Chemical Mechanisms in Toxicology

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> We pray that every field of science may contribute in bringing happiness—not disaster—to human beings.[1]

1 INTRODUCTION

This chapter deals with the mechanisms involved in the biotransformation of drugs to chemically reactive metabolites, current experimental techniques used to identify reactive metabolites, and the potential consequences of reactive metabolite formation as it relates to the discovery of nontoxic drugs. Many pharmaceutical researchers in the fields of drug metabolism and toxicology currently perceive chemically reactive metabolites as an unwanted feature of any drug or drug candidate (Baillie, 2008; Kumar *et al.*, 2008). Therefore, an imperative goal in drug discovery is to eliminate, or to substantially decrease, the metabolic activation liability of drug candidates leading to the increased probability of safer drugs being successfully developed (Baillie and Kassahun, 2001; Kalgutkar and Soglia, 2005; Park *et al.*, 2005b; Baillie, 2006; Doss and Baillie, 2006; Williams, 2006). Drug metabolism scientists today are trained in taking closer and closer looks at the metabolism of new chemical entities sometimes having greater and greater complexity. One of the most important objectives in the pharmaceutical industry is to be able to make knowledgeable judgments about hidden risks so that new drugs that could be potentially toxic to patients are never released (Evans *et al.*, 2004; Nassar and Lopez-Anaya, 2004; Evans and Baillie, 2005).

The history of the subject discussed in this chapter may have started more than 200 years ago with a report published by the English surgeon Percivall Pott (1714–1788; Pott, 1775). Pott is credited with recognizing one of the first known industrial-linked diseases when he described the association between working as a chimney sweep and

[1] A quotation from Kenichi Fukui. He was corecipient of the Nobel Prize in Chemistry in 1981 for investigations into the mechanisms of chemical reactions.

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