

# Historical Perspective

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## 1 CONTROVERSIES SPANNING PAST, PRESENT, AND FUTURE

Two major issues have been debated throughout the history of drug metabolism, and are still disputed to some degree. One is the name itself, the other is the physiological purpose of “drug” metabolism. In the 1800s and early 1900s, the generally agreed purpose of these reactions was reflected in the most widely used name, *detoxication mechanisms*. However, *detoxication* became widely recognized as a misnomer because not all parent compounds were toxic and not all metabolites were less or nontoxic. A better term was not invented until the 1950s when the term “drug metabolism” was coined. While handy, this term was still not entirely valid, and it needed silent agreement that “drug” be not restricted to medicinal compounds (Bachmann and Bickel, 1985–86). Thus, *xenobiotic metabolism* became popular starting in the 1970s, especially in circles studying carcinogens and environmental compounds. Xenobiotic, by definition, included all compounds foreign to the organism, not just medicinal ones. However, even in the early 1900s many examples were already known of metabolism of endogenous compounds, for example, steroids undergoing glucuronidation. These early examples of endogenous substrates were generally dismissed because they typically occurred at much higher concentrations than normally present, so-called “supraphysiological” concentrations. While none of these three terms could be considered ideal, in 1947 R.T. Williams concluded that the field of detoxication included “... all those metabolic processes not specifically covered by the main streams of fat, carbohydrate and protein intermediary metabolism” (Williams, 1947). Williams went on to explain that, “Detoxication is, in fact, the study of the metabolism of organic compounds other than lipids, carbohydrates, proteins and closely related natural compounds, although the lines of demarcation between these two groups is by no means a sharp one ...” (Williams, 1947; Bachmann and Bickel, 1985–86). Thereby, the earliest clear description of the field mainly described what it was not, and later terms were not much more precise.

The physiological purpose of these reactions was also widely debated. Of note is that several of the early theories are still considered at least partially valid. The first theories tried to answer the question of how these transformations were related to