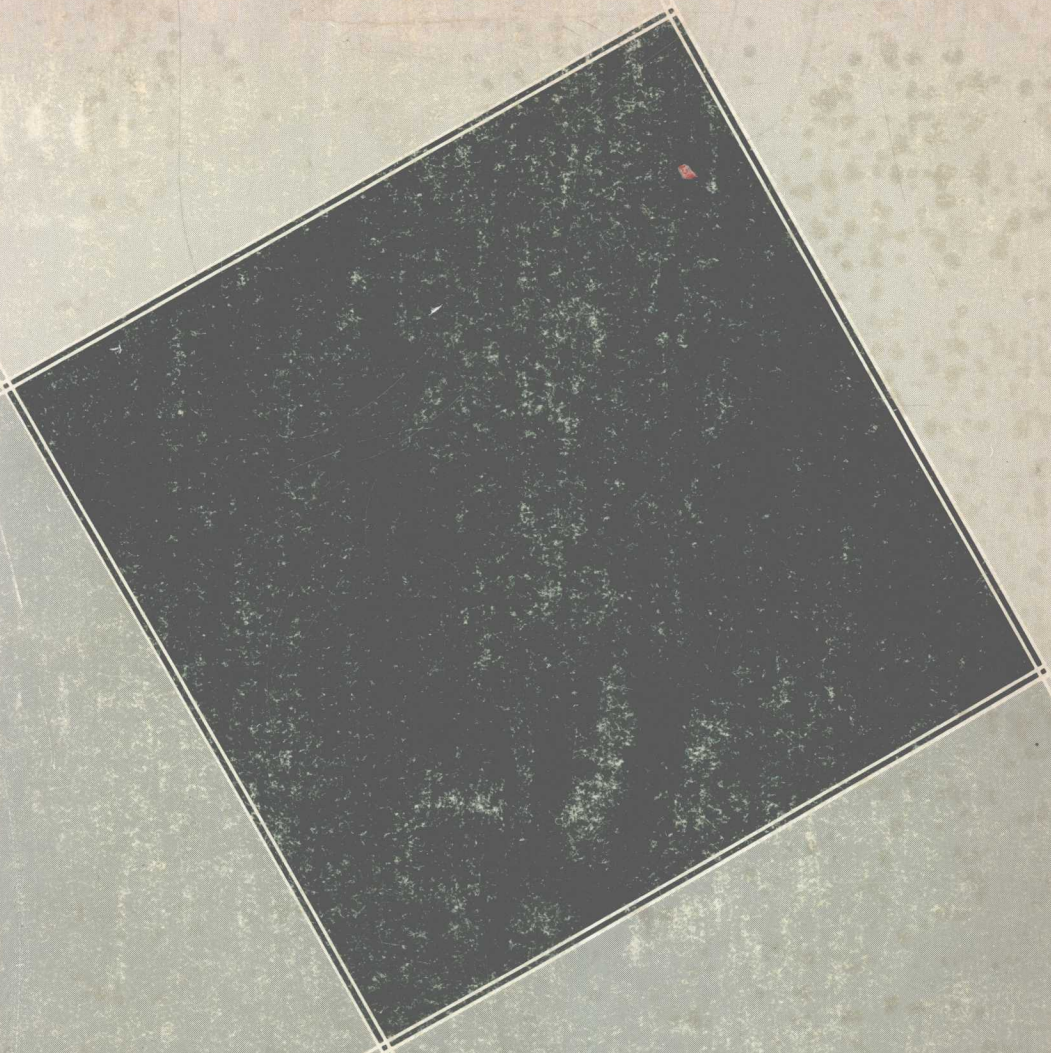

Drug Interactions Update 1984

by Edward A. Hartshorn

American Society of Hospital Pharmacists

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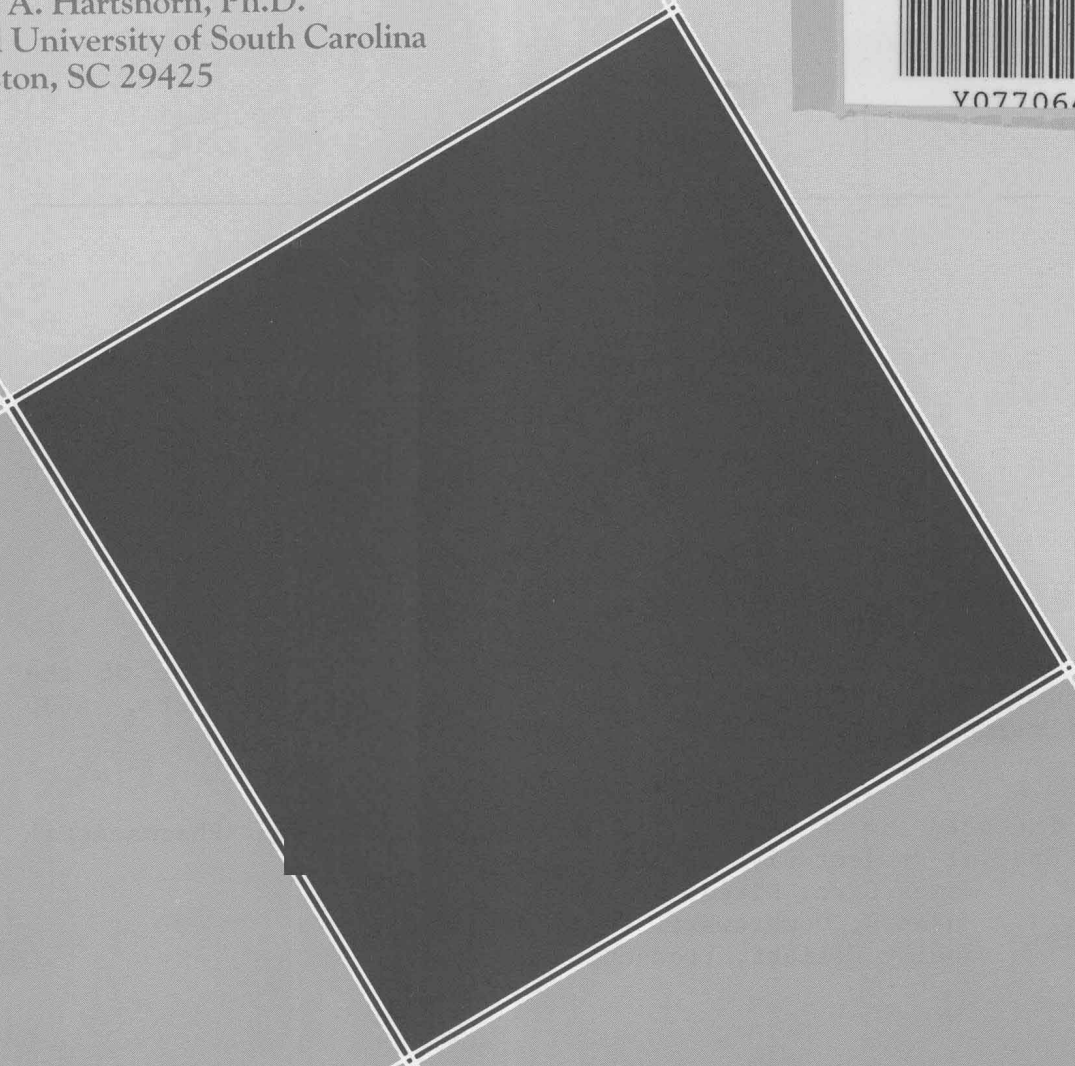

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DEDICATION

To Dr. J

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CONTENTS

DRUG INTERACTIONS UPDATE 1984

Introduction to the Publication

This is the third annual edition of Drug Interactions Update. Two drug interaction references now offer periodic updates. However, they concentrate on clinically important drug - drug interactions. This UPDATE includes reports of studies which reveal no interactions (this is discussed in more detail later), and, more importantly, it attempts to report factors and substances, such as foods, pathological factors (e.g., renal dysfunction), or physiological factors (e.g., age) which alter the pharmacokinetics or pharmacodynamics of drugs.

What This Update Is And What It Is Not

This update is essentially an annotated bibliography of the drug interaction references read during 1984. Some articles included herein were published in 1983. A few journals were not available to the writer, hence only the reference (without a summary) is given. On occasions, an abstract or review was found in a secondary source. In such cases I have condensed the abstract or comment, giving credit to the secondary source when I remembered to do so.

This UPDATE is NOT a drug interaction text reporting on the historical documentation of a particular drug interaction and suggesting appropriate actions to take. I have tried to give each interaction a personal interpretation as to its clinical relevance, and occasionally there is an editorial comment. For interactions which have been reported in past years (and, indeed, most of the interactions herein were reported previously), I would refer you to texts such as Hansten's Drug Interactions, [Philadelphia:Lea & Febiger, 1985?], Stockley's Drug Interactions [Boston:Blackwell Sci Pub Co., 1982], Drug Interaction Facts [St Louis:JB Lippincott, 1984] with its quarterly updates, or Shinn's Evaluations of Drug Interactions [St Louis: C.V.Mosby, 1985] with bimonthly updates. Use Drug Interactions Update 1984 to determine if an interaction has been reported after publication of the above basic texts or if there is new information about a previously reported interaction. More importantly, use this reference (and past editions) to determine if physiological or pathological factors alter drug action (the effect of cystic fibrosis on the kinetics of antibiotics seemed to be a "hot" topic for 1984). Such interactions are referenced by both drug name and physiological/pathological condition. For the use of a drug in an infant or geriatric patient, look under "Age"; for renal impairment or cirrhosis of the liver, look under "Renal Function" or "Hepatic Function" respectively. I have tried to think of various terms which might be used and have cross referenced them to the terms I used. Your suggestions on additional cross reference terms or other means to improve the usefulness of this UPDATE would be most gratefully accepted.

How to Use the Update

The reader is urged to use the INDEX to find a specific drug interaction. When more than one drug is studied (common with beta blockers and benzodiazepines), the interaction is listed under the object drug (see definition, p. 10, Introduction) of greatest importance or first alphabetically. The index will list all drugs studied and will indicate the title under which the interaction is listed. However, in drug interaction review articles, I will not try to list all the drugs discussed in the review. If the review is of a particular drug (e.g., cimetidine), the review will be found in the appropriate chapter. If the review is a general review, it will be placed alphabetically under "Drug Interactions" in the Miscellaneous Drug Section.

Most drugs are listed within broad pharmacological categories (see table of contents). However, the interaction description is generally given under the "object drug", that is, the drug whose action is altered in the interaction (see Introduction for further definitions).

Generic names of drugs are used when practical. A representative trade name may be included in parenthesis next to the generic name. The use of the trade name is only to assist those not familiar with the generic name; it does NOT imply that the trade named product was the one involved in the interaction. A trade name - generic name index is included in the back of the book immediately preceding the general index.

Reviewer's Code and Notes

Prepublication comments suggested that this review indicate in some manner an opinion of the clinical importance of the interaction. A numerical code (1, 2, 3, 4) is used; the number follows the "precipitant" drug heading. The code number implies one of the following meanings:

(1) This denotes a clinically important interaction which appears to produce adverse reactions in a substantial number of patients. A patient receiving these two drugs should be closely monitored when the precipitant drug is started, stopped, or given concurrently with the object drug. The dose of the object drug may need to be changed.

(2) Several interpretations may be made for an interaction coded as a "2". The drug interaction has been reported but it may be important in a few persons and only of slight or moderate importance in others. Or, clinical experience with the interaction is too limited to determine its true importance in the population as a whole. Or, clinicians disagree with the occurrence and/or importance of this interaction. Nevertheless, clinicians should be aware of the potential for altered drug effect when this combination of drugs is administered to a patient.

(3) This code number is used for interactions which are reported by one or more investigators but the interaction appears not to be clinically important, the validity of the report is questionable, or

other studies indicate opposite results or no interaction at all. In some instances, code "3" interactions may have extenuating circumstances which cloud the issue or which may be more important in altering the drug action or patient response than the "interacting" drug. The beta blockers, as object drugs, may fit category "3" well. There is little evidence of a close relationship between either beneficial results or many side effects and the drug's blood level. We can see drug-induced changes in the blood level of certain beta blockers without evidence of any change in clinical response.

(4) This number is used when the report indicates there is no interaction. In many instances, such reports are important, as discussed below.

What is Included in Drug Interactions Update?

- **Non Interactions:** A number of papers reported drug combinations which did not interact. These cannot be ignored, for they may contest other reports of interactions or may be indicative of differences among drugs of one therapeutic class (e.g., cimetidine vs ranitidine. Such information may be of value to clinicians attempting to choose drugs which do not interact .

- **Case Histories:** Some articles are merely reports of patients who received two (or more) drugs and had an unexpected reaction. Many of these appear as "Letters to the Editor". Such reports are often the first hint of a drug interaction problem; others document the clinical importance of interactions predicted by studies conducted in healthy subjects. The validity of a true interaction with some case reports may be questionable; other reports may precipitate a cascade of anecdotal comments in later issues of the journal. Often the observation of a possible interaction stimulates a practitioner to study the drug combination more carefully, either in other patients or in volunteers, to either confirm or dismiss the proposed interaction. Lancet, Drug Intelligence and Clinical Pharmacy, Clinical Pharmacy, and New England Journal of Medicine are journals whose articles were, to a large extent, made up of case histories.

- **Investigative Studies:** Investigative or research studies often use healthy volunteers but some use patients as subjects. Such studies frequently monitor certain pharmacokinetic parameters of the drug, such as blood level, area under the concentration-time curve (AUC), rate of excretion, half-life, etc. Such reports may or may not be concerned about toxic symptoms or changes in the subject's condition. Changes in kinetic parameters of a drug may occur consistently and be statistically significant without evidence of a clinical problem. Clinical Pharmacology and Therapeutics, British Journal of Clinical Pharmacology, and European Journal of Clinical Pharmacology frequently contain investigative studies.

- **Comments:** Some "Letters" (to the editor) and editorials are comments or criticisms of reports of drug interactions. They often add to our knowledge of the mechanism, suggest other factors which influence the change in drug action, or offer evidence supporting or refuting a reported drug interaction. Such letters and comments are so designated at the end of the individual reference.

- **Human Data:** Most reports in this UPDATE are based on human data. Occasionally an investigator will confirm the results of a drug interaction in humans by experiments in animals; sometimes an in vitro experiment will have important inferences to a human reaction. Such reports are then included and are clearly marked.

- **Pharmacological Interactions:** Some writers consider true interactions to be only those where there is an altered pharmacokinetic parameter. Others group pharmacological interactions with pharmacodynamic interactions. Pharmacological interactions are considered by some as merely expected side effects. Pharmacological interactions are often reported as an interaction only when there is a fatal or serious event because of the use of two or more drugs. The most common "pharmacological" interactions are those resulting from additive pharmacological properties of CNS depressants or anticholinergic drugs. This UPDATE attempts to avoid reporting articles where two or more drugs are combined logically and deliberately to obtain an additive pharmacological effect (as is so common with different antihypertensive drugs). This UPDATE does include reports where additive (or, occasionally, antagonistic) pharmacological actions of drugs produce unwanted, often serious, reactions.

- **Drug - Nondrug Interactions:** In the past few years I have received inquiries about the effect of certain pathological conditions on drug action, such as, "What effect will a low serum albumin level have on the blood level and effectiveness of theophylline?" In my dealings with drug interactions, I consider "drug-drug interactions" to be but a segment of a broad field of drug interactions. Drugs may interact with numerous conditions and chemicals, hence interactions with factors such as smoking, insecticides, foods, endogenous substances, and laboratory tests are included in this UPDATE. More importantly, a deliberate effort has been made to include abstracts of articles reporting physiological and pathological conditions (e.g., age, renal or hepatic impairment, obesity, etc.) which alter drug action. Such information should become a part of the clinician's knowledge required for assessing the reason for a change in a patient's condition or response to a drug. Foods, environmental factors, and physiologic or pathologic conditions which alter drug action are listed under the name of the drug affected. A "special classes" section near the end of the text lists interactions in which a drug affects foods, physiological organ function, or laboratory tests.

The basic criterion for including an article in this UPDATE has been whether the information will help the practitioner better understand a patient's response to a drug.

INTRODUCTION TO DRUG INTERACTIONS

Definitions

In 1966, I wrote, "Drug interaction is the phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another (or the same) drug" [Drug Intelligence 1968;2:5]. In the mid 1960s and early 1970s a drug-drug interaction was noted when the administration of one drug perceptibly altered the patient's response to another drug. Today many drug interaction studies report changes in pharmacokinetic parameters of a drug without any obvious change in the subject's response to the drug. Hence, today, a drug-drug interaction may be defined as the phenomenon which occurs when the effects and/or kinetics of one drug (occasionally, both drugs) are altered by the prior or concomitant administration of another drug. In my opinion, the term "drug interaction" encompasses a larger meaning as described later under "Scope of Drug Interactions."

Although drug interactions are often looked upon as harbingers of ill effects, many are beneficial (e.g., probenecid - penicillin). Hence, "drug interaction" is NOT "drug incompatibility" or "therapeutic incompatibility" or "adverse reaction". An interaction may be beneficial in one patient and harmful in another, or may be beneficial on one occasion and harmful on another.

In 1981, Aronson and Grahame-Smith used the terms "object drug" and "precipitant drug" [Br Med J 1981;282:288]. Although not acknowledging the terminology, Stockley's text, Drug Interaction Facts, and Evaluations of Drug Interactions list drug interactions principally by the object drug. According to Aronson and Grahame-Smith's description, an object drug is the drug whose action is altered in a drug interaction. The precipitant drug is the drug which causes the altered action. A drug may be an object drug on one occasion and a precipitant drug on another occasion (phenytoin is an excellent example; an enzyme inducer whose serum levels are altered by enzyme inhibitors). In some instances, both drugs in an interaction may have their action altered by the interactions taking place. With many pharmacological interactions, it is impossible to name an object or precipitant drug (e.g., excessive CNS depression in subjects receiving diazepam and methyldopa). Thus, while this terminology is a handy and perhaps logical manner to categorize drug interactions, a number of interactions still defy a clear description.

Mechanisms of Drug Interactions

- **Pharmacokinetic:** The classical drug interactions are likely to be "pharmacokinetic interactions." That is, one drug alters the rate or extent of absorption, distribution, metabolism, or excretion of another drug. This is often measured as maximum serum concentration, time to maximum serum concentration, percent protein binding, plasma half-life, elimination half-life, area under the concentration-time curve (AUC), etc.

- **Pharmacologic:** Drugs may have similar or opposite pharmacological effects even though they are categorized in completely different classes. Often these effects are considered secondary pharmacological actions or side effects (e.g., drowsiness with antihistamines). When adverse reactions are reported because of additive side effects, such reactions may be considered drug interactions. Deaths due to paralytic ileus in subjects receiving two or more drugs with anticholinergic actions (e.g., antidepressants plus antiparkinson drugs) is typical of a pharmacological drug interaction.

- **Pharmacodynamic:** Technically, pharmacodynamic interactions are all interactions where the pharmacodynamics (action) of a drug are altered by another drug. Hence, some consider all interactions not "pharmacokinetic" (i.e., all interactions with a change in drug action without a change in drug blood level) to be pharmacodynamic. There are some interactions which fail to fit neatly into either the pharmacokinetic or pharmacologic categories (e.g., digitalis toxicity as a result of thiazide-induced hypokalemia). Such reactions have been termed "pharmacodynamic" interactions by those who still use the "pharmacologic" category.

Scope of Drug Interactions

The definition of drug interaction given above was for a "drug - drug" interaction. This is most commonly interpreted as interactions between prescribed medications. Considering interactions in a broader sense, i.e., some chemical substance or some pathological change in body chemistry alters a drug's effect, or, a drug alters the patient's response to a stimulus, there are a number of potential problems to be considered under this broader umbrella of "drug interactions".

- **Over-The-Counter (OTC) Medications:** OTC medications may have a pharmacological action which is additive to that of prescribed medications; others may have the ability to complex with drugs in the gut and alter their rate or degree of absorption; still others may alter the rate of metabolism or excretion of another drug. Many of the classical "OTC-Drug interactions" are poorly documented and have questionable clinical relevance. A careful drug history must be taken to detect possible OTC-drug interactions. OTC drugs which have been reported to interact with other medications include antacids, adsorbants, antihistamines, sympathomimetics, and aspirin. These chemicals are found in many OTC antidiarrheal, stomach upset, cough, cold, decongestant, appetite suppressant, pain, fever, sleep, and anxiety medications.

- **Food and Nutrient Supplements:** Drugs may alter taste perception, cause nausea and loss of appetite, or cause increase in appetite. Such reactions are seldom considered as drug interactions. However, foods and nutrient substances may alter drug absorption, metabolism, or excretion. A number of foods contain pharmacologically active ingredients which may alter a patient's response to a drug. On the other hand, occasionally, drugs may interfere with the absorption, metabolism, or excretion of nutrients. One complex area seldom addressed is the effect of cancer

chemotherapeutics on the absorption, metabolism, or excretion of other drugs or food stuffs. Many drug - food interactions listed in review articles are poorly documented.

- **Physiological and Pathological Factors:** An important concept which, to my knowledge, has been ignored in review articles, is the effect of certain physiological or pathological factors on drug activity. Impaired renal function, impaired liver function, low serum proteins, very young or very old age, obesity, etc. may all affect a patient's response to drugs. At least one computer company has expressed an interest in incorporating such data into their information base. Such information may be important in determining the proper dosage regimen for a drug. On occasions, a drug may alter a physiological function, such as hepatic blood flow, which, in turn, may alter the effect of another drug. Abstracts of articles reporting such interactions are included in this UPDATE.

- **Environment and Environmental Contaminants:** An ingredient in cigarette smoke and charcoal broiled foods as well as certain vegetables has the capability of stimulating the activity of drug-metabolizing enzymes. Certain insecticides also stimulate enzyme activity while others inhibit enzyme activity. Certain brands of chewing tobacco contain sugar or licorice which have been reported to cause unexpected changes in a patient's response to drugs. The electrolyte content of water and foods and even environmental conditions (e.g., high heat and humidity) may alter a patient's response to a drug. Such interactions are included herein.

- **Endogenous Substances:** The action of many drugs is via the alteration of the availability of an endogenous chemical or hormone. However, certain unwanted events (e.g., folate deficiency, hypocalcemia, kernicterus, low testosterone levels) maybe caused by drugs and reported as drug interactions.

- **Laboratory Test Results:** Drugs may interfere with the accuracy or readability of laboratory test results, producing false information or making interpretation difficult. This may happen because a drug changes the body chemistry being evaluated, the drug imitates the substance being measured, or the drug somehow masks the test results. The October 1975 issue of Clinical Chemistry lists over 20,000 such interferences; A more recent review may be found in the July 1982 issue of Drugs. Hansten's text also includes a section on drug-laboratory test interactions.

Sources of Update Material

For the drug interactions listed in this annotated bibliography, a dozen or so medical and pharmacy journals are scanned routinely. In addition, the following secondary sources are reviewed:

- Current Contents, Life Sciences; Clinical Practice.
  Published weekly by the Institute for Scientific Information (Philadelphia, PA, 19104, $230/year), these publications reproduce the "contents" pages from approximately 2,000 journals. The sections on Pharmacology

and Clinical Medicine in the "Life Sciences" edition are the most valuable for finding articles on drug interactions. The index of Current Contents lists "drug interactions" but fails to index most of the articles.

- SDILINE, a MEDLARS II service.
The Medical University library obtains an off-line printout monthly of drug interaction articles to be included in the forth-coming issue of Index Medicus. Many of these reference citations include a brief (author's) abstract. A typical month has 60 to 100 listings, less than half of which are of value to this UPDATE.

- REACTIONS. ADIS PRESS, NEW YORK, 10013, $145/Year.
This pamphlet, once spelled RxEACTIONS, is published 22 times a year. It contains reports of adverse reactions to drugs, drug interactions, overdose, poisoning, abuse, and drug dependence articles. References are not complete in that they do not include the title of the articles.

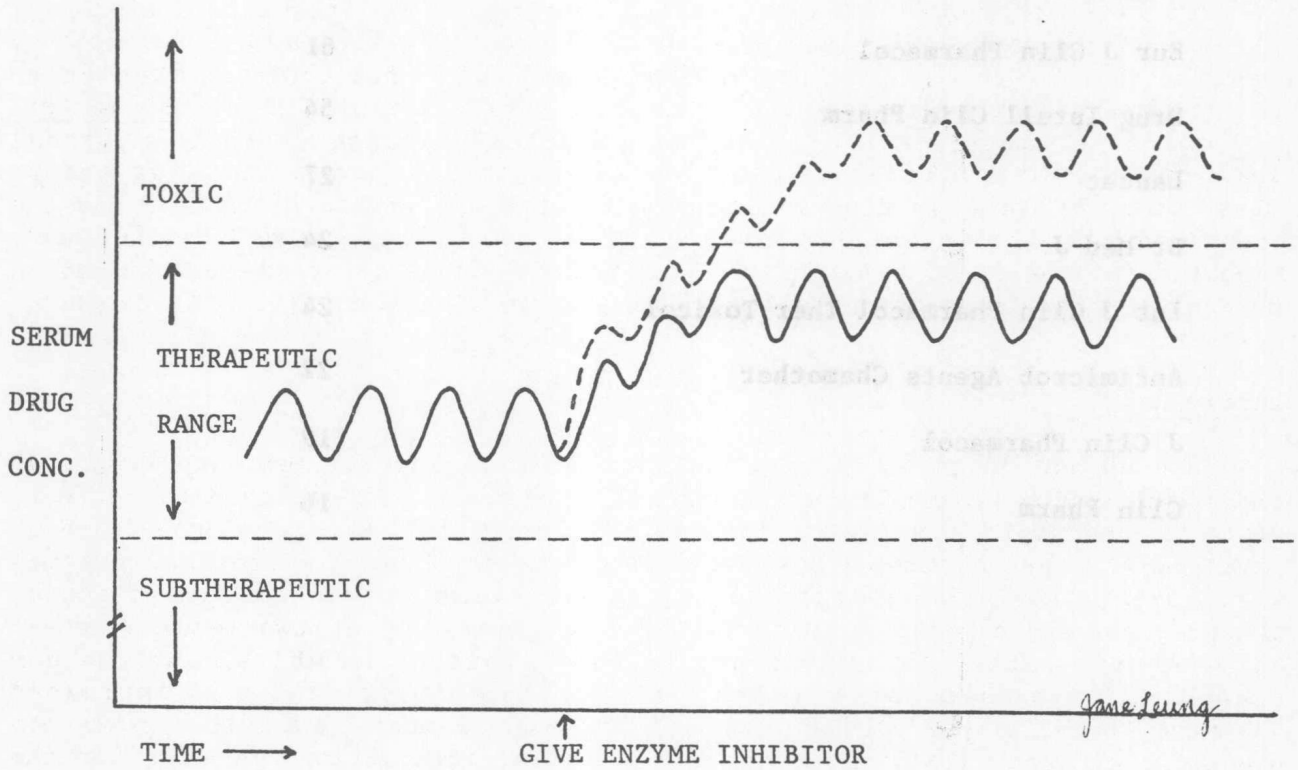
In 1984, this reviewer found over 975 articles on drug interactions, of which approximately 460 were reports of drug-drug interactions, in 210 different journals. The ten most productive journals (as far as drug interaction reports are concerned) are listed in table 1. Antimicrobial Agents Chemotherapy contains largely articles on the effect of disease state (e.g., renal failure; cystic fibrosis) on the kinetics of antibiotics. The drug groups most commonly found in drug interaction reports are listed in table 2 and the individual drugs in table 3. A number of interacting drug combinations were reported for the first time in 1984. (At least I could not find them listed in several popular interaction texts). These combinations are listed in table 4.

Interventions

The object drugs of clinical concern in drug interactions are generally those drugs with a narrow therapeutic index used for chronic conditions [e.g., digoxin, phenytoin, warfarin, lithium, cyclosporine, aminoglycosides, theophylline]. Some of these drugs are metabolized by hepatic microsomal enzymes which seem especially susceptible to the stimulating or inhibiting effect of other drugs. In clinically important interactions, one of two results generally occurs: either the drug's action is diminished in which case the patient's original symptoms may reappear, or, the drug's action is increased with the potential for producing drug toxicity. In most cases, it appears the practitioner need only be aware of the potential interaction, monitor for the expected change, and alter the dose of the object drug if necessary. The patient should be instructed on signs and symptoms which herald an unwanted reaction and which drugs and foods to avoid. Occasionally a non-interacting alternative precipitant or object drug may be preferred.

The frustrating part of practice is trying to predict which patient will suffer a clinically apparent and important reaction. Thus far, there has been no simple answer, although patients who are elderly, on multiple drug therapy, and with hepatic or renal impairment seem to be most susceptible. Two impor-

tant factors in determining the likelihood of an adverse response to a drug interaction are the relative serum level of the drug within the therapeutic range, and the degree of response of the individual to the precipitant drug. Subjects whose drug serum level is in the upper part of the therapeutic range may suffer toxic symptoms with relatively minor increases in serum level. On the other hand, if a subject's serum level is in the lower part of the therapeutic range, a 50 to 100% increase in serum level may not produce toxicity but a small decrease in level may leave the patient unprotected from the disease process. However, if the patient is very sensitive to the action of the precipitant drug (such as an enzyme inhibitor), the object drug serum level may change precipitously. Individual sensitivity appears to be a genetically determined trait. Drug interaction studies may report a mean increase in serum concentration of a drug of 50%, however the range may be from 0 to 300%. Such differences are partially responsible for the variability in reactions seen among patients receiving interacting drugs. The following diagram illustrates an "average" and "hypersensitive" response to an enzyme inhibitor for a drug in the lower part of the therapeutic range. My thanks to Yan-rane Jane Leung, a pharmacist in New York, for her drawing.



____ = "Average" Responder

_ _ = "Sensitive" Individual: response to enzyme inhibitor is greater than average

Table 1

MAJOR JOURNALS REPORTING DRUG INTERACTIONS IN 1984

Journal	# Articles
Br J Clin Pharmacol	108
Clin Pharmacol Ther	74
Eur J Clin Pharmacol	61
Drug Intell Clin Pharm	54
Lancet	27
Br Med J	24
Int J Clin Pharmacol Ther Toxicol	24
Antimicrob Agents Chemother	22
J Clin Pharmacol	19
Clin Pharm	16

Table 2

DRUG GROUPS MOST COMMONLY INCLUDED IN INTERACTIONS

Drug Group	# Articles
Anti-Infectives	67
Beta Blockers	64
Histamine-2 Blockers	63
Anticonvulsants	48
Antianxiety Agents	42
Digitalis Glycosides	40
Theophylline	40
Calcium Channel Blockers	39
Anti-Inflammatory Agents	35
Alcohol	35
Antiarrhythmics	32

Table 3

MOST COMMON DRUGS IN INTERACTION REPORTS

Drug	# Articles
Cimetidine	61
Theophylline	40
Digoxin	40
Propranolol	36
Alcohol	35
Phenytoin	30
Diazepam	25
Warfarin	24
Verapamil	18