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[illegible] FRIEND

# THE YEAR BOOK *of* DRUG THERAPY 1974

EDITED BY

DALE G. FRIEND, M.S., M.D.

*Associate Clinical Professor of Medicine, Harvard Medical School;*
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*Member, Revision Committee, U.S. Pharmacopeia, 1960-1970;*
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## INTRODUCTION

The past year has seen a further reduction in the number of new drugs released for therapeutic use in the United States. Those that have been accepted, such as trimethoprim-sulfamethoxazole and cromolyn, have been in use for several years in Europe, where they have proved to be effective.

This year I have asked Dr. Peter Goldman, Professor of Clinical Pharmacology at Harvard Medical School, to prepare an article on drug interaction, which he has graciously done. Drug interaction is now a major topic of concern for pharmacologists and physicians, since so many ramifications have developed and new discoveries are continually turning up. It is indeed surprising how many aspects of drug interactions have profound effect on therapeutic uses. Doctor Goldman has prepared an extremely succinct summary of the truly pertinent information; it should give the practicing physician a sound background in the major underlying principles.

There is still much concern about the therapeutic use of drugs in the United States. Unfortunately, such a drug as propoxyphene is still one of the most common prescriptions of physicians despite the fact that in several carefully controlled investigations it has proved to be no better than far less expensive aspirin. Paraminoacetophenol (paracetamol), more commonly known by the trade name of Tylenol, is being used indiscriminately by a large segment of the population. This drug has potentialities for severe toxicity, including hepatic damage and coma and death if taken in excessive amounts.

A few drugs are now being dated and this is certainly a step in the right direction. Much more needs to be done in this field, and it would be helpful if the USP could develop tables concerning the rate of deterioration of commonly used drugs as a guide to their wise medical use.

Some interesting developments have appeared concerning old and familiar drugs. Metronidazole has some unusual properties. It is not only effective in treating trichomonas infections but now is one of the best agents for treating amebic dysentery and giardia infections. It also has action against leishmaniasis and certain gram-negative organisms. Considerable new data have been developed in characterizing the action of digoxin now that new technics are available to follow its metabolism. An interesting study indicating that allopurinol may have action against the toxicity of cardiac glycosides if confirmed will add another agent for the treatment of this rather common occurrence. New information is still appearing on aspirin and its role in suppressing hyperimmune response by its action on lymphocytes. There are many other new and exciting developments and a few new agents that show promise: Propanolol is useful in non-Parkinson tremors. Levarterenol instilled in the bleeding stomach suppresses hemorrhage. Reportedly, diabetic retinopathy is slowed by salicylates. Two new and effective treatments have appeared for porphyria and its symptom complex. Glucagon looks promising for the treatment of acute pancreatitis.

D.G.F.

# DRUG INTERACTIONS

PETER GOLDMAN

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The likelihood is approximately 6% that a drug given to a hospitalized patient will lead to an adverse reaction.[1] Fortunately, only a small percentage of adverse reactions are classified as life threatening, but the figures on morbidity and dollar costs of adverse reactions are a matter of concern to all those interested in medical care.[2] Apparently drug interactions cause at least some of these adverse reactions.

A drug interaction can be defined simply as the alteration of the action of one drug by the action of a second drug. Used in this way, the term is general enough to avoid any implications as to mechanism. Clearly, some drug interactions can be used for therapeutic benefit, but in this discussion our attention will be directed to the problem of toxic or adverse drug interactions. A list of those that are known and discussion of various aspects of the problem are to be found in several recent publications.[3-5] In addition to drug interactions that can be understood in pharmacologic terms, there are those that are discovered by epidemiologic methods. In this discussion emphasis will be accorded to those adverse drug interactions that are verified in the clinic. Particular attention will also be given to various systems of dealing with the drug interaction problem. References have been selected to provide a limited number of articles that amplify some of the topics covered briefly in this review.

## Pharmaceutical Drug Interactions

One drug may affect another within the pharmaceutical preparation; the manufacturer generally provides some guidance, in the package insert, to avoid loss of drug activity in his preparations. The physician or nurse, however, often yields to the temptation of adding several drugs to an intravenous solution. This practice should only be conducted under the guidance of a hospital pharmacist, since many drugs are altered or inactivated because of incompatibilities that are not necessarily discernible by obvious means such as discoloration or the formation of a precipitate in the solution.[6]

## Pharmacokinetic Drug Interactions

The onset, duration and intensity of drug action will be determined by the presence of active drug at the receptor that is the target for that drug. As a rule, raising the dose of a drug increases the extent to which these receptor sites are occupied by the drug and increases the drug effect. The relationship between a dose of the drug and its effect will, however, be determined by pharmacokinetic factors such as the absorption, metabolism, excretion and tissue distribution of the drug; the term "pharmacokinetic drug interactions" has been used to describe how these factors

may be modified by the presence of other drugs.[7] Experimental data abound in this area, but their relevance to clinical practice is often uncertain.

### *Absorption*

Drug absorption from the gastrointestinal tract can be affected by interaction with other drugs. The decreased absorption of the tetracyclines in the presence of antacids was originally attributed to chelation of the tetracycline by CA(II), Mg(II) or Al(III) in the antacid preparation. Additional studies now show that sodium bicarbonate, which lacks chelating properties, also decreases the absorption of tetracycline, and thus it appears that this interaction results from the poor solubility of the tetracycline capsule in an alkaline medium.[8] Were it not for the solubilization of the drug preparation, the alkaline medium would be expected to increase the proportion of tetracycline in the uncharged form and hence to increase its rate of absorption.

The gastrointestinal absorption of drugs is complicated by other factors, such as the presence of food. In experimental animals, reduced gastrointestinal motility is associated with reduced absorption of drugs, and this may be the basis for the reduced absorption of griseofulvin and Dicumarol in human beings who also were taking barbiturates.[9, 10] Transit time of the drug can affect absorption because of differences in drug ionization that arise because of the pH difference between the stomach and duodenum.

The reduced absorptions of lincomycin in the presence of kaolin and of tetracycline and its derivatives in the presence of iron[11] are additional examples of documented drug interaction within the gastrointestinal tract. The binding of drugs to cholestyramine in animal studies suggests that this drug may affect the bioavailability of other drugs.[12]

### *Distribution*

After absorption, drugs are distributed to the tissues and become available both for their intended receptors and at receptors determining adverse reactions.[13] Alternatively, drugs can be sequestered in the tissues in an inactive form, such as bound to serum protein. Methotrexate, warfarin, diphenylhydantoin, salicylates, sulfonamides, antimalarials, phenylbutazone, tolbutamide and trichloroacetic acid (a metabolite of chloral hydrate) are among the drugs that are significantly bound to sites on serum protein. In this form, their availability may be inadvertently increased by the introduction of a second drug that displaces the first from its inactive site. Toxicity thus may arise from a drug given in a previously satisfactory dose after a second drug is introduced. This mechanism is particularly significant for drugs like warfarin and Dicumarol, which are over 90% bound to protein. When a second drug displaces only a fraction of the anticoagulant, the effective dose of free drug can readily be doubled, with consequent prolongation of the prothrombin time.[14]

### *Excretion*

Although drugs can be excreted through the biliary system, skin or lungs, only in renal excretion has the action of one drug been shown to alter the elimination of another. The effect may be at the glomerulus, where to the extent that drugs are strongly bound to protein they will not be filtered unless displaced from serum protein by another drug. Other interactions occur within the renal tubule, where diffusion back into the bloodstream is favored for neutral molecules. Alkalinizing the urine puts basic drugs, e.g., quinidine, into the neutral form while putting acid drugs, e.g., salicylate, into the charged form. Thus, alkalinizing the urine tends to favor excretion of basic drugs and retention of acidic drugs.[15] Competition among various drugs (and normal metabolites) for the carriers that mediate transport across the renal tubule is another area of drug interaction. Two separate carrier systems, one for weak acids and the other for weak bases, have been identified.[16] Experimental verification of the possible importance of interactions at these sites has been limited to the acid drugs,[17] which include salicylate, hippurate, probenecid, phenylbutazone, indomethacin, thiazide diuretics, acetazolamide, penicillin and the sulfonamides.[8] The prototype for interaction at the renal tubule is that between penicillin and probenecid; probenecid was designed specifically as an inhibitor for penicillin excretion and now has been shown to block penicillin transport out of the cerebrospinal fluid in experimental animals.[18]

### *Metabolism*

Competition for some of the conjugation pathways can cause one drug to interfere with the metabolism of another. The most frequent site, however, at which one drug can influence the metabolism of another is in the microsomal system of the liver. This system is stimulated (induced) by a wide variety of drugs as well as environmental compounds (DDT) and social drugs (cigarettes, marihuana). Conney and Burns have reviewed the exogenous compounds that affect the induction of this system in man.[19] The development of tolerance to ethanol in alcoholics can be attributed to induction of this system. As a consequence of this induction, alcoholics can have a high tolerance for other drugs, including the barbiturates.[20] A problem arises during acute alcoholic intoxication, when the normally active metabolism of drugs can be acutely diminished by the presence of alcohol. Under these circumstances the accustomed large dose of, for example, a barbiturate may not be metabolized in the usual manner and a prolonged and accentuated effect can occur. Other frequently used drugs that induce this system include phenylbutazone, diphenylhydantoin and glutethimide. Diphenylhydantoin, phenylbutazone, digitoxin, meprobamate and steroids are more rapidly metabolized as the result of such induction. Of particular importance is the altered metabolism of the coumarin anticoagulants (warfarin and Dicumarol) in response to these drugs.[14] In this connection, attention should be called to the barbiturates, which are apt to be used as a sedative

while the patient is in the hospital having his anticoagulant dosage adjusted. When the patient leaves the hospital the sedative may be discontinued, causing a diminished microsomal metabolism of the anticoagulant. Under these circumstances the same dose of anticoagulant will have a greater effect, with a consequent increase in the danger of hemorrhage.

Genetic differences among patients can lead to altered drug response,[21] and in some instances genetic differences in drug metabolism can be responsible for decreased metabolism of a second drug; patients who are slow acetylators have an increased risk of isoniazid toxicity, but for some unexplained reason, when taking isoniazid they also have an increased risk of diphenylhydantoin toxicity as the result of high diphenylhydantoin blood levels.[22]

### Blood Levels of Drugs

Each of the foregoing examples illustrates how one drug can influence the activity of another by altering its concentration at the drug receptor. For many drugs the concentration of drug at the receptor is in equilibrium with the concentration of drug in body fluids. Hence it is possible, in principle, that blood levels of certain drugs can be used by the clinician to guide him in adjusting drug dosage in accordance with the requirements of the individual patient. Analytic methods are now available for measuring many drugs, and the usefulness of this approach in detecting inadequate or excessive blood levels of drugs in various clinical situations has been reviewed.[23] The value of blood levels depends on the particular drug and the therapeutic situation in which it is used. For example, a good correlation has been shown between blood levels of procainamide and the effectiveness and toxicity of this drug.[24] On the other hand, because of the other factors that may be involved in determining the toxicity of digoxin, blood levels of this drug are less reliable as a guide to drug toxicity.[25] The costs and benefits of extending the use of blood levels of drugs as a guide to drug use have not been evaluated.

### Other Physiologic Mechanisms of Drug Interaction

Another class of drug interactions comprises those that occur by virtue of competition between two drugs for the drug receptor itself. The morphine antagonists nalorphine and naloxone act directly at the receptor site in competition with morphine. This direct antagonism is the basis for the use of these drugs in clinical practice.

Other drug interactions occur because one drug alters a physiologic parameter that affects the action of a second drug. The thiazide and furosemide diuretics diminish the body stores of potassium, leading to increased likelihood of an adverse effect of the cardiac glycosides on the heart.[26] There is also evidence that depletion of cardiac catecholamines by reserpine may increase the cardiac sensitivity to quinidine.

### Computerized Data on Drug Information

So far we have considered drug interactions that are known and whose mechanisms are known. In principle these interactions can be discerned either from blood levels of drugs or blood (or tissue) levels of normal body constituents that may be altered by drugs. There still remains the problem of keeping in mind the clinically significant interactions that have been reported and of keeping alert to interactions that experimental data have suggested as possible. Only if the suspicion of a drug interaction is present can appropriate steps be taken to make the diagnosis.

A computer has been programmed to supply this information in an experimental approach now being evaluated on the medical wards at Stanford University Medical Center.[27] Information on all the drugs that a patient is taking are stored in the computer so that when a drug is added to the therapeutic regimen the possible complications and interactions are displayed for the knowledge of those involved in the care of the patient. Each drug interaction is assigned to a category based on its clinical significance with regard to severity and possible immediacy of the complication. The computer then issues an alert that is appropriate for the guidance of those concerned with decisions about drug administration. Clearly, this possible solution to the drug interaction dilemma is no better than the information on which the computer program is based; furthermore, this approach to the problem still must be evaluated for general use. The experience gained from this sort of drug monitoring can be used to validate the assignment of risk made initially by the staff in setting up the computer program. For example, an interaction between drugs that has been reported from animal studies can be assigned a questionable status for clinical practice. An alert supported by this kind of evidence may not be sufficient to dissuade the clinician from prescribing these two drugs. A record will then be generated of the clinical experience with these two drugs; in time, this will generate the clinical significance of the animal data.

### Drug Surveillance

In a sense it is reassuring to gain more information about drug interactions and to learn of previously undiscovered mechanisms by which they occur. This information can guide future therapeutic practices. On the other hand, the fact that suggestions about possible mechanisms of drug interaction come to light often long after the drug has been in use tends to diminish confidence in our current handling of the problem. How does the clinician clearly identify drug interactions? It has been pointed out that adverse drug reactions are often erroneously ascribed to manifestations of the patient's disease and are apt to be considered merely as idiosyncratic responses.[28]

One approach to identifying drug reactions is the use of surveillance that is removed somewhat from the subjective factors that might influence the individual physician. Surveillance methods can be classified in several ways. Study of the reactions and their frequency in a group

of patients taking a given drug is said to be drug-oriented surveillance.[29] Event-oriented surveillance is illustrated by a study that shows certain pathologic conditions are increased in association with the use of a given drug. This type of surveillance is illustrated by the finding that diethylstilbestrol given to pregnant women is associated with the later development of cancer of the vagina in postadolescent daughters born of these pregnancies.[30] In this instance the event was linked to the offending drug only because of the rarity of the condition in the affected age group and the alertness of the physicians who observed the cases. Similarly, the relative rarity of thromboembolic phenomena in young women made it possible to associate this condition with the use of the birth control pill.[31] A drug will only be considered as causative of a complication when the complication occurs with a frequency noticeably above the expected value within the population at risk. It will then be necessary to use appropriate epidemiologic criteria to associate the presumed complication with the prior administration of a drug.

Patient-oriented surveillance is exemplified by the Boston Collaborative Drug Surveillance Program.[1] The characteristics of each patient and the drugs he has taken are monitored along with a variety of clinical events that might be caused by drugs. Data of this kind have now been obtained on more than 14,000 patients in hospitals in several countries; in computerized form these data can be scanned for evidence of previously undetected drug interactions. In principle, a correlation can be sought between a patient's prior medication and any of a variety of signs and symptoms that he may later have.

When there is a significant drug interaction, the incidence of an adverse effect is greater in the group of patients that have taken both of the drugs than in the patients who received only one of them. For example, the incidence of rash was 22.4% in patients taking ampicillin and allopurinol, whereas it was 7.5% in patients taking ampicillin alone and 2.1% in patients taking allopurinol alone.[32] A drug interaction could not be proved in this instance, however, since the patients taking allopurinol also tended to have hyperuricemia. Thus the data do not allow a distinction to be made between hyperuricemia and allopurinol as the factor associated with the increased incidence of penicillin rash. This deduction can only be determined when enough patients are monitored who take ampicillin and have either hyperuricemia untreated by allopurinol or who take allopurinol for other reasons.

The increased incidence of rash in patients taking ampicillin and allopurinol would have been considered a drug interaction if it were not recognized that hyperuricemia was another characteristic of the group taking allopurinol. In this case hyperuricemia is the confounding variable that must be recognized lest erroneous conclusions be drawn from surveillance technics. It has been noted, for example, that there is an association between cigarette smoking and ethanol ingestion in the general population. For this reason the increased incidence of drowsiness as a side effect of the benzoxydiazepine drugs in patients who were nonsmokers had to be examined with regard to the habits of ethanol consumption in the population where the association was noted. In this case ethanol was not a confounding variable since it could be shown that

smokers had a diminished response to benzothiazine regardless of their habits of alcohol consumption.[33] The relationship between cigarette smoking and the response to the benzoxydiazepines shows the importance of environmental chemicals as well as other drugs in obtaining the complete picture of the drug interaction problem.[19]

Differences in drug effects between smokers and nonsmokers can be explained by the induction of the hepatic microsomal drug oxidation system by cigarette smoke leading to a more rapid metabolism of the drug; the surveillance of hospitalized patients indicates the extent to which this phenomenon may be important in clinical practice. Surveillance can thus put data obtained from experimental situations into proper perspective for clinical practice. As a converse, surveillance can identify drug interactions that cannot be predicted on the basis of present theory and may provide suggestions for further laboratory investigation of the drug interaction problem. The apparent interaction between allopurinol (or hyperuricemia) and penicillin is an example of a phenomenon whose basis may now be sought in the laboratory.

The interaction between chloral hydrate and warfarin illustrates the problem of using laboratory data as a basis for formulating a clinical approach to drug interactions. It was found in the laboratory that trichloroacetic acid (a metabolite of chloral hydrate) displaces warfarin from its binding site on serum protein.[34] This observation seemed to have clinical significance, since a prolongation of the prothrombin time and increased renal excretion of warfarin were noted in 3 normal volunteers who took warfarin and chloral hydrate for a week. In another protocol of clinical investigation, however, chloral hydrate was found to have no effect in prolonging the prothrombin time in anticoagulated patients.[35]

The data from the Boston Collaborative Drug Surveillance Program were then examined to test the validity of this drug interaction in actual practice. An analysis of the experience with patients taking both drugs did not show any increase in hemorrhagic complications as the result of this interaction. However, the interaction is not merely a laboratory curiosity since patients receiving chloral hydrate required a lower average warfarin maintenance dose during the first 4 days of anticoagulant therapy than those on warfarin alone.[36] Presumably the hemorrhagic complications of this drug interaction were averted by monitoring the prothrombin time and adjusting the warfarin dose accordingly. This example illustrates how surveillance can place drug interactions into perspective for the clinician. Furthermore, it illustrates how even in the presence of a significant interaction that is not recognized by the clinician, side effects can be avoided if the effect of the drug is carefully monitored.

## Conclusions

Drug interactions are a problem, but an appropriate solution will not be found until the extent of the problem is carefully evaluated. Adverse reactions themselves have extensive consequences.[2] Many of these may be due to drug interactions. Support for this idea comes from the observation that the likelihood of an adverse reaction of a given drug is increased in patients who are taking a large number of other drugs.[37] How-

ever, it must be recognized that patients who receive more drugs are generally sicker than those taking fewer drugs and it may be their greater illness that makes them more susceptible to the adversities of drug therapy. Recently a number of books and articles have attempted to provide handy lists of drug interactions in a form that will provide easy education for the physician. These lists are a formidable challenge to the memory and unfortunately many of them are uncritical compilations of data that have not been verified clinically.

Many of the laboratory values on which clinical practice are based may be misinterpreted because of the drugs a patient is taking.[4, 38] Although these are not drug interactions as defined previously, this kind of information increases our awareness and perhaps our uncertainty about "what else" the therapeutic agents may be doing. The great volume of information that has been published and its lack of convenient format as an aid to prescription practice may initiate general anxiety about current use of drugs.

The portion of the physician's memory that is devoted to drug interactions will necessarily be relatively small, and hence he must select his information on the basis of its value to his use of drugs. Primary emphasis should be on interactions that may lead to acute irreversible life-threatening complications.[1] Heading this list would be interactions with the coumarin anticoagulants which may increase the likelihood of hemorrhage[14] and interactions with the use of diuretics which may increase the cardiac toxicity of digitalis.[39] Other interactions can only be remembered if the physician is parsimonious in his use of drugs. He should limit his prescriptions to those drugs he knows well and for which there is a clear therapeutic indication. Additional drug information needed for specific therapeutic situations often can be obtained from services now available in many hospital pharmacies. Drug interactions that are not yet recognized will doubtless be discerned in the future. However, the physician who uses only drugs he understands for clear therapeutic indications is less likely to provide the case reports for these discoveries from among his patients.

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