxidized nicotinamide adenine dinucleotide phosphate; NADH = reduced nicotinamide adenine dinucleotide phosphate. (Reproduced, with permission, from Le T, et al. First Aid for the USMLE Step 1: 2011. New York: McGraw-Hill, 2011: 100.)

Does this patient have a greater-than-normal or lower-than-normal proton concentration in the intermembrane space of his mitochondria?
The man has a lower proton concentration. The electron transport chain fuels the transport of protons from the mitochondrial matrix to the intermembrane space. Because this patient ingested cyanide and thus inhibited this process, his proton gradient is weakened; therefore, he has a lower concentration of protons in the intermembrane spaces of his mitochondria.

What is the appropriate treatment for this condition?
Amyl nitrite is used to treat cyanide poisoning. Amyl nitrate oxidizes hemoglobin to methemoglobin. This is normally undesirable because this form of hemoglobin binds oxygen less avidly. However, methemoglobin strongly binds cyanide, preventing it from further disrupting electron transport.

What other substances inhibit the electron transport chain?
Amytal, rotenone, antimycin A, azide, and carbon monoxide also inhibit the electron transport chain.

What other substances act within the mitochondria and reduce adenosine triphosphate (ATP) synthesis?
- Oligomycin is an example of a chemical that can directly inhibit mitochondrial ATP synthase. Although the proton gradient forms, ATP is not produced. As a result, electron transport ceases.
- Uncoupling agents such as 2,4-dinitrophenol allow protons to cross the inner mitochondrial membrane. Electron transport is not disrupted, but protons are able to flow into the matrix from the intermembrane space. This reduces the proton gradient that drives ATP formation.
### CASE 3

A 6-month-old boy with a history of frequent infections is brought to the emergency department because of stiff muscles and difficulty feeding. On examination he is found to have a carpopedal spasm, and tapping on his face in front of his ears leads to spasm of the facial muscle.

<table>
<thead>
<tr>
<th><strong>What is the most likely diagnosis?</strong></th>
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<tr>
<td>This child has DiGeorge syndrome (22q11 syndrome), which is characterized by hypoparathyroidism and T-cell deficiency. Severe combined immunodeficiency may cause both B- and T-cell deficiencies or T-cell deficiency exclusively in a given host. Hyper-IgM syndrome, IgA deficiency, and Bruton agammaglobulinemia all primarily affect B cells.</td>
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<th><strong>What is the etiology of this condition?</strong></th>
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<td>DiGeorge syndrome is caused by a developmental defect involving the third and fourth pharyngeal pouches. It results in a hypoplastic thymus and parathyroid glands. Laboratory tests of this patient would show hypocalcemia and low T-cell count. The hypocalcemia causes tetany and carpopedal spasm. Chvostek sign involves tapping on the facial nerve in front of the ear and observing spasm of the facial muscle; it is another indication of hypocalcemia.</td>
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<th><strong>This patient is at risk for developing what type of infections?</strong></th>
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<td>Because of the aplastic thymus, patients with this disorder have ineffective T cells and are particularly susceptible to viral and fungal infections.</td>
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<th><strong>What abnormality may be observed on an x-ray of the chest in this patient?</strong></th>
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<tr>
<td>An x-ray of the chest in a child with DiGeorge syndrome may show a reduced thymic shadow.</td>
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<th><strong>What other abnormalities are associated with this condition?</strong></th>
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<td>CATCH 22 is a mnemonic for the 22q11 syndrome, which involves a deletion in this region of chromosome 22. Clinical manifestations include Cardiac abnormalities, Abnormal facies, Thymic hypoplasia, Cleft palate, and Hypocalcemia. Velocardiofacial syndrome also arises from this gene and involves cardiac abnormalities, abnormal facies, and cleft palate.</td>
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A 12-year-old mentally retarded boy is brought into a health clinic in Peru. His parents have noted that he seems to have difficulty with his vision. Physical examination reveals bilateral dislocated lenses and a tall, thin body habitus with especially long extremities. Laboratory studies show increased levels of serum methionine and serum homocysteine.

What is the most likely diagnosis?
Homocystinuria.

What is the biochemical defect in this condition?
The most common form of inherited homocystinuria results from reduced activity of cystathionine synthase, an enzyme that converts homocysteine to cystathionine (Figure 2-8).

![Cystathionine Synthase Diagram]


What vitamin supplementation is appropriate in this condition?
Vitamin B₆ (pyridoxine) is a necessary cofactor with cystathionine synthase. Vitamin B₆ supplementation has been successful in many patients with this enzyme deficiency.

In addition to vitamin supplementation, what other dietary changes should be made?
The absence of cystathionine synthase means that cysteine cannot be formed from methionine. Therefore, cysteine becomes an essential amino acid. This child should be given a diet low in methionine and high in cysteine.

This boy has a marfanoid body habitus and lens subluxation, two characteristics of this condition. For which other conditions is this patient at greatly increased risk?
This child is at increased risk for cardiovascular disease. Elevated plasma homocysteine increases risk of coronary artery disease, stroke, and peripheral artery disease. He is also at risk for osteoporosis. Homocysteine inhibits collagen cross-linking and over time can cause osteoporosis.

What enzyme deficiency is most likely to be found in a patient with increased serum homocysteine but decreased serum methionine?
This could be caused by a deficiency of methionine synthase. This enzyme catalyzes the conversion of homocysteine to methionine. Like patients with cystathionine synthase deficiency, these patients often have central nervous system dysfunction and vascular disease.
CASE 8

A 5-month-old girl is brought to the pediatrician by her parents because she has been very sleepy lately and has been vomiting and sweating profusely at night. The infant’s mother says that their daughter was doing fine during the first months of life but began showing these changes shortly after she began weaning from breast milk. Laboratory testing reveals a serum glucose level of 30 mg/dL, and urinalysis is positive for reducing sugar but negative for glucose.

What is the most likely diagnosis?
Fructose intolerance.

What intermediate is elevated within the liver cells in this condition?
Fructose-1-phosphate is elevated in fructose intolerance.

What enzyme is deficient in this condition?
Aldolase B is deficient in this disorder.

How does this condition cause hypoglycemia?
Aldolase B catalyzes the conversion of fructose-1-phosphate into glyceraldehyde and dihydroxyacetone phosphate (DHAP) (Figure 2-7). Its absence results in accumulation of fructose-1-phosphate in liver cells and a consequent depletion of adenosine triphosphate (ATP). A low cellular supply of ATP inhibits glycogenolysis and gluconeogenesis leading to very low serum glucose. Excess fructose is lost in the urine.

FRUCTOSE METABOLISM (LIVER)

Fructose → Fructose-1-P
Fructokinase

ATP → ADP

Aldolase B

Fructose-1-P → Glyceraldehyde
Dihydroxyacetone-P

Triose kinase

Glycerol
NADH

Glyceraldehyde-3-P → Glycolysis
NAD

ATP → ADP

*Deficiency = fructose intolerance
• Deficiency = essential fructosuria


What is the appropriate treatment for this condition?
The condition is treated through the removal of fructose, sucrose (a disaccharide of glucose and fructose), and sorbitol from the diet.

Why did the infant exhibit no symptoms while exclusively fed breast milk?
Carbohydrates in breast milk derive largely from lactose rather than fructose.
A 2-year-old boy is brought to the pediatrician by his mother, who is visibly upset. The mother reports that her son has recently been biting his fingers and scratching his face incessantly. She says he was normal for the first months of his life but has become increasingly irritable since about 3 months of age. The mother also mentions that her son often has “orange-colored sand” in his diapers. Laboratory studies reveal a serum uric acid level of 55 mg/dL. Urinalysis reveals crystalluria and microscopic hematuria.

**What is the most likely diagnosis?**
Lesch-Nyhan syndrome.

**What is the biochemical defect in this condition?**
Lesch-Nyhan syndrome is characterized by a deficiency in hypoxanthine-guanine phosphoribosyltransferase (HGPRT).

**What is the function of the deficient enzyme?**
HGPRT plays a key role in the purine salvage pathway (Figure 2-10), recycling hypoxanthine and guanine to the purine nucleotide pool. In the absence of this enzyme, purine bases are degraded into uric acid, thus causing hyperuricemia. Uric acid crystals in the urine give rise to the crystalluria.

![Purine salvage pathway](image)

**What is the appropriate treatment for this condition?**
Allopurinol is a drug that inhibits xanthine oxidase, thus preventing the formation of uric acid from the more soluble hypoxanthine and xanthine. Hypoxanthine and xanthine can more easily be excreted in the urine. Doses should be titrated to normalize serum uric acid levels. To prevent self-injury, affected children often need lifelong benzodiazepine or barbiturate sedation, restraints, and behavioral therapy.

**What associated conditions are likely if this condition is not treated?**
Kidney stones, renal failure, gouty arthritis, and subcutaneous tophus deposits will result if the disorder is left untreated.

CASE 12

A 35-year-old man visits a fertility specialist with his 27-year-old wife. They have been trying to conceive for more than 13 months but have been unsuccessful. The husband has no previous children but the wife has two children from a prior marriage. Their past medical history is unremarkable except for repeated sinus infections and a chronic cough in the husband. Physical examination reveals a point of maximum impulse located at the right fifth intercostal margin.

What is the most likely diagnosis?
The fact that the wife has had prior children suggests that the cause of infertility lies in the husband. Given the history, Kartagener syndrome is most likely. This is a genetic disorder with an autosomal recessive inheritance pattern.

What is the cause of their infertility?
Abnormality in dynein, which is an adenosine triphosphatase that acts as a molecular motor and is responsible for retrograde transport of material along microtubules. In addition, it is required for movement of cilia and flagella. If this enzyme is not functional, it results in immotile sperm.

What is the cause of the husband's recurrent sinus infections?
The cilia of the respiratory epithelium require functional dynein for motility. Without it, they are unable to transport bacteria and particles out of the respiratory tract. The retained particles and bacteria can lead to infections as well as a chronic cough with sputum production.

What abnormality might be observed on x-ray of the chest?
Situs inversus, which on the chest x-ray, the heart is found predominantly on the right side of the thorax. It may also show bronchiectasis, with signs of dilated bronchioles.

What condition is caused by a mutation in microtubule polymerization?
Chédiak-Higashi syndrome is an autosomal recessive disorder caused by a defect in microtubule polymerization resulting in impaired migration of immune cells, such as neutrophils, and impaired lysosome fusion, which results in large granules visible within the cytoplasm (Figure 2-9). These both contribute to immune deficiency. Patients present with recurrent bacterial infections with staphylococci and streptococci.

There are a number of antimicrobial drugs that inhibit microtubule function. What are some examples?
Mebendazole and related drugs inhibit microtubule activity in helminths. Griseofulvin is an antifungal that acts on microtubules. A number of chemotherapeutic agents also interfere with microtubule function, such as vincristine, vinblastine, and taxols such as paclitaxel.