

# Evolution of Drug–Drug Interactions: A Personal Viewpoint

Edward A Hartshorn

In 1966, Dr. Don Francke discussed with me his intention to publish a new pharmacy journal, to be called *Drug Intelligence*. He asked if I would review a symposium, “Clinical Effects of Interactions Between Drugs,” in the *Proceedings of the Royal Society of Medicine* from 1965 and write an article on drug interactions for his new journal. Don suggested that monitoring for drug interactions would be an important role for pharmacists.

With the impetus of this symposium, a series of drug interaction articles was published in *Drug Intelligence* beginning with the first issue of 1968 (volume 2) and continuing through 1976. The articles reviewed the literature of drug–drug interactions by drug class (eg, antiinfectives, psychotropics). Don compiled these articles into a *Handbook of Drug Interactions*, first published in 1970.

In 1971, Dr. Philip Hansten, whose interest also was aroused by the symposium, published one of the first books on drug interactions that listed specific drug–drug combinations, giving the mechanism and probable clinical importance, and suggested intervention. During the following 4 decades, a number of drug interaction texts have been published using the same format developed by Dr. Hansten.

## Major Breakthroughs

### DRUG INTERACTION STUDIES

The term “drug interaction” was not recognized by *Index Medicus*, the primary reference source in the 1960s. To locate articles on drug interactions, one had to use the search terms drug synergism, drug antagonism, and drug toxicity.

The literature of drug–drug interactions in the 1960s was based primarily on animal experiments, with a few case reports. Clinical reports seemed to focus on oral anti-coagulants or interactions of the monoamine oxidase inhibitors. With practitioners noting more drug interactions in the 1970s and 1980s, publication of both case reports

and clinical studies increased. Because of the large number of reports, drug interaction texts attempted to categorize the interactions based on their potential severity and documentation, often on a scale of 1 (established or avoid this combination) to 5 (interaction is unlikely). Many screening programs limited their screening to only the more “important” interactions (ie, categories 1–3). In the 1980s, a method was proposed for estimating the probability of an adverse reaction (Naranjo probability scale). Although not developed for drug interactions, this method is now widely used for drug interactions in an attempt to provide more stringent guidelines for supporting clinical observation.

## Enzyme Systems

Drug interaction reports from the 1960s described enzyme induction and inhibition simply in terms of hepatic enzymes. In the 1970s, cytochrome P450 was found to be a major hepatic drug-metabolizing enzyme, capable of being induced or inhibited by other drugs. Today we recognize that the cytochrome P450 gene families are particularly important in oxidative metabolism of many drugs. We also recognize that, within specific isoenzymes, there are genetic variations that influence the rate of drug metabolism among individuals and ethnic groups. In vitro studies with isoenzymes are conducted to predict drug interactions and, in vivo, probe drugs are used to determine the effect of a drug on a specific isoenzyme system.

## Drug Transport Systems

Unrecognized between the 1960s and 1980s, drug transport proteins were recently discovered to pose another variable to drug disposition. One of the first substances to be recognized as transporting drugs across plasma membranes was P-glycoprotein, a member of the adenosine triphosphate-binding cassette transporters. Today we recognize a myriad of drug transport systems, both influx and efflux. The role of many of these systems in drug kinetics and interactions is yet to unfold.

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## Computer Programs

In the 1960s, a search of the literature involved using the paperbound *Index Medicus*. From articles referenced there, drug interaction information was abstracted and typed, and the data gave birth to or modified monographs in various drug interaction books. In the 1970s, several groups computerized patient records and drug interaction screening programs. Today, most pharmacies have a computerized drug interaction screening program, many associated with computerized patient records.

## The Future

Systems are being developed to assist in predicting the likelihood of a drug–drug interaction. With advances in pharmacogenomics, we will be able to genetically type individuals as to their drug-metabolizing enzyme activity. We will know from both in vitro and in vivo studies how

drugs are metabolized or eliminated and whether they affect the kinetics of other drugs. Pathological conditions that affect drug disposition will be loaded into the computer, and programs will indicate the likelihood of an adverse drug–drug interaction in specific disease states and suggest appropriate intervention.

Clinical pharmacists have become the most knowledgeable healthcare providers on drug interactions. As the number of drugs increases, so does the potential for interactions. In light of individual variability and changing circumstances influencing the interaction between drugs, the safe and effective use of drugs remains the domain of the pharmacotherapist.

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