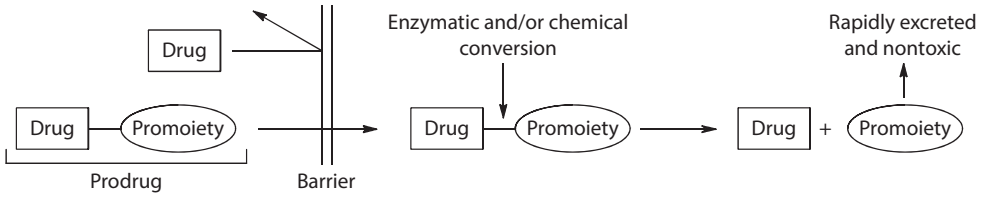

FIGURE 10.1 Simplified illustration of the prodrug concept.

do not contain an obvious promoiety, but these prodrugs form the active compound through one, or with today's increasing levels of technical sophistication, through a cascade of metabolic reactions such as oxidation, reduction, hydrolysis, or phosphorylation in vivo. In some rare cases, a prodrug may consist of two active drugs which are merged together in a single molecule. These derivatives, in which each drug acts as a promoiety for the other, are called codrugs. Finally, also soft drugs rely upon bioconversion to dictate their course of action. However, soft drugs are not a class of prodrugs. Opposite of prodrugs, soft drugs are active molecules that become deactivated by the bioconversion process after exerting their therapeutic effect. The prodrug concept is illustrated in Figure 10.1.

10.3 HISTORY AND CURRENT PREVALENCE OF PRODRUGS

The term "prodrug" was first introduced by Adrien Albert in 1958. However, the prodrug concept had been implemented long before Albert's publication. Early examples of prodrugs (Figure 10.2) are methenamine (or hexamine) and acetylsalicylic acid (or aspirin) which were introduced in 1899. Methenamine was intentionally designed to release antibacterial formaldehyde along with ammonium ions in acidic urea for the treatment of urinary tract infection. In the similar way, acetylsalicylic acid was designed to be a less-irritating and better-tasting replacement for the anti-inflammatory drug salicylic acid. Unlike methenamine and acetylsalicylic acid, prontosil that was introduced in 1935 and isoniazid that was introduced in 1952 were not intentionally designed as prodrugs, but their prodrug nature was revealed in hindsight. The discovery of sulfanilamide being the active antibacterial metabolite released from prontosil by reductive enzymes gave rise to the era of sulfonamide antibiotics. The prodrug nature of the antituberculosis drug isoniazid was discovered in hindsight more than 40 years after its launch. Bioconversion of isoniazid is catalyzed by the mycobacterial catalase-peroxidase called KatG. The reactive species generated by bioconversion form adducts with NAD^+ and $NADP^+$ which are potent inhibitors of biosynthesis of mycolic acid required for the mycobacterial cell wall.

Since the 1960s, there has been an explosive increase in the use of prodrugs in drug discovery and development. Today, the interest in prodrugs is evident based on published journal articles,

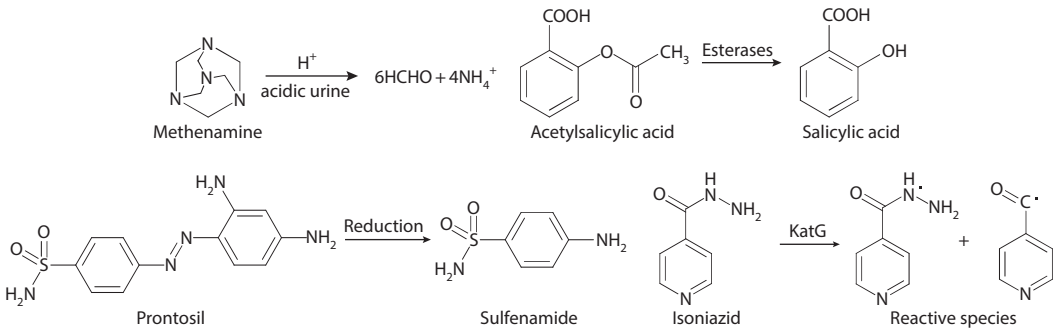

FIGURE 10.2 Early prodrug examples in clinical use.