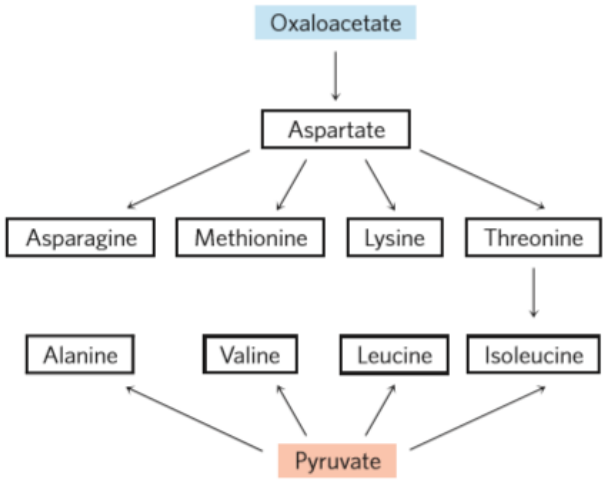
UNIT 3

Three nonessential and six essential amino acids are synthesized form Oxaloacetate and Pyruvate



Alanine and aspartate are synthesized from pyruvate and oxaloacetate, respectively, by transamination from glutamate. Asparagine is synthesized by amidation of aspartate, with glutamine donating the NH_4^+. These are nonessential amino acids, and their simple biosynthetic pathways occur in all organisms.

Malignant lymphocytes present in childhood acute lymphoblastic leukemia (ALL) require serum asparagine for growth. The chemotherapy for ALL is administered together with an L-asparaginase derived from bacteria, with the enzyme functioning to reduce serum asparagine. The combined treatment results in a greater than 95% remission rate in cases of childhood ALL (L-asparaginase treatment alone produces remission in 40% to 60% of cases). However, the asparaginase treatment has some deleterious side effects, and about 10% of patients who achieve remission eventually suffer relapse, with tumors resistant to drug therapy.

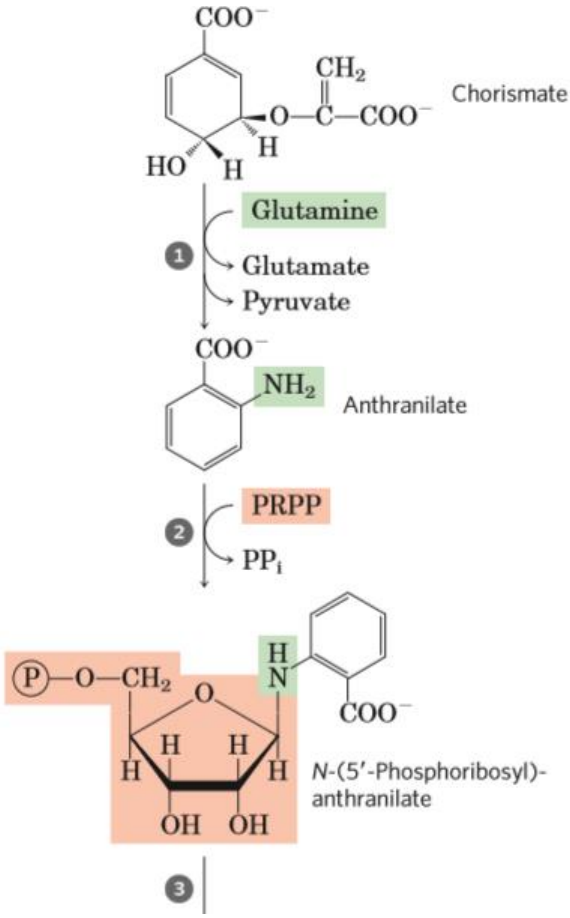
Methionine, threonine, lysine, isoleucine, valine, and leucine are essential amino acids; humans cannot synthesize them. Their biosynthetic pathways are complex and interconnected. In some cases, the pathways in bacteria, fungi, and plants differ significantly. Aspartate gives rise to methionine, threonine, and lysine. Branch points occur at aspartate semialdehyde, an intermediate in all three pathways, and at homoserine, a precursor of threonine and methionine. Threonine, in turn, is one of the precursors of isoleucine. The valine and isoleucine pathways share four enzymes. Pyruvate gives rise to valine and isoleucine in pathways that begin with condensation of two carbons of pyruvate (in the form of hydroxyethyl thiamine pyrophosphate) with another molecule of pyruvate (the valine path) or with α-ketobutyrate (the isoleucine path). The α-ketobutyrate is derived from threonine in

a reaction that requires pyridoxal phosphate. An intermediate in the valine pathway, ketoisovalerate, is the starting point for a four-step branch pathway leading to leucine.

Chorismite is a Key Intermediate in the Synthesis of Tryptophan, Phenylalanine and Tyrosine

Branched pathway to tryptophan, phenylalanine, and tyrosine, occurring in bacteria, fungi, and plants, is the main biological route of aromatic ring formation.

The first four steps produce shikimate, a seven-carbon molecule derived from erythrose 4-phosphate and phosphoenolpyruvate (metabolic precursors). Shikimate is converted to chorismate in three steps that include the addition of three more carbons from another molecule of phosphoenolpyruvate. **Chorismate** is the first branch point of the pathway, with one branch leading to tryptophan, the other to phenylalanine and tyrosine. The indole ring of tryptophan is derived from the ring carbons and amino group of anthranilate plus two carbons derived from PRPP.



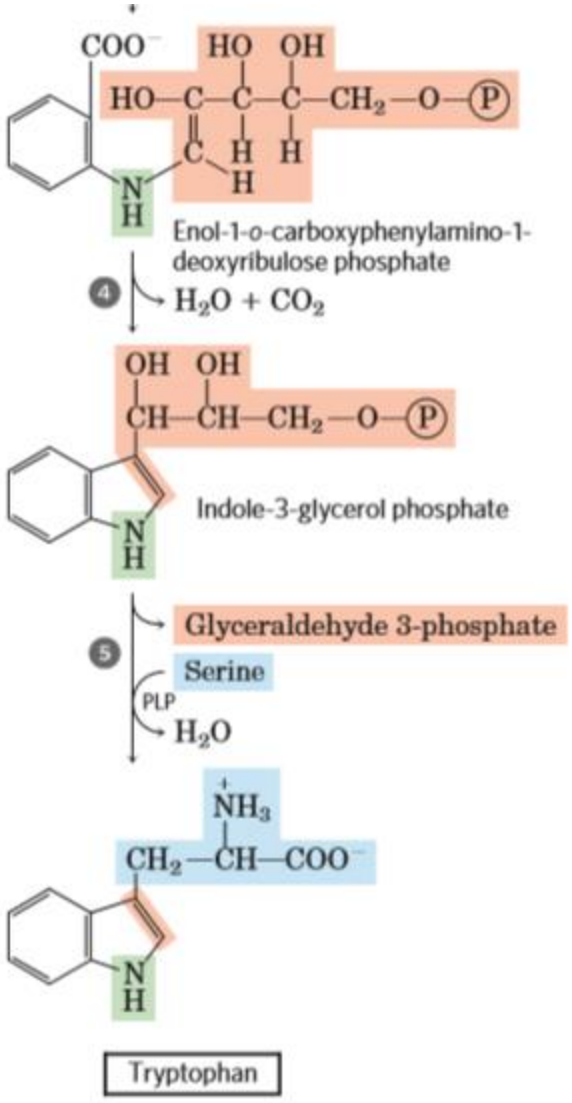


Figure: Biosynthesis of Tryptophan from Chorismate.

The final reaction in the sequence is catalyzed by **tryptophan synthase**. This enzyme has an α2β2 subunit structure and can be dissociated into two α subunits and a β2 unit that catalyze different parts of the overall reaction. The second part of the reaction requires pyridoxal phosphate. Indole formed in the first part is not released by the enzyme, but instead moves through a channel from the α-subunit active site to one of the β-subunit active sites, where it condenses with a Schiff base intermediate derived from serine and PLP.

Pathway enzymes are generally components of a large, multienzyme complex in both bacteria and eukaryotes (reaction is efficient, better regulated and avoids diffusion of substrate/product).

In plants and bacteria, phenylalanine and tyrosine are synthesized from chorismate in pathways much less complex than the tryptophan pathway. The common intermediate is

prephenate (Fig. 22–21). The final step in both cases is transamination with glutamate. Animals can produce tyrosine directly from phenylalanine through hydroxylation at C-4 of the phenyl group by phenylalanine hydroxylase; this enzyme also participates in the degradation of phenylalanine (see Figs 18–23, 18–24). **Tyrosine is considered a conditionally essential amino acid, or as nonessential insofar as it can be synthesized from the essential amino acid phenylalanine.**

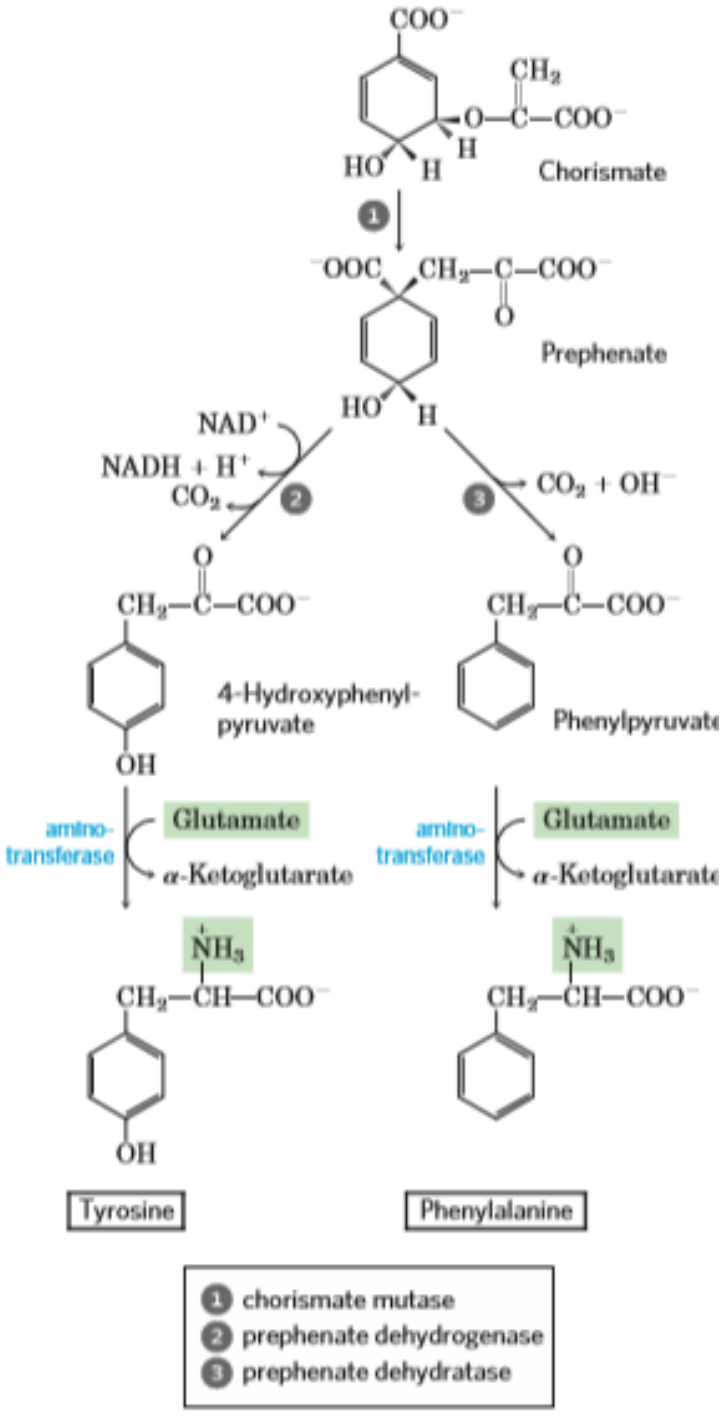


FIGURE 22–21 Biosynthesis of phenylalanine and tyrosine

Histidine biosynthesis uses precursors of purine biosynthesis

Histidine is derived from three precursors:

- PRPP contributes five carbons
- Purine ring of ATP contributes a nitrogen and a carbon
- Glutamine supplies the second ring nitrogen

Use of ATP as a metabolite: The use of ATP as a metabolite rather than a high-energy cofactor is unusual—but not wasteful, because it dovetails with the purine biosynthetic pathway. The remnant of ATP that is released after the transfer of N-1 and C-2 is 5-aminoimidazole-4carboxamide ribonucleotide (AICAR), an intermediate of purine biosynthesis that is rapidly recycled to ATP.

Amino acid biosynthesis is under Allosteric Regulation

Regulation takes place in part through **feedback inhibition**: first reaction is inhibited by the end product of the pathway. This first reaction is often catalyzed by an allosteric enzyme that plays an important role in the overall control of flux through that pathway. For example, Figure 22–23 shows the allosteric regulation of isoleucine synthesis from threonine.

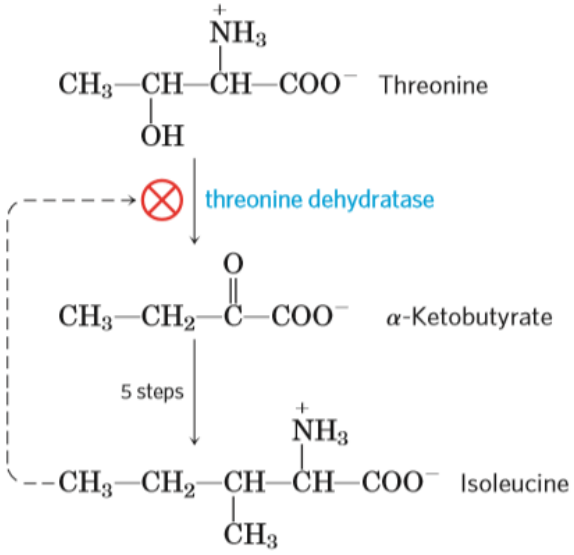


FIGURE 22–23 Allosteric regulation of isoleucine biosynthesis. The first reaction in the pathway from threonine to isoleucine is inhibited by the end product, isoleucine. This was one of the first examples of allosteric feedback inhibition to be discovered. The steps from α-ketobutyrate to isoleucine correspond to steps 18 through 21 in Figure 22-17 (five steps, because 19 is a two-step reaction).

Allosteric regulation of an individual enzyme can be considerably more complex. An example is the remarkable set of allosteric controls exerted on glutamine synthetase of *E. coli*. Six products derived from glutamine serve as negative feedback modulators of the enzyme, and the overall effects of these and other modulators are more than additive. Such regulation is called **concerted inhibition**.

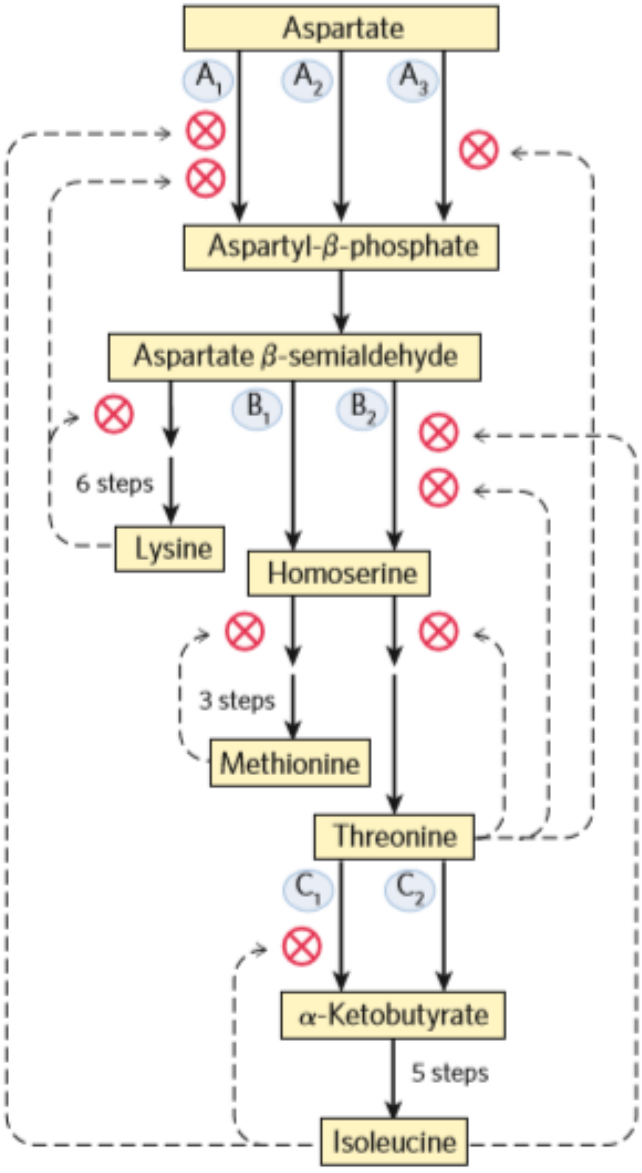


FIGURE 22–24: Interlocking regulatory mechanisms in the biosynthesis of several amino acids derived from aspartate in *E. coli*. Three enzymes (A, B, C) have either two or three isozyme forms, indicated by numerical subscripts. In each case, one isozyme (A2, B1, and C2) has no allosteric regulation; these isozymes are regulated by changes in the amount of enzyme synthesized. Synthesis of isozymes A2 and B1 is repressed when methionine levels

are high, and synthesis of isozyme C2 is repressed when isoleucine levels are high. Enzyme A is aspartokinase; B, homoserine dehydrogenase; C, threonine dehydratase.