Nitrogen metabolism

I- Amino acids: disposal of nitrogen

Overview:

Unlike fats and carbohydrates, amino acids are not stored by the body, that is, no protein exists whose sole function is to maintain a supply of amino acids for future use.

Any amino acids in excess of the biosynthetic needs of the cell are rapidly degraded.

- The first phase of catabolism involves the removal of the α-amino groups (usually by transamination and subsequent oxidative deamination), forming ammonia and the corresponding α-keto acid—the “carbon skeletons” of amino acids.
- A portion of the free ammonia is excreted in the urine.
- In the second phase of amino acid catabolism, the carbon skeletons of the α-ketoacids are converted to common intermediates of energy producing, metabolic pathways.

Overall nitrogen metabolism:

- The amount of protein in the body (about 12 kg in a 70-kg man).
- Amino acid pool is defined as all the free amino acids are present in the body, for example, in cells, blood, and the extracellular fluids, is small (90-100 g of amino acids).

This pool is supplied by three sources:
1) Amino acids provided by the degradation of body proteins.
2) Amino acids derived from dietary protein.
3) Synthesis of nonessential amino acids from simple intermediates of metabolism.

Conversely, the amino pool is depleted by three routes:
1) Synthesis of body protein.
2) Amino acids consumed as precursors of essential nitrogen-containing small molecules.
3) Conversion of amino acids to glucose, glycogen, fatty acids, ketone bodies, or CO2 + H2O

Most proteins in the body are constantly being synthesized and then degraded, permitting the removal of abnormal or unneeded proteins.

Removal of nitrogen from amino acids:

The presence of the α-amino group keeps amino acids safely locked away from oxidative breakdown. Removing the α-amino group is essential for producing energy from any amino acid, and is an obligatory step in the catabolism of all amino acids.

Once removed, this nitrogen can be incorporated into other compounds or excreted, with the carbon skeletons being metabolized. This section describes transamination and oxidative deamination—reactions that ultimately provide ammonia and aspartate, the two sources of urea nitrogen.
A. Transamination: the funneling of amino groups to glutamate

The first step in the catabolism of most amino acids is the transfer of their α-amino group to α-ketoglutarate. The products are an α-keto acid (derived from the original amino acid) and glutamate.

α-Ketoglutarate plays a pivotal role in amino acid metabolism by accepting the amino groups from most amino acids, thus becoming glutamate.

This transfer of amino groups from one carbon skeleton to another is called transamination and catalyzed by a family of enzymes called aminotransferases (formerly called trans-aminases). These enzymes are found in the cytosol and mitochondria of cells throughout the body—especially those of the liver, kidney, intestine, and muscle.

All amino acids, with the exception of lysine and threonine, participate in transamination at some point in their catabolism. [Note: These two amino acids lose their α-amino groups by deamination.)]

1- Substrate specificity of aminotransferases:

Each aminotransferase is specific for one or, at most, a few amino group donors. Aminotransferases are named after the specific amino group donor, because the acceptor of the amino group is almost always α-ketoglutarate. The two most important aminotransferase reactions are catalyzed by alanine aminotransferase (ALT) and aspartate aminotransferase (AST)).

2- Diagnostic value of plasma aminotransferases:

Amino transferases are normally intracellular enzymes, with the low levels found in the plasma representing the release of cellular contents during normal cell turnover. The presence of elevated plasma levels of aminotransferases indicates damage to cells rich in these enzymes.

a. Liver disease: Plasma AST and ALT are elevated in nearly all liver diseases, but are particularly high in conditions that cause extensive cell necrosis, such as severe viral hepatitis, toxic injury, and prolonged circulatory collapse. ALT is more specific than AST for liver disease, but the latter is more sensitive because the liver contains larger amounts of AST.
b. Nonhepatic disease: Aminotransferases may be elevated in nonhepatic disease, such as myocardial infarction and muscle disorders. However, these disorders can usually be distinguished clinically from liver disease. Alanine transaminase (ALT) also called as glutamate pyruvate transaminase (GPT) and Aspartate transaminase (AST) also called as glutamate oxaloacetate transaminase (GOT) are the two most important transaminases of clinical importance.

B. Glutamate dehydrogenase: the oxidative deamination of amino acids
In contrast to transamination reactions that transfer amino groups, oxidative deamination by glutamate dehydrogenase results in the liberation of the amino group as free ammonia (NH3) (Figure 19.11). These reactions occur primarily in the liver and kidney. They provide α-keto acids that can enter the central pathway of energy metabolism, and ammonia, which is a source of nitrogen in urea synthesis.
1. **Glutamate dehydrogenase**: As described above, the amino groups of most amino acids are ultimately funneled to glutamate by means of transamination with α-ketoglutarate. Glutamate is unique in that it is the only amino acid that undergoes rapid oxidative deamination—a reaction catalyzed by glutamate dehydrogenase (see Figure 19.11).

Therefore, the sequential action of transamination (resulting in the collection of amino groups from most amino acids onto α-ketoglutarate to produce glutamate) and the oxidative deamination of that glutamate (regenerating α-ketoglutarate) provide a pathway whereby the amino groups of most amino acids can be released as ammonia.

![Figure 19.11](image)

**Figure 19.11**
Oxidative deamination by glutamate dehydrogenase.

**C. Transport of ammonia to the liver**

Two mechanisms are available in humans for the transport of ammonia from the peripheral tissues to the liver for its ultimate conversion to urea.

- The first, found in most tissues, uses glutamine synthetase to combine ammonia (NH₃) with glutamate to form glutamine—a nontoxic transport form of ammonia (Figure 19.13). The glutamine is transported in the blood to the liver where it is cleaved by glutaminase to produce glutamate and free ammonia.

- The second transport mechanism, used primarily by muscle, involves transamination of pyruvate (the end product of aerobic glycolysis) to form alanine (see Figure 19.8). Alanine is transported by the blood to the liver, where it is converted to pyruvate, again by transamination. In the liver, the pathway of gluconeogenesis can use the pyruvate to synthesize glucose, which can enter the blood and be used by muscle—a pathway called the glucose-alanine cycle.
Urea cycle:
Urea is the major disposal form of amino groups derived from amino acids, and accounts for about 90% of the nitrogen-containing components of urine. One nitrogen of the urea molecule is supplied by free ammonia and the other nitrogen by aspartate. [Note: Glutamate is the immediate precursor of both ammonia (through oxidative deamination by glutamate dehydrogenase) and aspartate nitrogen (through transamination of oxaloacetate by AST).] The carbon and oxygen of urea are derived from CO2. Urea is produced by the liver, and then is transported in the blood to the kidneys for excretion in the urine.

The Urea Cycle:
The first two reactions leading to the synthesis of urea occur in the mitochondria, whereas the remaining cycle enzymes are located in the cytosol.

1. Formation of carbamoyl phosphate:
Formation of carbamoyl phosphate by carbamoyl phosphate synthetase I is driven by cleavage of two molecules of ATP. Ammonia incorporated into carbamoyl phosphate is provided primarily by the oxidative deamination of glutamate by mitochondrial glutamate dehydrogenase (see Figure 19.11). Ultimately, the nitrogen atom derived from this ammonia becomes one of the nitrogens of urea.

2. Formation of citrulline:
The carbamoyl portion of carbamoyl phosphate is transferred to ornithine by ornithine transcarbamoylase as the high-energy phosphate is released as Pi. The reaction product, citrulline, is transported to the cytosol. Ornithine is regenerated with each turn of the urea cycle, much in the same way that oxaloacetate is regenerated by the reactions of the citric acid cycle.

3. Synthesis of argininosuccinate:
Argininosuccinate synthetase combines citrulline with aspartate to form argininosuccinate. The α-amino group of aspartate provides the second nitrogen that is ultimately incorporated into urea. The formation of argininosuccinate is driven by the cleavage of ATP to adenosine monophosphate (AMP) and pyrophosphate. This is the third and final molecule of ATP consumed in the formation of urea.
4. Cleavage of argininosuccinate:
Argininosuccinate is cleaved by argininosuccinatelyase to yield arginine and fumarate. The arginine formed by this reaction serves as the immediate precursor of urea. Fumarate produced in the urea cycle is hydrated to malate, providing a link with several metabolic pathways.

5. Cleavage of arginine to ornithine and urea:
Arginase cleaves arginine to ornithine and urea, and occurs almost exclusively in the liver. Thus, whereas other tissues, such as the kidney, can synthesize arginine by these reactions, only the liver can cleave arginine and, thereby, synthesize urea.

6. Fate of urea:
Urea diffuses from the liver, and is transported in the blood to the kidneys, where it is filtered and excreted in the urine. A portion of the urea diffuses from the blood into the intestine, and is cleaved to CO2 and NH3 by bacterial urease. This ammonia is partly lost in the feces, and is partly reabsorbed into the blood. In patients with kidney failure, plasma urea levels are elevated, promoting a greater transfer of urea from blood into the gut. The intestinal action of urease on this urea becomes a clinically important source of ammonia, contributing to the hyperammonemia often seen in these patients.
Figure 19.14
Reactions of the urea cycle.
METABOLISM OF AMMONIA

Ammonia is produced by all tissues during the metabolism of a variety of compounds, and it is disposed of primarily by formation of urea in the liver. However, the level of ammonia in the blood must be kept very low, because even slightly elevated concentrations (hyperammonemia) are toxic to the central nervous system (CNS). There must, therefore, be a metabolic mechanism by which nitrogen is moved from peripheral tissues to the liver for ultimate disposal as urea, while at the same time maintaining low levels of circulating ammonia.

A. Sources of ammonia

1. Amino acids are quantitatively the most important source of ammonia.

1. From glutamine: The kidneys generate ammonia from glutamine by the actions of renal glutaminase (Figure 19.17) and glutamate dehydrogenase. Most of this ammonia is excreted into the urine as NH4 +.

2. From bacterial action in the intestine: Ammonia is formed from urea by the action of bacterial urease in the lumen of the intestine. This ammonia is absorbed from the intestine by way of the portal vein and is almost quantitatively removed by the liver via conversion to urea.

3. From amines: Amines obtained from the diet, and monoamines that serve as hormones or neurotransmitters, give rise to ammonia by the action of amine oxidase.

4. From purines and pyrimidines: In the catabolism of purines and pyrimidines, amino groups attached to the rings are released as ammonia.

B. Transport of ammonia in the circulation

Although ammonia is constantly produced in the tissues, it is present at very low levels in blood. This is due both to the rapid removal of blood ammonia by the liver, and the fact that many tissues, particularly muscle, release amino acid nitrogen in the form of glutamine or alanine, rather than as free ammonia.

1. Urea: Formation of urea in the liver is quantitatively the most important disposal route for ammonia. Urea travels in the blood from the liver to the kidneys, where it passes into the glomerular filtrate.

2. Glutamine: This amide of glutamic acid provides a nontoxic storage and transport form of ammonia (Figure 19.18). The ATP-requiring formation of glutamine from glutamate and ammonia by glutamine synthetase occurs primarily in the muscle and liver, but is also important in the CNS where it is the major mechanism for the removal of ammonia in the brain.

Glutamine is found in plasma at concentrations higher than other amino acids—a finding consistent with its transport function. Circulating glutamine is removed by the liver and the kidneys and deaminated by glutaminase. In the liver, the NH3 produced is detoxified through conversion to urea, and in the kidney it can be used in the excretion of protons. The metabolism of ammonia is summarized in Figure 19.19.

C. Hyperammonemia

The capacity of the hepatic urea cycle exceeds the normal rates of ammonia generation, and the levels of serum ammonia are normally low (5–35 µmol/L). However, when liver function is compromised, due either to genetic defects of the urea cycle or liver disease, blood levels can rise above 1,000 µmol/L. Such hyperammonemia is a medical emergency, because ammonia has a direct neurotoxic effect on the CNS.
For example, elevated concentrations of ammonia in the blood cause the symptoms of ammonia intoxication, which include tremors, slurring of speech, somnolence, vomiting, cerebral edema, and blurring of vision. At high concentrations, ammonia can cause coma and death.
Figure 19.19
Metabolism of ammonia. Urea content in the urine is reported as urinary urea nitrogen or UUN. Urea in blood is reported as BUN (blood urea nitrogen). The enzymes glutamate dehydrogenase, glutamine synthetase, and carbamoyl phosphate synthetase I fix ammonia (NH₃) into organic molecules.
II-Synthesis and degradation of amino acids:

GLUCOGENIC AND KETOGENIC AMINO ACIDS
Amino acids can be classified as glucogenic, ketogenic, or both based on which of the seven intermediates are produced during their catabolism.

A. Glucogenic amino acids
Amino acids whose catabolism yields pyruvate or one of the intermediates of the citric acid cycle are termed glucogenic. These intermediates are substrates for gluconeogenesis and, therefore, can give rise to the net formation of glucose in the liver and kidney.

B. Ketogenic amino acids
Amino acids whose catabolism yields either acetoacetate or one of its precursors (acetyl CoA or acetoacetyl CoA) are termed ketogenic (see Figure 20.2). Acetoacetate is one of the ketone bodies.

CATABOLISM OF THE CARBON SKELETONS OF AMINO ACIDS:

A. Amino acids that form oxaloacetate
B. Amino acids that form α-ketoglutarate via glutamate
C. Amino acids that form pyruvate.
D. Amino acids that form fumarate.
E. Amino acids that form succinyl-CoA.
F. Amino acids that form acetyl CoA or acetoacetyl CoA.
METABOLIC DEFECTS IN AMINO ACID METABOLISM

A. Phenylketonuria
Phenylketonuria (PKU), caused by a deficiency of phenylalanine hydroxylase (Figure 20.15), is the most common clinically encountered inborn error of amino acid metabolism (prevalence 1:15,000). Biochemically, it is characterized by accumulation of phenylalanine (and a deficiency of tyrosine).

1. Characteristics of classic PKU:
   a. Elevated phenylalanine: Phenylalanine is present in elevated concentrations in tissues, plasma, and urine. Phenyllactate, phenylacetate, and phenylpyruvate, which are not normally produced in significant amounts in the presence of functional phenylalanine hydroxylase, are also elevated in PKU (Figure 20.17). These metabolites give urine a characteristic musty (“mousey”) odor. [Note: The disease acquired its name from the presence of a phenylketone (now known to be phenylpyruvate) in the urine.]
   
   b. CNS symptoms: Mental retardation, failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow are characteristic findings in PKU. The patient with untreated PKU typically shows symptoms of mental retardation by the age of 1 year, and rarely achieves an IQ greater than 50 (Figure 20.18). [Note: These clinical manifestations are now rarely seen as a result of neonatal screening programs.]
   
   c. Hypopigmentation: Patients with phenylketonuria often show a deficiency of pigmentation (fair hair, light skin color, and blue eyes). The hydroxylation of tyrosine by tyrosinase, which is the first step in the formation of the pigment melanin, is competitively inhibited by the high levels of phenylalanine present in PKU.

2. Neonatal screening and diagnosis of PKU: Early diagnosis of phenylketonuria is important because the disease is treatable by dietary means. Because of the lack of neonatal symptoms, laboratory testing for elevated blood levels of phenylalanine is mandatory for detection. However, the infant with PKU frequently has normal blood levels of phenylalanine at birth because the mother clears increased blood phenylalanine in her affected fetus through the placenta. Normal levels of phenylalanine may persist until the newborn is exposed to 24–48 hours of protein feeding. Thus, screening tests are typically done after this time to avoid false negatives. For newborns with a positive screening test, diagnosis is confirmed through quantitative determination of phenylalanine levels.

B. Albinism
Albinism refers to a group of conditions in which a defect in tyrosine metabolism results in a deficiency in the production of melanin. These defects result in the partial or full absence of pigment from the skin, hair, and eyes. Albinism appears in different forms, and it may be inherited.
Figure 20.15
A deficiency in phenylalanine hydroxylase results in the disease phenylketonuria (PKU).

Figure 20.17
Pathways of phenylalanine metabolism in normal individuals and in patients with phenylketonuria.
III- Conversion of amino acids to specialized products:

In addition to serving as building blocks for proteins, amino acids are precursors of many nitrogen-containing compounds that have important physiologic functions. These molecules include porphyrins, neurotransmitters, hormones, purines, and pyrimidines.

1- PORPHYRIN METABOLISM

Porphyrins are cyclic compounds that readily bind metal ions—usually Fe2+ or Fe3+. The most prevalent metalloporphyrin in humans is heme, which consists of one ferrous (Fe2+) iron ion coordinated in the center of the tetrapyrrole ring of protoporphyrin.

Heme is the prosthetic group for hemoglobin, myoglobin, the cytochromes, catalase, nitric oxide synthase, and peroxidase. These heme proteins are rapidly synthesized and degraded. For example, 6–7 g of hemoglobin are synthesized each day to replace heme lost through the normal turnover of erythrocytes. Coordinated with the turnover of heme proteins is the simultaneous synthesis and degradation of the associated porphyrins, and recycling of the bound iron ions.

B. Biosynthesis of heme

The major sites of heme biosynthesis are the liver, which synthesizes a number of heme proteins (particularly cytochrome P450 proteins), and the erythrocyte-producing cells of the bone marrow, which are active in hemoglobin synthesis. [Note: Over 85% of all heme synthesis occurs in erythroid tissue.]

D. Degradation of heme

After approximately 120 days in the circulation, red blood cells are taken up and degraded by the reticuloendothelial system, particularly in the liver and spleen (Figure 21.9). Approximately 85% of heme destined for degradation comes from senescent red blood cells, and 15% is from turnover of immature red blood cells and cytochromes from nonerythroid tissues.

1. Formation of bilirubin:

The first step in the degradation of heme is catalyzed by the microsomal heme oxygenase system of the reticuloendothelial cells. The green pigment biliverdin is produced as ferric iron and CO are released (see Figure 21.9). [Note: The CO has biologic function, acting as a signaling molecule and vasodilator.] Biliverdin is reduced, forming the redorange bilirubin. Bilirubin and its derivatives are collectively termed bile pigments. [Note: The changing colors of a bruise reflect the varying pattern of intermediates that occurs during heme degradation.]

2. Uptake of bilirubin by the liver:

Bilirubin is only slightly soluble in plasma and, therefore, is transported to the liver by binding noncovalently to albumin. [Note: Certain anionic drugs, such as salicylates and sulfonamides, can displace bilirubin from albumin, permitting bilirubin to enter the central nervous system. This causes the potential for neural damage in infants.] Bilirubin dissociates from the carrier albumin molecule, enters a hepatocyte via facilitated diffusion, and binds to intracellular proteins, particularly the protein ligand.
Figure 21.9
Formation of bilirubin from heme. UDP = uridine diphosphate.
Figure 21.10
Catabolism of heme: 
- **B** = bilirubin
- **BG** = bilirubin diglucuronide
- **U** = urobilinogen
- **O** = urobilin
- **A** = sterocobilin

1. Senescent red cells are a major source of heme proteins.
2. Breakdown of heme to bilirubin occurs in macrophages of the reticuloendothelial system (tissue macrophages, spleen, and liver).
3. Unconjugated bilirubin is transported through the blood (complexed to albumin) to the liver.
4. Bilirubin is taken up via facilitated diffusion by the liver and conjugated with glucuronic acid.
5. Conjugated bilirubin is actively secreted into bile and then the intestine.
6. In the intestine, glucuronic acid is removed by bacteria. The resulting bilirubin is converted to urobilinogen.
7. Some of the urobilinogen is reabsorbed from the gut and enters the portal blood.
8. A portion of this urobilinogen participates in the enterohepatic urobilinogen cycle.
9. The remainder of the urobilinogen is transported by the blood to the kidney, where it is converted to yellow urobilin and excreted, giving urine its characteristic color.
10. Urobilinogen is oxidized by intestinal bacteria to the brown sterocobilin.
3. **Formation of bilirubin diglucuronide:** In the hepatocyte, the solubility of bilirubin is increased by the addition of two molecules of glucuronic acid. [Note: This process is referred to as conjugation.]

4. **Secretion of bilirubin into bile:** Bilirubin diglucuronide (conjugated bilirubin) is actively transported against a concentration gradient into the bile canaliculi and then into the bile. This energy-dependent, rate-limiting step is susceptible to impairment in liver disease. Unconjugated bilirubin is normally not secreted.

5. **Formation of urobilins in the intestine:** Bilirubin diglucuronide is hydrolyzed and reduced by bacteria in the gut to yield urobilinogen, a colorless compound. Most of the urobilinogen is oxidized by intestinal bacteria to stercobilin, which gives feces the characteristic brown color. However, some of the urobilinogen is reabsorbed from the gut and enters the portal blood. A portion of this urobilinogen participates in the enterohepatic urobilinogen cycle in which it is taken up by the liver, and then resecreted into the bile. The remainder of the urobilinogen is transported by the blood to the kidney, where it is converted to yellow urobilin and excreted, giving urine its characteristic color. The metabolism of bilirubin is summarized in Figure 21.10.

**E. Jaundice**
Jaundice refers to the yellow color of skin, nail beds, and sclerae (whites of the eyes) caused by deposition of bilirubin, secondary to increased bilirubin levels in the blood (hyperbilirubinemia). Although not a disease, jaundice is usually a symptom of an underlying disorder.

**Jaundice in newborns:** Newborn infants, particularly if premature, often accumulate bilirubin, because the activity of hepatic bilirubin glucuronyltransferase is low at birth—it reaches adult levels in about 4 weeks. Elevated bilirubin, in excess of the binding capacity of albumin, can diffuse into the basal ganglia and cause toxic encephalopathy (kernicterus). Thus, newborns with significantly elevated bilirubin levels are treated with blue fluorescent light, which converts bilirubin to more polar and, hence, water-soluble isomers. These photoisomers can be excreted into the bile without conjugation to glucuronic acid.

**Catecholamines**

Dopamine, norepinephrine, and epinephrine are biologically active (biogenic) amines that are collectively termed catecholamines. Dopamine and norepinephrine are synthesized in the brain and function as neurotransmitters. Norepinephrine is also synthesized in the adrenal medulla, as is epinephrine.
**Histamine**

Histamine is a chemical messenger that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and possibly neurotransmission in parts of the brain. A powerful vasodilator, histamine is formed by decarboxylation of histidine in a reaction requiring PLP (Figure 21.17). It is secreted by mast cells as a result of allergic reactions or trauma. Histamine has no clinical applications, but agents that interfere with the action of histamine have important therapeutic applications.

**Creatine**

Creatine phosphate (also called phosphocreatine), the phosphorylated derivative of creatine found in muscle, is a high-energy compound that provides a small but rapidly mobilized reserve of high-energy phosphates that can be reversibly transferred to ADP (Figure 21.9) to maintain the intracellular level of ATP during the first few minutes of intense muscular contraction. [Note: The amount of creatine phosphate in the body is proportional to the muscle mass.]

**Figure 21.19**

Synthesis of creatine.

**Figure 21.17**

Biosynthesis of histamine. PLP = pyridoxal phosphate.
IV-Nucleotide Metabolism

NUCLEOTIDE STRUCTURE
Nucleotides are composed of a nitrogenous base, a pentose monosaccharide, and one, two, or three phosphate groups. The nitrogen containing bases belong to two families of compounds: the purines and the pyrimidines.

A. Purine and pyrimidine structures
Both DNA and RNA contain the same purine bases: adenine (A) and guanine (G). Both DNA and RNA contain the pyrimidine cytosine (C), but they differ in their second pyrimidine base: DNA contains thymine (T), whereas RNA contains uracil (U). T and U differ in that only T has a methyl group (Figure 22.1).

B. Nucleosides
The addition of a pentose sugar to a base produces a nucleoside. If the sugar is ribose, a ribonucleoside is produced; if the sugar is 2-deoxyribose, a deoxyribonucleoside is produced (Figure 22.3A).

C. Nucleotides
The addition of one or more phosphate groups to a nucleoside produces a nucleotide. If one phosphate group is attached to the 5'-carbon of the pentose, the structure is a nucleoside monophosphate, like adenosine monophosphate (AMP) (also called adenylyl). If a second or third phosphate is added to the nucleoside, a nucleoside diphosphate (for example, adenosine diphosphate or ADP) or triphosphate (for example, adenosine triphosphate or ATP) results (Figure 22.4).
DEGRADATION OF PURINE NUCLEOTIDES
Degradation of dietary nucleic acids occurs in the small intestine, where a family of pancreatic enzymes hydrolyzes the nucleic acids to nucleotides. Inside the intestinal mucosal cells, purine nucleotides are sequentially degraded by specific enzymes to nucleosides and free bases, with uric acid as the end product of this pathway.

A. Degradation of dietary nucleic acids in the small intestine
Ribonucleases and deoxyribonucleases, secreted by the pancreas, hydrolyze dietary RNA and DNA primarily to oligonucleotides. Oligonucleotides are further hydrolyzed by pancreatic phosphodiesterases, producing a mixture of 3'- and 5'-mononucleotides. In the intestinal mucosal cells, a family of nucleotidases removes the phosphate groups hydrolytically, releasing nucleosides that are further degraded to free bases. Dietary purine bases are not used to any appreciable extent for the synthesis of tissue nucleic acids. Instead, they are generally converted to uric acid in intestinal mucosal cells. Most of the uric acid enters the blood, and is eventually excreted in the urine.

B. Formation of uric acid
A summary of the steps in the production of uric acid and genetic diseases associated with deficiencies of specific degradative enzymes are shown in Figure 22.15. [Note: The bracketed numbers refer to specific reactions in the figure.]

C. Diseases associated with purine degradation
1. Gout: Gout is a disorder characterized by high levels of uric acid—the end product of purine catabolism—in blood (hyperuricemia), as a result of either the overproduction or underexcretion of uric acid. The hyperuricemia can lead to the deposition of mono-sodium urate crystals in the joints, and an inflammatory response to the crystals, causing first acute and then progressing to chronic gouty arthritis. Formation of uric acid stones in the kidney (urolithiasis) may also be seen.

   a. Underexcretion of uric acid.
   b. Overproduction of uric acid.
**ADENOSINE DEAMINASE (ADA) DEFICIENCY**

- This autosomal recessive deficiency causes a type of severe combined immunodeficiency (SCID), involving T-cell, B-cell and NK-cell depletion (lymphopenia).
- Untreated ADA-deficient children usually die before 2 years of age from overwhelming infection; treatments include BMT, ERT and gene therapy.

**PURINE NUCLEOSIDE PHOSPHORYLASE (PNP) DEFICIENCY**

- This autosomal recessive deficiency is rarer and less severe than ADA deficiency.
- Affects only T-cells.
- Characterized by recurrent infections and neurodevelopmental delay.

**GOUT**

- This disorder is characterized by hyperuricemia with recurrent attacks of acute arthritic joint inflammation, caused by deposition of monosodium urate crystals.
- In gout, the hyperuricemia results primarily from the underexcretion of uric acid. Overproduction of uric acid is less common, and known causes involve certain inborn errors of metabolism or increased availability of purines.
- Crystal deposition (tophi) may be seen in soft tissue and in kidney (urolithiasis).
- Treatment with allopurinol inhibits xanthine oxidase, resulting in an accumulation of hypoxanthine and xanthine—compounds more soluble than uric acid.

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Figure 22.15

The degradation of purine nucleotides to uric acid, illustrating some of the genetic diseases associated with this pathway. [Note: The numbers in brackets refer to the corresponding numbered citations in the text.]