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Adverse Drug Reactions

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Preface

Adverse drug reactions (ADRs) remain a major health issue. A recent study in the United Kingdom found that 6.5% of hospital admissions were precipitated by an ADR (Pirmohamed et al. 2004). In addition, they markedly increase the cost and uncertainty of drug development. Two decades ago, the major problem leading to drug candidate failure involved problems with metabolism and pharmacokinetics; now, the major problems are lack of efficacy and toxicity, and from 1975 to 2000, over 10% of the drugs approved by the FDA either had to be withdrawn or achieved a "black box" warning because of unexpected adverse reactions (Lasser et al. 2002). The basic mechanisms of the most common "type A" ADRs such as gastrointestinal bleeding caused by nonsteroidal antiinflammatory drugs and bleeding caused by warfarin are well known. However, the mechanisms of most ADRs, especially idiosyncratic drug reactions, are not understood, and that makes it impossible to predict which drug candidates will cause such reactions and which patients are at high risk. This is unlikely to change rapidly because the unpredictable nature and virtual lack of animal models makes mechanistic studies very difficult. It is worrisome that, despite thousands of person/years of work and the availability of good animal models, our understanding of the mechanism of acetaminophen liver toxicity is not complete, and this is touched on in several chapters in this book. It is likely that advances in understanding basic mechanisms of ADRs will depend on advances in other fields of biomedical sciences, especially immunology.

In this book, we attempt to describe the current state of knowledge in this field with a focus on idiosyncratic drug reactions because they are the most difficult to deal with. It starts with a general description of the major targets for ADRs followed by a description of what are presently believed to be mediators and biochemical pathways involved in idiosyncratic IDRs. There is also a description of several examples of ADRs that serve to illustrate specific aspects of ADR mechanisms. Ultimately, better methods are needed to predict which drug candidates are likely to cause ADRs and which patients are at increased risk, but as mentioned above, we are far from this goal. There are a few examples where specific genotypes have been linked to specific ADRs, and the number of cases where this will prove useful is

likely to markedly increase in the future; however, it is unlikely that genotype alone will predict all, or even most, ADRs. With respect to screening drug candidates for ADR potential, it is my opinion that screening out candidates that form large amounts of reactive metabolite and making drugs more potent has made drugs safer, but there is no clear evidence to support this opinion, and this strategy will not eliminate ADRs. At present, there are no general biomarkers that predict ADR risk.

Despite the magnitude of human and financial costs of ADRs, the amount of basic research in this area is very limited. This field certainly has its challenges but the potential rewards are great.

Toronto, Canada Jack Uetrecht

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