cyclooxgenases, called COX-1 and COX-2. COX-1 is produced in response to inflammatory stimuli and is also constitutively expressed in most tissues, where it may serve a homeostatic function (e.g., fluid and electrolyte balance in the kidneys, cytoprotection in the gastrointestinal tract). In contrast, COX-2 is induced by inflammatory stimuli and thus generates the prostaglandins that are involved in inflammatory reactions, but it is low or absent in most normal tissues.

Prostaglandins are divided into series based on structural features as coded by a letter (PGD, PGE, PGF, PGG, and PGH) and a subscript numeral (e.g., 1, 2), which indicates the number of double bonds in the compound. The most important ones in inflammation are PGE_2, PGD_2, PGF_{2a}, PGI_2 (prostacyclin), and TxA_2 (thromboxane A2), each of which is derived by the action of a specific enzyme on an intermediate in the pathway. Some of these enzymes have restricted tissue distribution. For example, platelets contain the enzyme thromboxane synthase, and hence TxA_2 is the major product in these cells. TxA_2, a potent platelet-aggregating agent and vasoconstrictor, is itself unstable and rapidly converted to its inactive form TxB_2. Vascular endothelium lacks thromboxane synthase but possesses prostacyclin synthase, which is responsible for the formation of prostacyclin (PGI_2) and its stable end product PGF_{1a}. Prostacyclin is a vasodilator and a potent inhibitor of platelet aggregation, and also markedly potentiates the permeability-increasing and chemotactic effects of other mediators. A thromboxane-prostacyclin imbalance has been implicated as an early event in thrombus formation in coronary and cerebral blood vessels. PGD_2 is the major prostaglandin made by mast cells; along with PGE_2 (which is more widely distributed), it causes vasodilation and increases the permeability of postcapillary venules, thus potentiating edema formation. PGF_{2a} stimulates the contraction of uterine and bronchial smooth muscle and small arterioles, and PGD_2 is a chemoattractant for neutrophils.

In addition to their local effects, the prostaglandins are involved in the pathogenesis of *pain* and *fever* in inflammation. PGE_2 is hyperalgesic and makes the skin hypersensitive to painful stimuli, such as intradermal injection of suboptimal concentrations of histamine and bradykinin. It is involved in cytokine-induced fever during infections (described later).

Leukotrienes

***Leukotrienes* are produced by leukocytes and mast cells by the action of lipoxygenase and are involved in vascular and smooth muscle reactions and leukocyte recruitment.** There are three different lipoxygenases, 5-lipoxygenase being the predominant one in neutrophils. This enzyme converts AA to 5-hydroxyeicosatetraenoic acid, which is chemotactic for neutrophils, and is the precursor of the leukotrienes. LTB_4 is a potent chemotactic agent and activator of neutrophils, causing aggregation and adhesion of the cells to venular endothelium, generation of ROS, and release of lysosomal enzymes. The cysteinyl-containing leukotrienes LTC_4, LTD_4, and LTE_4 cause intense vasoconstriction, bronchospasm (important in asthma), and increased permeability of venules. Leukotrienes are more potent than is histamine in increasing vascular permeability and causing bronchospasm.

Lipoxins

***Lipoxins* are also generated from AA by the lipoxygenase pathway, but unlike prostaglandins and leukotrienes, the lipoxins suppress inflammation by inhibiting the recruitment of leukocytes.** They inhibit neutrophil chemotaxis and adhesion to endothelium. They are also unusual in that two cell populations are required for the transcellular biosynthesis of these mediators. Leukocytes, particularly neutrophils, produce intermediates in lipoxin synthesis, and these are converted to lipoxins by platelets interacting with the leukocytes.

Pharmacologic Inhibitors of Prostaglandins and Leukotrienes

The importance of eicosanoids in inflammation has driven attempts to develop drugs that inhibit their production or actions and thus suppress inflammation. These anti-inflammatory drugs include the following.

- **Cyclooxygenase inhibitors** include aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. They inhibit both COX-1 and COX-2 and thus inhibit prostaglandin synthesis (hence their efficacy in treating pain and fever); aspirin does this by irreversibly acetylating and inactivating cyclooxygenases. Selective COX-2 inhibitors are a newer class of these drugs; they are 200-300 fold more potent in blocking COX-2 than COX-1. There has been great interest in COX-2 as a therapeutic target because of the possibility that COX-1 is responsible for the production of prostaglandins that are involved in both inflammation and homeostatic functions (e.g., fluid and electrolyte balance in the kidneys, cytoprotection in the gastrointestinal tract), whereas COX-2 generates prostaglandins that are involved only in inflammatory reactions. If this idea is correct, the selective COX-2 inhibitors should be anti-inflammatory without having the toxicities of the non-selective inhibitors, such as gastric ulceration. However, these distinctions are not absolute, as COX-2 also seems to play a role in normal homeostasis. Furthermore, selective COX-2 inhibitors may increase the risk of cardiovascular and cerebrovascular events, possibly because they impair endothelial cell production of prostacyclin (PGI_2), a vasodilator and inhibitor of platelet aggregation, but leave intact the COX-1-mediated production by platelets of thromboxane A_2 (TxA_2), an important mediator of platelet aggregation and vasoconstriction. Thus, selective COX-2 inhibition may tilt the balance towards thromboxane and promote vascular thrombosis, especially in individuals with other factors that increase the risk of thrombosis. Nevertheless, these drugs are still used in individuals who do not have risk factors for cardiovascular disease when their benefits outweigh their risks.
- **Lipoxygenase inhibitors.** 5-lipoxygenase is not affected by NSAIDs, and many new inhibitors of this enzyme pathway have been developed. Pharmacologic agents that inhibit leukotriene production (e.g., Zileuton) are useful in the treatment of asthma.
- **Corticosteroids** are broad-spectrum antiinflammatory agents that reduce the transcription of genes encoding COX-2, phospholipase A_2, proinflammatory cytokines (e.g., IL-1 and TNF), and iNOS.