14

Pharmacokinetic Variability—Drug Interactions

Antagonism or potentiation of the effects of one drug by another is a well-known phenomenon. We are now aware that in many cases these drug-drug interactions have a pharmacokinetic rather than pharmacologic basis. The absorption, distribution, excretion, or metabolism of a drug may be affected by the concomitant administration of a second drug, leading to differences in clinical effects.

Few topics in clinical pharmacology have attracted more attention than drug-drug interactions that may result in a loss of therapeutic effectiveness or an increase in adverse effects. Thousands of experimental, clinical, and epidemiologic studies have been reported. Hundreds of review articles on interactions between drugs have appeared, and more than a dozen books as well as a newsletter have been devoted to the subject. Many of these contributions contain important and useful information that increases our understanding of the mechanisms and clinical consequences of drug interactions.[1-8] On the other hand, some lack criticality and a clinical perspective.

The clinical problem presented by interactions between drugs has been vastly overestimated by some authors. In fact, only a relatively small number of the thousands of drug interactions listed in some published compilations are of clinical significance. Of these, most are predictable and preventable, usually by appropriate dosage adjustment, and few are potentially disabling or life threatening.[9]

Although drug interactions probably contribute less to the total incidence of iatrogenic disease than some authors have suggested in the past, this does not minimize the hazards of multiple drug therapy. Epidemiologic studies demonstrate that the rate of adverse reactions to drugs increases from 4.2% when 5 or fewer drugs are given to 45% when 20 or more drugs are prescribed.[10] Another investigation, based on more than 10,000 patients hospitalized on a general medical service during a 5-year period, found that the average number of drugs received during hospitalization by each patient was 7.9, but the average number of drugs received by patients who experienced an adverse drug reaction was 13.4.[11] The adverse reaction rate was 4% in patients receiving 5 or fewer drugs, 10% in patients receiving 6 to 10 drugs, 28% in patients receiving 11 to 15 drugs, and 54% in patients receiving 16 to 20 drugs.

The risk of clinical consequences from drug-drug interactions is higher with some drug categories than with others. This is evident in Figure 14–1, which shows the percentage of hospitalized patients, categorized by drug group, who experienced adverse drug reactions.[11] Patients receiving anticoagulant or antihypertensive drugs were at a much greater risk than patients receiving other kinds of drugs. Of nine drug categories, the anticoagulants and antihypertensives were the only two for which the occurrence of adverse reactions increased significantly when the number of different drugs received by patients increased (Fig. 14–2).

Koch-Weser and Greenblatt proposed that clinically important drug interactions rarely involve drugs other than oral anticoagulants, cardiac glycosides, antiarrhythmics, sympathomimetic amines, antihypertensives, anticonvulsants, oral hypoglycemics, or cytotoxic drugs.[9] Common manifestations are hemorrhage, cardiac arrhyth-

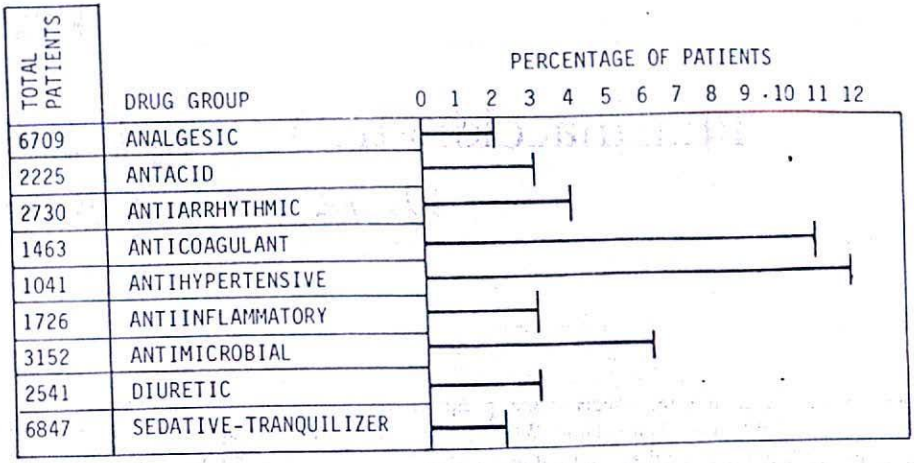

Fig. 14–1. Percentage of hospitalized patients, categorized by drug group, who experienced adverse drug reactions. (Data from May, F.E., Stewart, R.B., and Cluff, L.E.[11])

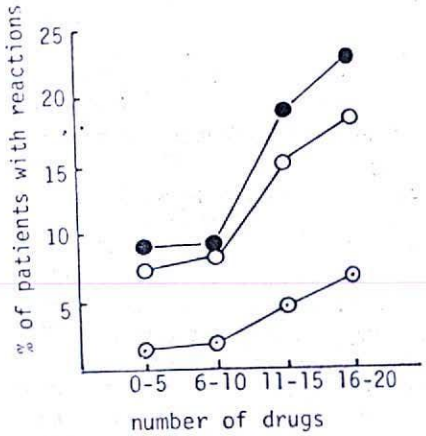

Fig. 14–2. Effects of the total number of drugs received by the patient on the percentage of patients experiencing an adverse drug reaction to a specific drug group. Key: (●) antihypertensives; (○) anticoagulants; (⊙) other drug groups (including analgesics, antacids, antiarrhythmics, anti-inflammatories, antimicrobial agents, diuretics, and sedatives-tranquilizers). (Data from May, F.E., Stewart, R.B., and Cluff, L.E.[11])

mias, severe hypertension or hypotension, convulsive seizures, or hypoglycemia. These are the interactions that prescribers should be made aware of.

This chapter largely concerns interactions between drugs and, to a small extent, drug interactions with environmental chemicals. Emphasis is given to the mechanisms of interaction and to clinically important interactions.

DRUG ABSORPTION

Interactions that interfere with drug absorption usually involve binding or chelation of drugs in the gastrointestinal tract or effects on gastric emptying or gastrointestinal motility.

One of the earliest reported drug-drug interactions was that between tetracycline antibiotics and antacids. Antacid drugs, particularly those containing aluminum, markedly decrease the absorption of most tetracyclines by forming an insoluble complex in the gastrointestinal tract.[12] The interaction is most pronounced when the drugs are given simultaneously.

Simultaneous administration of ferrous sulfate also impairs the absorption of tetracycline, oxytetracycline, methacycline, and doxycycline, probably by means of a chelation mechanism.[13] No interaction is observed when the iron salt is given 3 hr before or 2 hr after the tetracycline.[14]

Since these early studies, coadministration of antacids has been found to interfere with the ab-

sorption of other drugs including indomethacin,[15] nitrofurantoin,[16] diflusinal,[17] fluoride,[18] phenytoin,[19] and cimetidine.[20] Magnesium trisilicate reduces the absorption of nitrofurantoin by more than 50%.[16] These interactions are usually easily avoided by administering the antacid some time before or after the drug.

Sucralfate, a poorly absorbed complex of aluminum hydroxide and sulfated sucrose, used for treating peptic ulcers, interacts with some drugs in the gastrointestinal tract resulting in reduced absorption. One study found that concomitant administration of 1 g sucralfate reduced the absorption of 300 mg phenytoin capsules by 20% as measured by area under the curve from 0–48 hr.[21] Peak phenytoin levels were 3.7 μg/ml when it was given with placebo and 2.9 μg/ml when given with sucralfate.

More recently, the effect of sucralfate on the absorption of oral norfloxacin, a quinolone antibacterial agent, was evaluated.[22] On each occasion, subjects were given 400 mg norfloxacin alone, with 1 g sucralfate, or 2 hr after 1 g of sucralfate. When sucralfate was given concurrently, the bioavailability of norfloxacin was less than 2%. Administration of norfloxacin 2 hr after sucralfate resulted in a smaller but nevertheless substantial interaction. Bioavailability was 55 to 60% relative to the administration of norfloxacin alone.

Aluminum- and magnesium-containing antacids also dramatically decrease the absorption of norfloxacin and other oral quinolones. In each case, the mechanism appears to involve an interaction of the heavy metal ion with the quinolone nucleus, perhaps resulting in an insoluble complex. Considering norfloxacin concentrations in urine and minimum inhibitory concentrations (MICs) for relevant bacteria, the investigators concluded that administration of norfloxacin with antacids or sucralfate is likely to result in treatment failure for urinary tract infections. The investigators also pointed out that although the interaction with sucralfate "has not been studied with all quinolone antimicrobial agents, one would expect it to occur with all members of this class."

Absorption may also be reduced when drugs are given with adsorbents, such as kaolin or bismuth subsalicylate, or ion exchange resins, such as cholestyramine or colestipol. Antidiarrheal mixtures containing kaolin impair the absorption of lincomycin[23] and promazine.[24] Concomitant administration of 2 oz of a kaolin-pectin mixture reduces the absorption of digoxin by 40%.[25] Oral coadministration of a bismuth subsalicylate antidiarrheal mixture reduced the absorption of tetracycline[26] and doxycycline[27] by about 35 to 40%. A multiple dose regimen of bismuth subsalicylate mixture, typical of usage in traveler's diarrhea, reduced doxycycline absorption by about 50%.[27]

Ion exchange resins are now used for the treatment of elevated plasma cholesterol or bile acid levels. They are not absorbed but exert their effects by binding bile acids in the intestine, preventing their reabsorption. These resins also bind certain anionic and neutral drugs in the intestine and are known to interfere with the absorption of anticoagulants[28] and thyroxine.[29]

Brown et al.[30] gave either two 0.25 mg digoxin tablets or two 0.20 digoxin soft gelatin capsules (containing a nonaqueous solution of the drug) once a day, alone or with cholestyramine, 8 g once daily, to healthy adult subjects. Bioavailability was determined from steady-state 24-hour area under the serum concentration-time curve (AUC). The AUCs for tablets alone and with cholestyramine were 32.8 and 22.4 ng-hr/ml, respectively, while corresponding values for capsules were 31.7 and 24.7. Cholestyramine administration with digoxin tablets produced a 32% decrease in mean digoxin AUC, whereas a 22% decrease was measured when the resin was given with digoxin capsules. These differences suggest that digoxin capsules, the more rapidly dissolving form of digoxin, are perhaps less prone to drug interactions than digoxin tablets.

Certain drugs are metabolized in the gastrointestinal tract and only a fraction of the dose reaches the systemic circulation. Slow absorption, resulting from impaired gastric emptying, could result in a greater fraction of the dose undergoing metabolism in the gut and in a lower bioavailability. This mechanism may explain the effects of drugs with anticholinergic activity on the absorption of levodopa. Imipramine[31] and trihexyphenidyl[32] have been found to significantly reduce the bioavailability of levodopa in healthy human subjects. Concomitant administration of trihexyphenidyl with levodopa, a likely combination, may decrease the efficacy of levodopa.

Anticholinergics and other drugs that reduce gastric emptying usually decrease the rate but not the extent of drug absorption. Drugs, such as cimetidine, that reduce gastric acid output may decrease

Table 14–1. Effect of Antibiotic Therapy on Steady-State Digoxin Concentrations in Serum*

Subject no.	Serum digoxin concentration (ng/ml)	
	Control period	Antibiotic period
1	0.72	1.03
2	0.76	1.33
3	0.37	0.80

*Data from Lindenbaum, J., et al.[33]

the solubility of certain basic drugs in the stomach and impair absorption.

A particularly interesting interaction has been reported between digoxin and certain antibiotics.[33] Oral digoxin is slowly absorbed; a considerable fraction of the dose may reach the lower intestine where it is reduced to inactive metabolites by the bacterial flora. Bacterial metabolism limits the bioavailability of slowly dissolving preparations of digoxin in many patients and that of rapidly dissolving products in a much smaller number of patients. About 10% of patients receiving conventional oral digoxin tablets metabolize more than 40% of the dose to cardioinactive compounds in the lower intestine.

Certain oral antibiotics, including tetracycline and erythromycin, alter the bacterial flora and decrease the inactivation of digoxin.[33] Table 14–1 shows steady-state serum levels of digoxin before and during treatment with oral antibiotics. Digoxin levels were increased 43 to 116% by antibiotic treatment. It is possible that therapy with antimicrobial agents in certain patients occasionally precipitates digoxin toxicity.

Not all antimicrobial agents affect digoxin absorption in this manner; in fact, treatment with neomycin[34] or sulfasalazine[35] reduces the bioavailability of digoxin. When neomycin was given with maintenance doses of digoxin, steady-state serum digoxin concentrations were reduced, on the average, by 30%.[34] Similar effects on digoxin absorption have been observed after a 6-day treatment with sulfasalazine.[35] The mechanisms of these effects are not known.

Another interaction for which the mechanism is obscure is that observed with griseofulvin and phenobarbital.[36] Phenobarbital has no effect on the distribution or elimination of griseofulvin; however, phenobarbital reduces the plasma levels of griseofulvin and also reduces the cumulative urinary recovery of its principal metabolite, suggesting that phenobarbital interferes with the absorption of griseofulvin. A similar interaction has been reported to occur between heptabarbital and dicumarol.[37]

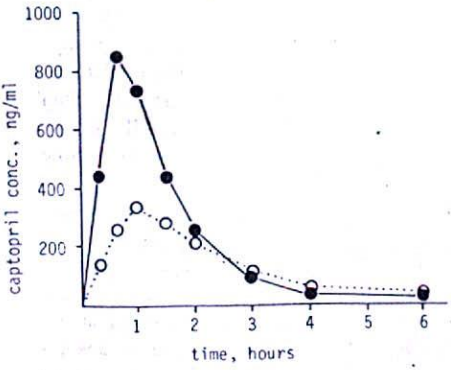

Fig. 14–3. Captopril concentrations in blood after a single 100-mg oral dose to fasted (●) and fed (○) healthy subjects. (Data from Singhvi, S.M., et al.[42])

The effect of food on drug absorption has been considered in Chapter 3. In some cases, administration of a drug after a meal may seriously reduce clinical efficacy. The salivary suppression produced by propantheline is virtually abolished when it is given immediately after a meal.[38] The relative bioavailability of lincomycin is reduced to about 60% when given 1 hr before breakfast and to about 20% when given immediately after breakfast, compared to that observed after oral administration to fasting subjects.[39] The bioavailability of captopril, a potent angiotensin-converting enzyme inhibitor used in hypertension, is decreased 35 to 40% after a meal (Fig. 14–3).[40]

A potentially dangerous situation may arise because of delayed absorption of hypnotic agents in nonfasting patients. With the hypnotic capuride, a 42 min difference in onset of absorption has been observed between fasting and nonfasting subjects.[41] Failure to obtain early sleep could encourage additional doses and lead to toxicity.

Hydralazine blood levels were reduced almost 50% when the drug was given after a meal compared with levels measured in fasting subjects.[42] The higher blood levels in fasted subjects resulted in a greater change in mean arterial pressure (MAP). The maximum fall in MAP was 18 mm Hg in fasted subjects compared with 11 mm mg in subjects taking hydralazine after breakfast.

Food, particularly high-fat meals, have been found to have a profound effect on theophylline absorption after oral administration of some pro-

longed-release products. Both increased and decreased absorption have been reported depending on the product.

The unexpected and dramatic increase in the release rate of theophylline from a once a day product (Theo-24) when it was given with a high-fat meal sent regulatory agencies scrambling to revise guidelines for approval of prolonged-release products. In the US, a single-dose food study is now required as part of the submission for all controlled-release products.

Theo-24 is incompletely absorbed in fasted subjects. A high-fat meal not only increases the extent of absorption, but also dramatically increases the rate of absorption. About half the daily dose is absorbed over a 4-hr period, giving rise to excessively high blood levels of theophylline.[43]

Another slow-release product, Theo-Dur Sprinkle, specifically developed for pediatrics, is well absorbed in fasted subjects but bioavailability decreases by more than 50% when it is taken after a heavy breakfast.[44] A comprehensive review of food interactions with prolonged-release theophylline preparations is available.[45]

A meal may also have large effects on the absorption of drugs given in single-unit enteric-coated dosage forms. The mean time to a measurable plasma concentration of salicylate (lag time) after administration of enteric-coated aspirin tablets was 2.7 hr in fasted subjects and 7.9 hr when the tablets were given 30 min after breakfast, followed 4 hr later by lunch.[46] A 5-hr difference was also observed in the time to peak salicylate concentration in plasma. No effect was noted on the total amount of aspirin absorbed from enteric-coated tablets.

Under these conditions, gastric residence time (GRT), determined by a radio-telemetric device called a Heidelberg capsule, was 0.8 hr in fasted subjects and 5.9 hr in fed subjects. Female subjects had a significantly longer GRT than male subjects.[47] A strong ($r = 0.94$) correlation was observed between lag times of aspirin from enteric-coated tablets and GRTs.

In all cases, the lag time was greater than the GRT, consistent with the idea that the enteric coating remains intact in the stomach and a finite time in the small intestine is needed for the coating to disrupt and release aspirin. The average time for dissolution and absorption of enteric-coated aspirin after entering the small intestine (i.e., the lag time minus GRT) was about 2 hr for both fed and fasted subjects. The time to reach a peak level of salicylate after gastric emptying was also independent of feeding status.

These studies confirm long-held beliefs that most of the variability in lag time following administration of enteric-coated tablets can be explained by differences in gastric residence time. Mojaverian et al.[46] concluded that "marked delays in the absorption of aspirin from enteric-coated tablets may be observed when they are consumed with food. This effect is particularly pronounced in women."

DRUG BINDING IN PLASMA

Competition between drugs for common binding sites on plasma proteins is an almost ubiquitous drug interaction. Mefenamic acid, ethacrynic acid, nalidixic acid, and diazoxide,[48] as well as phenylbutazone, thyroxine, sulfaphenazole, and clofibrate,[49] significantly displace warfarin from human serum albumin. Tolbutamide, indomethacin, and sulfamethoxypyridazine competitively inhibit the binding of phenylbutazone to serum albumin.[50] Various fatty acids displace both phenylbutazone and warfarin from human albumin.[50] Salicylic acid, sulfisoxazole, and phenylbutazone, at concentrations that are observed clinically, decrease phenytoin binding to plasma proteins.[51] Many more examples can be found in the literature.

These interactions between drugs usually produce considerable pharmacokinetic changes with respect to the drug that is displaced from plasma protein binding sites, but they are rarely of clinical importance. The following example may help to understand the reason for this.

A patient who has received drug A for a long period is now also given daily doses of drug B, which competitively inhibits the binding of A to plasma proteins. If the elimination of drug A is rate-limited by the intrinsic ability of the eliminating organs to clear it, rather than by renal or hepatic blood flow (HBF), the clearance of A from the blood or plasma will increase because of the increase in the fraction unbound. Therefore, the plasma levels of total A (bound and unbound) will decrease until a new and lower steady-state concentration is established. At the new steady-state, the free concentration of A is the same as the free concentration at the original steady-state, before treatment with drug B was initiated. It is conceivable that during the period from one steady-state to another, free drug level may be transiently elevated but this does not seem to be an important event.

This situation is almost the same as that described in Chapter 13 for the consequences of disease-related impairment of drug binding. It applies only when drug B simply displaces drug A from binding sites in the plasma but has no effect on the intrinsic clearance of A. Therefore, displacement interactions should be of little clinical significance. Although the total levels of A in the plasma are depressed when the two drugs are given together, there is no need to change the dosage of drug A because free levels are unchanged.[52]

Addition of valproic acid to an existing drug treatment regimen in epileptic patients results in a substantial fall in steady-state serum levels of phenytoin. One study found that phenytoin levels decline from about 20 to 15 μg/ml.[53] This is a result of displacement of phenytoin from plasma proteins by valproic acid. Unbound phenytoin increased from 9% in patients on phenytoin alone to 13 to 19% in patients with valproic acid levels less than 90 μg/ml and to greater than 20% in patients with valproic acid levels exceeding 90 μg/ml.[53]

Decreased binding also results in an increase in the clearance and apparent volume of distribution of phenytoin.[54,55] However, free phenytoin concentrations remain unchanged in the presence of valproic acid, despite the reduction in total phenytoin levels.[56] There is probably no need to adjust phenytoin dosage when valproate is added to the treatment regimen.

The effect of high-dose aspirin on the disposition of tenoxicam, a nonsteroidal antiinflammatory drug (NSAID) related to piroxicam, was studied in healthy human subjects.[57] In one study, subjects were given a single dose of tenoxicam, followed by a course of aspirin treatment; toward the end of the aspirin treatment period, a second dose of tenoxicam was given.

Aspirin was associated with a decrease in the half-life and with increases in the apparent volume of distribution and clearance of tenoxicam. Mean clearance was 97 ml/hr during the control period and 191 ml/hr during aspirin treatment. These changes suggested a competitive protein binding interaction between salicylate and tenoxicam. Binding studies indicated that percent unbound tenoxicam increased from 0.56% in the absence of aspirin to 1.24% in the presence of aspirin.

Although nearly all agree that pure plasma protein displacement interactions may be safely ignored, the chloral hydrate-warfarin interaction is frequently cited as an exception to this rule. Trichloroacetic acid (TCA), a major metabolite of chloral hydrate, displaces warfarin from its binding sites on plasma albumin. Sellers and Koch-Weser[58] have concluded that this displacement results, for a short time, in elevated plasma levels of unbound warfarin, thereby increasing the anticoagulant activity of warfarin.

Administration of chloral hydrate to subjects on warfarin has been reported to increase its hypoprothrombinemic effect by 40 to 80%.[58] Triclofos, a hypnotic that also forms TCA, similarly prolongs prothrombin time in patients on chronic anticoagulant therapy with warfarin.[59]

Data from a comprehensive drug surveillance program were analyzed to determine the clinical importance of the interaction between chloral hydrate and warfarin.[60] Patients receiving continuous chloral hydrate therapy required significantly less warfarin (15.4 mg vs 22.3 mg) during the induction phase (second to fourth days) of anticoagulation than those receiving no chloral hydrate. Patients given occasional chloral hydrate required an intermediate dose of warfarin. All patients received a similar loading dose of warfarin on day 1 and similar maintenance doses from the fifth day onward. The results indicate that the interaction between these drugs is important; to prevent excessive hypoprothrombinemia, temporary reduction in warfarin requirement should be anticipated when chloral hydrate therapy is begun.

DRUG EXCRETION

The renal excretion of a drug may be affected by a coadministered drug that modifies urine pH, and thereby suppresses or promotes tubular reabsorption, one that interferes, competitively or noncompetitively, with tubular secretion, or one that alters glomerular filtration rate (GFR) or renal blood flow. Biliary excretion of a drug may be affected by a coadministered drug that inhibits transport in the hepatobiliary system or one that modifies bile flow rate.

Urine pH

The effects of urine pH on drug excretion have been discussed in Chapter 11. Changes in urine pH may be the result of certain diseases, dietary factors, or simultaneous administration of certain drugs. The ability of ammonium chloride to acidify and of sodium bicarbonate to alkalinize urine is well known; these materials are used in studies on

the renal excretion of drugs to clarify renal excretion mechanisms.

Regular administration of usual doses of commonly used antacids can also affect urine pH.[61] Magnesium hydroxide (Milk of Magnesia) and calcium carbonate suspensions increased urine pH by 0.4 to 0.5 U, on the average, whereas aluminum-magnesium hydroxide suspension increased urine pH by an average of 0.9 U. Such elevations are sufficient to significantly alter the elimination of drugs such as salicylate or amphetamine.

Steady-state salicylate levels have been compared in subjects receiving aspirin or aspirin and sodium bicarbonate.[62] With aspirin alone, urine pH ranged from 5.6 to 6.1 and plasma salicylate concentration averaged 27 mg/dl. With aspirin and sodium bicarbonate, urine pH ranged from 6.2 to 6.9 and plasma salicylate concentration averaged only 15 mg/dl. The average difference in urine pH between studies was less than 1 U.

In another study, designed to determine if the common practice of giving antacids to patients on salicylate therapy has an effect on serum salicylate concentration, aluminum-magnesium hydroxide gel was given with aspirin to 3 children with rheumatic fever.[63] Urine pH increased and serum salicylate concentration decreased by 30 to 70%.

The hazards of unanticipated changes in urine pH in patients receiving intensive salicylate therapy are considerable. A salicylate dosage regimen yielding plasma concentration of 20 to 30 mg/dl in a patient with a urine pH of 6.5 is likely to produce plasma concentrations more than twice as high, and therefore in the toxic range, when urine pH decreases to about 5.5. Appropriate precautions are necessary, particularly in patients who may not recognize the typical symptoms of salicylism.

Patients receiving amphetamine or related drugs may also be placed at risk by relatively small changes in urine pH. The time course of amphetamine psychosis and amphetamine level in the plasma in amphetamine-dependent patients are shown in Figure 14–4.[64] Patients with alkaline urine had intense psychoses lasting more than 3 days after the last dose of amphetamine.

Probenecid

Probenecid is an old drug, indicated for the long-term management of patients with elevated uric acid levels associated with gout. Probenecid promotes the excretion of uric acid by blocking active reabsorption in the tubules; it also blocks the tubular secretion of other weak acids. Probenecid decreases the renal clearance of many drugs, including penicillins, cephalosporins, dapsone, rifampin, nitrofurantoin, sulfonamides, and thiazide diuretics.[65]

Methotrexate, an important drug for the treatment of neoplastic diseases, is largely eliminated by renal excretion; renal clearance accounts for about 95% of the total plasma clearance of the drug. Administration of probenecid reduces the renal clearance of methotrexate, from 108 to 69 ml/min, and prolongs and enhances serum methotrexate concentrations.[66] Smaller doses of methotrexate may be given with probenecid to achieve the same serum concentrations as when methotrexate is given alone. It may be possible to reduce the cost of treatment with methotrexate without decreasing its efficacy. This may also be true for some of the newer and costly antibiotics.

Because of its effect on renal excretion, probenecid is indicated as an adjunct to penicillin therapy and is used as an adjunct to cephalosporin antibiotic therapy. Probenecid is used primarily when high antibiotic levels in plasma and tissues are required (e.g., in the treatment of gonorrhea).

An interesting interaction has been reported between probenecid and ceftriaxone.[67] The pharmacokinetics of ceftriaxone are unusual because its plasma protein binding is concentration-dependent over the concentration range resulting from therapeutic doses. The percentage of free ceftriaxone in plasma increases from 4% to about 17% with a change in total plasma concentration from 0.5 to 300 μg/ml.

On the average, about half of an iv dose of ceftriaxone is excreted unchanged in the urine. But urinary excretion is variable and may range from 30 to 65% of the dose; the rest is excreted in the bile. Suspecting that tubular secretion and active biliary excretion played a role in the elimination of ceftriaxone, Stoekel et al. studied the effects of probenecid on its pharmacokinetics.

Unexpectedly, concurrent administration of probenecid *increased* the clearance of total (bound + unbound) ceftriaxone from 0.24 to 0.31 ml/min/kg and decreased its half-life from 8.1 to 6.5 hr. That probenecid *also* inhibited the elimination of ceftriaxone was evident from kinetic parameters based on free (unbound) ceftriaxone. Probenecid decreased the renal clearance of unbound ceftriaxone from 2.1 to 1.7 ml/min/kg and the nonrenal (biliary) clearance from 2.8 to 1.9 ml/min/kg.

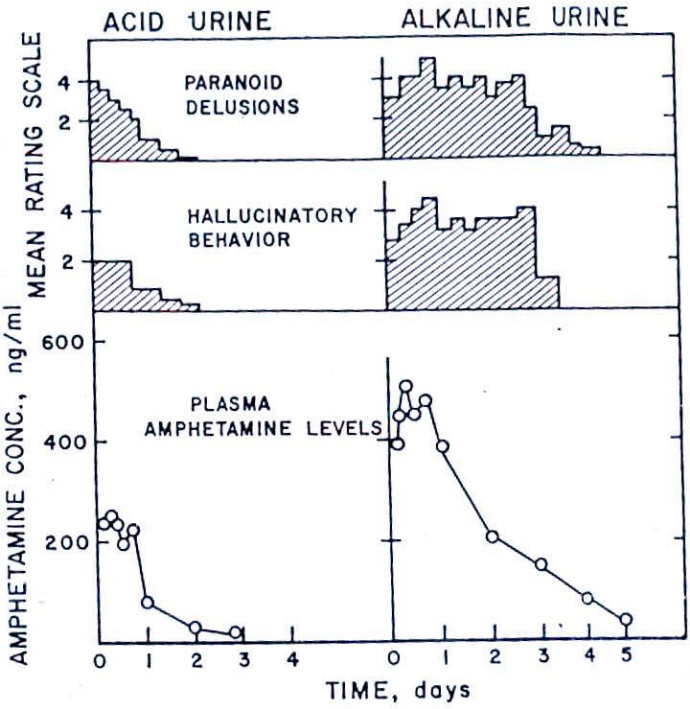

Fig. 14–4. Time course of amphetamine psychosis in patients with acid (pH 5.0 to 6.0) and alkaline (pH 6.5 to 7.1) urine, after a 150-mg oral dose. (Data from Anggard, E., et al.[64])

These findings suggested that probenecid substantially decreases the plasma protein binding of ceftriaxone. In vitro studies revealed that probenecid increased the average free fraction of ceftriaxone in plasma from 0.050 to 0.087, nearly a 75% change. Because the clearance of total ceftriaxone is strongly dependent on the free fraction in plasma, the substantial displacement of ceftriaxone from plasma protein binding sites by probenecid explains the increase in clearance of total drug even in the face of decreased renal and biliary clearance of unbound drug.

Cimetidine

As noted in an earlier section of the text, at least two transport systems have been characterized in the proximal renal tubule: one that handles anions and another that transports cations. The 'probenecid interaction' is the classic example of an acid drug inhibiting the tubular secretion of other acid drugs. Our understanding of the mutual active transport of basic drugs in the kidney, however, is far less developed. The hypothesis that basic drugs can compete for active tubular secretion was evaluated in healthy subjects by comparing the pharmacokinetics of a single 1 g dose of oral procainamide before and during cimetidine administration.[68]

Cimetidine had a marked effect on the kinetics of both procainamide and its active metabolite, N-acetylprocainamide (NAPA). The total area under the procainamide concentration in plasma-time curve was increased by 44%; this change could be almost wholly accounted for by a decrease in renal clearance of procainamide from 347 ml/min during the control period to 197 ml/min during cimetidine administration. The average levels of NAPA in plasma also increased, by about 25%, during the cimetidine phase of the study, consistent with a decrease in the renal clearance of NAPA from 258 to 197 ml/min.

The results suggested that cimetidine inhibits the tubular secretion of both procainamide and NAPA. The report by Somogyi et al. appears to be the first example of this type of interaction with basic drugs in humans. The specific findings of the study are

also of interest in that steady-state levels of procainamide would be expected to increase by nearly 50% during cimetidine administration, and NAPA levels are predicted to rise by 25% or more. Both compounds have a relatively narrow therapeutic index and there may be a need to reduce the dose of procainamide in patients also being treated with cimetidine, to avoid adverse effects.

More recently, van Crugten et al.[69] demonstrated in healthy human subjects that cimetidine also inhibits the renal clearance of ranitidine, another base, and cephalexin, a zwitterion. The renal clearance of ranitidine decreased by more than 40% with concurrent cimetidine, from 326 to 244 ml/min. A significant but smaller effect was observed with cephalexin. Renal clearance decreased in the presence of cimetidine from 267 to 208 ml/min. No effect of cimetidine was found on the renal clearance of cephalothin, an acid with a renal clearance > 500 ml/min. The investigators concluded that their findings "confirmed the hypothesis that cimetidine-mediated inhibition of renal drug clearance in humans is selective for a common cationic secretory transport mechanism in the proximal tubule of the kidney, rather than a nonspecific action on renal function."

Anti-Inflammatory Drugs

Certain anti-inflammatory drugs significantly affect renal function; this is related to their inhibition of prostaglandin synthesis. Clinically important interactions have been observed when these drugs are given with lithium.

Lithium is used widely in the treatment of patients with manic depression and other psychiatric disorders. It is eliminated almost exclusively by the kidneys. Lithium ions are filtered by the glomeruli, but 80% of the filtered load is reabsorbed by the renal tubules. The renal clearance of lithium is, therefore, about 20% of creatinine clearance or 15 to 30 ml/min in patients with normal renal function.

The effects of indomethacin on plasma lithium concentrations were studied in psychiatric patients and healthy subjects.[70] After steady-state plasma lithium levels had been reached, all subjects received indomethacin (50 mg 3 times a day) for 7 days. Indomethacin increased plasma lithium concentration, by 60% in the psychiatric patients and 30% in the healthy subjects, and suppressed the renal excretion of lithium (Fig. 14–5). In some

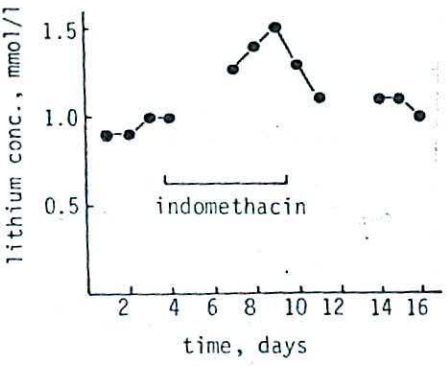

Fig. 14–5. Effect of indomethacin on steady-state lithium concentrations in plasma in a psychiatric patient. (Data from Frölich, J.C., et al.[70])

patients, the increase in plasma lithium levels was sufficient to lead to toxicity.

Diclofenac, another prostaglandin synthesis-inhibiting, nonsteroidal anti-inflammatory drug (NSAID), was found to decrease the renal clearance of lithium by 23% and to increase lithium plasma levels by 26%.[71] Care should be taken when using an inhibitor of prostaglandin synthesis in a patient being treated with lithium.

Aspirin and other NSAIDs also have the potential to reduce the antihypertensive effects of diuretics by directly competing for transport sites in the organic acid secretory system of the proximal renal tubules.[72] According to McGiff, "this secretory system serves as the major route of access of thiazide diuretics, furosemide, and potassium-sparing agents to their active sites within the renal tubules. As this route can be blocked by NSAIDs, diminished efficacy of the diuretic agent may occur . . ."

Thyss et al.[73] reported serious and, in some cases, lethal methotrexate (MTX) toxicity when it was administered with ketoprofen, a recently approved NSAID. Toxicity was associated with unusually high serum levels of MTX. The investigators suggested that the mechanism of this interaction might involve "inhibition of renal prostaglandin synthesis by ketoprofen which would decrease renal perfusion rate and thus inhibit MTX clearance. An alternative suggestion, which is not mutually exclusive, would be competitive renal secretion of these two drugs, which are both eliminated to a large extent by the kidney."

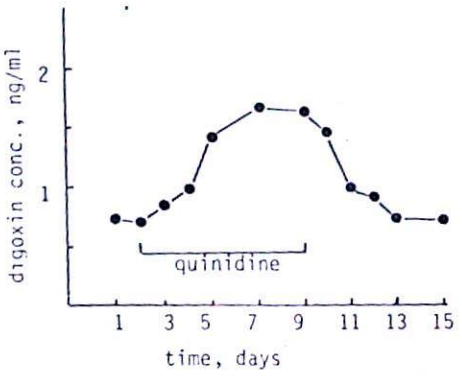

Fig. 14–6. Effect of quinidine on steady-state digoxin concentrations in serum. (Data from Doering, W.[77])

Furosemide

Furosemide is a potent diuretic that acts by inhibiting active chloride transport in the loop of Henle. Its effects on the kidney may alter the renal excretion of other drugs.

Studies in healthy subjects indicate that furosemide decreases inulin clearance, a measure of GFR; inulin clearance is also reduced in water-loaded subjects.[74] On the average, furosemide decreased inulin clearance from 130 to 80 ml/min. This change was paralleled by changes in the renal clearance of practolol, an early β-blocker no longer used today, gentamicin, and cephaloridine, but not of digoxin. Furosemide reduced the renal clearance of gentamicin from 142 to 110 ml/min and of cephaloridine from 213 to 136 ml/min. There is concern that furosemide may enhance the ototoxicity of aminoglycoside antibiotics and the nephrotoxicity of cephaloridine, particularly in patients with renal impairment.

Digoxin-Quinidine Interaction

Although digoxin and quinidine have been used in combination for more than 50 years in the treatment of cardiac arrhythmia, not until 1978 was it recognized that a major interaction occurs between these drugs, one that may put a patient at risk of digitalis toxicity. Since 1978 dozens of reports have been published on the subject.

In 1978, Ejvinsson reported on 12 patients who received the combination of digoxin and quinidine; all patients showed a rise in serum digoxin concentration.[75] Serum digoxin levels rose above the usual therapeutic concentration range in 6 patients. Leahey and co-workers found increased serum digoxin concentration in 25 of 27 patients receiving digoxin and quinidine, an incidence of 93%.[76] Gastrointestinal side effects, typical of digoxin toxicity, developed in 16 patients. Lowering the dose of digoxin alone substantially reduced the incidence of adverse effects. In 1979, Doering reported on 79 patients who demonstrated a significant average increase in digoxin concentration from 1.0 to 2.5 ng/ml when quinidine was added.[77] The time course of the interaction is shown in Figure 14–6.

An important question is why was this interaction overlooked for so long. Doherty suggests several reasons: quinidine alone and digoxin alone cause adverse effects; patients requiring both drugs are usually quite sick, which makes it difficult to determine whether symptoms are related to treatment or disease; the use of other drugs confuses the issue.[78]

The basis for the quinidine-digoxin interaction is unusually complicated. Steady-state concentrations of digoxin increase because quinidine decreases the clearance of digoxin. One report found that the total plasma clearance of digoxin in healthy subjects fell from 3.1 to 2.0 ml/min per kg in the presence of quinidine;[79] a 56% decrease in total clearance of digoxin was found in patients with atrial fibrillation.[80]

Part of the reason for the lower plasma clearance of digoxin is quinidine's effect on the renal clearance of digoxin. In healthy subjects quinidine reduced the renal clearance of digoxin from 1.6 to 1.1 ml/min per kg;[79] in patients with cardiac disease quinidine reduced the renal clearance of digoxin from 53 ml/min per 1.73 m^2 to 35 ml/min per 1.73 m^2.[81] Quinidine has no effect on creatinine clearance; it is thought that quinidine inhibits the tubular secretion of digoxin.

Renal clearance only accounts for about half of the elimination of digoxin. On the average, usual doses of quinidine decrease the renal clearance of digoxin by about 50% and increase steady-state levels by about 100%. Suppression of renal clearance can only account for about half of the increase in steady-state digoxin concentration. Therefore, quinidine must also inhibit the nonrenal clearance of digoxin to a similar degree.[80,82] The mechanism for the decrease in nonrenal clearance of digoxin is unknown. Quinidine may inhibit the biliary secretion of digoxin, the hepatic metabolism of digoxin, or both.

More direct evidence of the effect of quinidine on the nonrenal elimination of digoxin is available

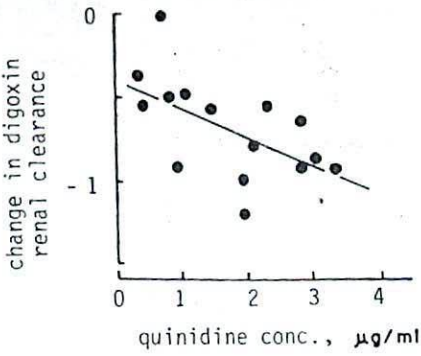

Fig. 14–7. Relationship between reduction in renal clearance (ml/min per kg) of digoxin and serum quinidine concentration. (Data from Leahey, E.B., et al.[82])

from a study of the quinidine-digoxin interaction in patients with end-stage renal failure (serum creatinine = 10.2–16.8 mg/dl).[83] In these patients, quinidine markedly decreased the total clearance of digoxin from 1.9 to 1.1 L/hr; the half-life of digoxin increased from 5.2 to 9.6 days. The renal clearance of digoxin is negligible in these patients and the decrease in total clearance of digoxin must be the result of an effect of quinidine on the nonrenal clearance of digoxin.

The effects of quinidine on digoxin are dose-related. Doses of less than 500 mg quinidine per day produced no appreciable effect on serum digoxin.[77] Leahey and co-workers reported that the decrease in renal clearance of digoxin was related to serum quinidine concentration (Fig. 14–7).[82] The change in nonrenal clearance was independent of serum quinidine.

The dependence of the digoxin-quinidine interaction on serum quinidine concentration is also seen in a case report concerned with sequential drug interactions.[84] A 94-year-old woman was stable when treated with a combination of quinidine, digoxin, and pentobarbital. Discontinuation of the barbiturate resulted in a 3-fold increase in serum digoxin levels, from about 1.4 to about 4.5 ng/ml, and symptoms of digitalis toxicity. Induction of quinidine metabolism by pentobarbital maintained serum levels of quinidine that were too low to significantly affect digoxin elimination. The elevated levels of quinidine on discontinuing the barbiturate substantially inhibited the clearance of digoxin.

Quinidine also decreases the apparent volume of distribution of digoxin, apparently by displacing digoxin from extravascular binding sites (i.e., by decreasing the tissue binding of digoxin). In healthy subjects, quinidine decreased the volume of distribution of digoxin from 10.9 to 7.4 L/kg;[79] a decrease from 11.1 to 6.8 L/kg was observed in patients with atrial fibrillation.[80]

About 50% of digoxin in the body is found in skeletal muscle. Studies in patients with atrial fibrillation indicate that the ratio of digoxin concentration in skeletal muscle to that in serum decreases from 43 before quinidine treatment to 33 during quinidine treatment.[85] This change can largely account for the decrease in digoxin distribution volume in the presence of quinidine.

This additional effect of quinidine on the apparent volume of distribution of digoxin is interesting but unrelated to the elevation in serum digoxin concentration produced by quinidine. The clinical implications of this aspect of the digoxin-quinidine interaction are not clear.

More recently, it has come to light that some investigators find no evidence of digitalis toxicity when serum digoxin levels rise with concurrent quinidine. In fact, one study reported that the inotropic effects noted during digoxin therapy alone were markedly attenuated or completely antagonized when quinidine was added, despite a doubling of the serum digoxin concentration.[86] Positive inotropic effects reappeared on withdrawal of quinidine.

The conflicting reports may reflect the difficulty in defining the relationship between serum digoxin and myocardial effects in the presence of quinidine, because quinidine can produce symptoms similar to those of digoxin. This problem has been highlighted by Walker et al.[87] who reviewed inpatient data to determine the incidence of adverse effects in patients treated with digoxin alone, quinidine alone, and digoxin and quinidine.

The incidence of cardiac and gastrointestinal side effects nearly tripled when quinidine was added to digoxin therapy, compared with that recorded during treatment with digoxin alone, but most of the increased incidence of toxicity could be accounted for by the frequency with which quinidine itself produces similar symptoms. The investigators noted that "simple additivity of rates observed in this study suggests that there was little or no clinical interaction of digoxin and quinidine in the production of adverse reactions. Rather, these data reflect the general finding that patients receiving two drugs

have more adverse reactions than those who receive only one."

In an attempt to clarify the question, Warner et al.[88] studied the relationship between serum digoxin and digoxin effects in the presence of quinidine in dogs, using inhibition of myocardial cation transport as a measure of effect. The inotropic and toxic effects of digoxin are associated with an inhibition of myocardial Na,K-ATPase, which results in a reduction in monovalent cation transport. Cation transport is usually evaluated by measuring rubidium uptake.

Quinidine alone had no effect on myocardial cation transport, whereas digoxin inhibited rubidium uptake by the left ventricular myocardium in a concentration-dependent manner. A statistically significant correlation was found between rubidium uptake and serum digoxin concentration in dogs receiving digoxin alone as well as in those receiving digoxin with quinidine, but the slopes of these regression lines were different. At equivalent serum digoxin levels, dogs that were given digoxin and quinidine had less inhibition of Rb^+ uptake than those that received only digoxin.

Warner et al. concluded that the increase in serum digoxin seen with quinidine was not accompanied by a proportional increase in digoxin effects. In fact, the excess digoxin concentration resulting from the interaction with quinidine appeared to have no effect on Rb^+ uptake. It seems, therefore, that quinidine not only inhibits the elimination of digoxin, it also inhibits the inotropic effect of digoxin. Although extrapolation of these findings to the clinical setting must be done carefully, questions are raised concerning the value of serum digoxin as a predictor of the effects of digoxin in the presence of quinidine.

The results suggest that reducing the dosage of digoxin in proportion to changes in serum levels when digoxin is used with quinidine may be inappropriate. Inhibition of myocardial Rb^+ uptake is related to the effects of digoxin on contractility and ventricular arrhythmias. Patients receiving both digoxin and quinidine may have less inotropic effect and less likelihood of developing tachyarrhythmia at a given serum digoxin concentration than patients on digoxin alone.

On the other hand, the effects of digoxin on the sinus and AV node is indirect, mediated through the autonomic nervous system and unrelated to myocardial cation transport. The same is true for the gastrointestinal toxicity of digoxin, which is neurally mediated. Until the clinical effects of digoxin in the presence of quinidine are further clarified, Warner et al. recommend that digoxin dosing be based on clinical evaluation, as well as on serum digoxin concentration measurements.

Digoxin and Other Antiarrhythmic Drugs

Leahey and co-workers compared the effects of quinidine on digoxin with those of other type I membrane active antiarrhythmic drugs, including procainamide and disopyramide, which are used frequently in the United States as alternatives to quinidine, and mexiletine, which is widely used in Europe.[89] Quinidine increased serum digoxin concentration and prolonged the P-R interval on the electrocardiogram, a finding consistent with earlier studies, but none of the other drugs affected serum digoxin levels or P-R interval.

On the other hand, verapamil, a calcium channel blocker used for treating patients with angina and arrhythmias, affects digoxin in the same way as quinidine.[90] In healthy subjects, verapamil decreased the total plasma clearance of digoxin from 3.3 to 2.2 ml/min per kg by inhibiting both renal and nonrenal clearance. Unlike quinidine, verapamil had no effect on the apparent volume of distribution of digoxin. Amiodarone, a long-acting antiarrhythmic drug, also inhibits the elimination of digoxin.[91]

Renal Blood Flow

Drug-related changes in renal blood flow can affect the urinary excretion of drugs, particularly drugs subject to tubular secretion. The effect of vasodilator therapy on the renal clearance of digoxin was studied in patients with congestive heart failure (CHF).[92] Intravenous nitroprusside or hydralazine increased cardiac index, para-aminohippurate (PAH) clearance, renal blood flow, and the renal clearance of digoxin. The results are summarized in Table 14–2. If this improvement in renal hemodynamics is achieved during chronic treatment with vasodilators, then maintenance digoxin doses may need to be increased to maintain therapeutic drug concentrations in serum.

Biliary Excretion

Difficulties in measuring drug concentrations in bile have all but precluded clinical or human experimental investigations on drug-drug interactions that affect biliary excretion. The few interactions that we are aware of derive from indirect evidence.

Table 14–2. Effects of Vasodilators on Hemodynamics, Renal Function, and Digoxin Excretion*

Variable	Control	Nitroprusside	Hydralazine
Cardiac index (L/min per m²)	2.00	2.65	3.28
Paraaminohippurate clearance (ml min)	200	289	425
Renal blood flow (ml/min)	337	480	718
Digoxin renal clearance (ml/min)	104	152	147

*Data from Cogan, J.J., et al.[92]

Probenecid significantly inhibits the elimination of indomethacin; plasma clearance of indomethacin was 174 ml/hr per kg in the control period and 107 ml/hr per kg in the presence of probenecid.[93] There was no change in the renal clearance of indomethacin during probenecid treatment; but probenecid decreased nonrenal clearance from 168 ml/hr per kg to 104 ml/hr per kg. It is likely that probenecid inhibits the biliary excretion of indomethacin.

A more general interaction has been reported between drugs that are excreted, either in the bile or directly, into the gastrointestinal tract and nonabsorbable ion exchange resins that bind drugs in the gut and prevent reabsorption. The effect of cholestyramine on the pharmacokinetics and pharmacodynamics of a single intravenous dose of phenprocoumon, the oral anticoagulant of choice in Europe, was studied in healthy subjects.[94] Cholestyramine treatment led to increased elimination in all subjects; half-life decreased from 5 days to 3.1 days and clearance increased from 17 ml/day per kg to 29 ml/day per kg. Cholestyramine reduced the area under the anticoagulant effect versus time curve from 660 to 344 U. Concomitant use of these drugs should probably be avoided. Higher doses of phenprocoumon would be required in the presence of cholestyramine to achieve satisfactory anticoagulation. From a different point of view, cholestyramine may be useful in the treatment of phenprocoumon overdosage.

DRUG METABOLISM

Interactions between two drugs that affect the metabolism of one or both constitute most of the clinically important drug interactions. Many drugs stimulate or induce the activity of hepatic drug metabolizing enzymes, thereby reducing blood levels and clinical effects of drugs given concurrently. We now recognize that a wide range of drugs can inhibit drug metabolizing enzymes and lead to accumulation and toxicity of coadministered drugs. The effects of drug metabolizing enzyme inducers or inhibitors may be particularly pronounced when drugs subject to presystemic hepatic metabolism are given at the same time. Drug metabolism may be affected not only by other drugs but also by environmental chemicals; these interactions are sometimes important.

Induction of Drug Metabolizing Enzymes

A wide range of chemically unrelated substances can stimulate the activity of mixed function oxidases by enzyme induction. The molecular mechanism of enzyme induction is not fully understood nor have the molecular characteristics essential for induction been defined. Enzyme inducers are lipophilic, bind to cytochrome P-450 enzymes, and have relatively long half-lives, but not all drugs with these characteristics are enzyme inducers.

Induction is usually associated with an increase in liver weight and in the amounts of microsomal protein, cytochrome P-450, and other oxidative enzymes in the liver. The enzyme systems involved in conjugation, such as glutathione transferase and glucuronyl transferase, can also be induced. The time course of induction varies with the inducing agent. A powerful enzyme inducer such as rifampin can produce measurable changes in the activity of drug metabolizing enzymes within 48 hr, but less potent inducers may require a longer time.

Enhancement of drug metabolism by ethanol, tobacco smoking, and diet also involves enzyme induction. Induction of drug metabolizing enzymes usually leads to a reduction in drug efficacy, but it may also enhance the toxicity of certain drugs with active metabolites. The clinical implications of enzyme induction have been reviewed by Park and Breckenridge.[95]

Anticonvulsant Drugs. Phenobarbital, phenytoin, and carbamazepine are potent inducers of drug metabolizing enzymes and are often used in combination in the treatment of patients with epilepsy. Patients treated with anticonvulsant drugs have, in general, an above average ability to metabolize many drugs and often require higher than average dosages. Pharmacokinetic interactions with antiepileptic drugs have been reviewed by Perucca.[96]

A study comparing epileptic patients receiving phenytoin alone or phenytoin with phenobarbital or carbamazepine with healthy subjects found that epileptic patients had much higher cytochrome P-450 levels in liver biopsies and metabolized antipyrine considerably faster than control subjects.[97]

In a more recent investigation, antipyrine kinetics were studied in patients with epilepsy who were to have phenytoin, carbamazepine, or valproic acid discontinued as part of a planned simplification of therapy.[98] Antipyrine was given before and 4 weeks after discontinuation of one drug.

Removal of carbamazepine was associated with a nearly 50% decrease in antipyrine clearance in those patients who were also treated with either valproic acid or ethosuximide, neither of which is an enzyme-inducing agent. There was no change in antipyrine clearance after removal of carbamazepine in those patients treated with phenytoin and/or barbiturates. Removal of phenytoin was associated with a 10 to 15% decrease in antipyrine clearance in those patients who were also receiving carbamazepine, with or without barbiturates. As expected, removal of valproic acid had no effect on antipyrine clearance.

When carbamazepine was the only enzyme inducing agent being taken, its removal resulted in a marked decrease in antipyrine clearance. However, if an enzyme inducer (e.g., phenytoin, barbiturates) was also being taken, the removal of carbamazepine had no effect on antipyrine clearance.

These results suggest that carbamazepine has no additional effect on antipyrine clearance beyond that of phenytoin and/or barbiturates. Phenytoin, on the other hand, has enzyme inducing activity over and above that of carbamazepine, or carbamazepine and barbiturates, and appears to be a more powerful inducer of hepatic enzyme activity than is carbamazepine. Although differences between carbamazepine and phenytoin may exist, carbamazepine is nevertheless a strong inducer, capable of reducing the efficacy of drugs given concurrently (see Fig. 14–9).

Consistent with the findings on antipyrine kinetics, the investigators also found that removal of phenytoin resulted in elevated blood levels of carbamazepine and valproic acid, and removal of carbamazepine resulted in increased levels of valproic acid and ethosuximide. It also follows from these results that, for a given dose of anticonvulsant, serum levels may be higher in those patients receiving monotherapy than in those treated with additional drugs. This has been demonstrated with valproic acid by Chiba et al.[99] in children. Plasma clearance of valproate was 13 ml/hr/kg in patients receiving only valproic acid and 23.5 ml/hr/kg in those treated with valproic acid and other anticonvulsants.

Blood level studies of quinidine in healthy subjects before and at the end of a 4-week course of phenobarbital or phenytoin showed that the anticonvulsant drugs decreased the half-life and the total area under the concentration-time curve after a single oral dose by more than 50%. Quinidine half-life ranged from 3.0 to 6.1 hr during the control period but fell to 1.6 to 2.6 hr during the anticonvulsant drug period.[100] In two patients, the concomitant use of primidone or phenytoin resulted in inadequate blood levels of quinidine with standard dosages of the drug (i.e., 300 mg every 4 hr). In another patient, oral doses of quinidine sulfate up to 800 mg every 4 hr were required to obtain therapeutic plasma quinidine concentrations.[100]

The pharmacokinetics of diazepam after intravenous administration were determined in healthy subjects and in epileptic patients receiving chronic anticonvulsant drug therapy, including combinations of carbamazepine, valproate sodium, phenytoin, clonazepam, or primidone.[101] Large differences in half-life and clearance were observed. The half-life of diazepam was only 13 hr in the patients with epilepsy compared to a value of 34 hr in control subjects. The clearance of diazepam increased from 20 ml/min in control subjects to 52 ml/min in epileptic patients. Considerably larger doses of antianxiety drugs may be required for adequate clinical effects in patients being treated for epilepsy.

Some of the literature on oral contraceptives suggests that OCs are not predictably effective in preventing conception in women taking anticonvulsant medication.[102] Failure rates are higher in groups of women taking enzyme-inducing anticonvulsants than in control groups. Evidence shows that the most common cause of failure in these women is insufficient steroid (estrogen or progestin) levels to block ovulation. These reduced levels are probably the result of increased steroid metabolism as a consequence of induction of microsomal oxidative enzymes by the antiepileptic drugs.

Drugs subject to first-pass metabolism after oral administration appear to be particularly susceptible to the enzyme inducing effects of anticonvulsants.

A good example is provided by studies with felodipine, an investigational dihydropyridine calcium channel blocker.[103] Felodipine undergoes extensive first-pass hepatic metabolism and ordinarily has an oral bioavailability of about 15%.

Felodipine disposition was studied in patients on chronic anticonvulsant therapy for control of seizures and normal subjects matched for age and sex. Plasma felodipine levels after an oral dose were dramatically lower in the patients with epilepsy. Mean peak concentrations in plasma were about 9 nmol/L in controls and 1.6 nmol/L in patients. The relative bioavailability of felodipine in the patients with seizure disorders was less than 10% of that in the control subjects. Therefore, the mean oral bioavailability of felodipine in subjects receiving anticonvulsants is about 1%. "Patients on anticonvulsant medication will require substantially higher doses of felodipine to achieve plasma concentrations equivalent to those in non-induced subjects."[103]

Phenytoin. Phenytoin can induce the metabolism of many drugs, including antipyrine, hydrocortisone, dexamethasone, dicumarol, digitoxin, and thyroxine; it does not, however, stimulate its own metabolism.[95]

Phenytoin is usually used with other drugs in the treatment of epilepsy. Although it has little effect on phenobarbital, phenytoin does stimulate the metabolism of clonazepam and primidone. Long-term treatment with phenytoin lowers the blood levels of clonazepam after a single oral dose by more than 50%.[104] Phenytoin stimulates clonazepam metabolism to a considerably greater extent than does phenobarbital.

Primidone is a widely used anticonvulsant drug; it is converted to two active metabolites, phenylethylmalonamide (PEMA) and phenobarbital. Whether or not primidone has pharmacologic activity of its own is not known. The steady-state serum concentration ratio of derived phenobarbital to unmetabolized primidone is higher in patients treated with a combination of primidone and phenytoin than in patients treated with primidone alone (2.2 vs 1.6);[105] a twofold difference in serum concentration ratio was found in another investigation.[106] Phenytoin also increases the steady-state serum concentration ratio of derived PEMA to primidone.[106]

Phenytoin accelerates the metabolism of most corticosteroids; it has a clinically important effect on the elimination of prednisolone. Phenytoin decreased the half-life of prednisolone by about 50% and increased its clearance from plasma by about 80%.[107] The average oral dose, given at midnight, required to suppress the 8 A.M. plasma level of endogenous hydrocortisone (cortisol) to 5 μg/dl was doubled following treatment with phenytoin.

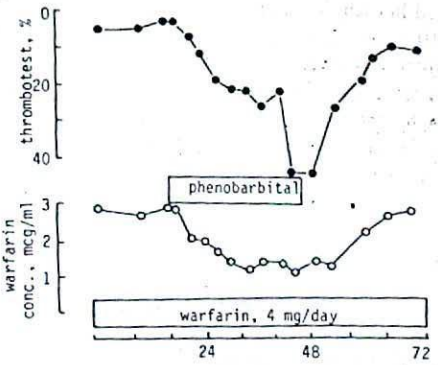

Fig. 14–8. Warfarin-phenobarbital interaction. Phenobarbital (120 mg/day) reduces plasma warfarin levels and antagonizes its anticoagulant effect. (Data from Breckenridge, A.M., and Orme, M.L.E.[110])

Drugs that influence the activity of hepatic drug metabolizing enzymes may have particularly pronounced effects on coadministered drugs subject to presystemic metabolism. Phenytoin treatment increases the systemic clearance of meperidine by about 25%, from 1017 ml/min to 1280 ml/min. Phenytoin also increases the extent of hepatic first-pass metabolism of meperidine after oral administration; bioavailability is reduced from 61% to 43%. To achieve comparable blood levels of meperidine, about twice the oral dose is required in patients treated with phenytoin as is needed in patients who are not induced.[108] This means that patients on phenytoin tend to have high levels of normeperidine, the metabolite of meperidine closely associated with its adverse effects. It may be preferable to give intravenous rather than oral meperidine to these patients.

Unexpectedly, phenytoin also appears to increase the metabolism of theophylline. This was first noted in a case study. A 49-year-old man with asthma and epilepsy who was receiving 400 mg/day phenytoin responded poorly to apparently adequate doses of theophylline. This observation prompted a study of the effects of phenytoin on the elimination of theophylline in adult nonsmoking healthy subjects.[109] Phenytoin dosage was ad-

justed in each individual to achieve a serum level of 10 to 20 μg/ml before the test dose of theophylline was given.

Phenytoin administration reduced the half-life of theophylline from 10 to 5 hr. The results suggest that the dosage of theophylline should be increased by 50 to 100% when phenytoin is added to long-term theophylline therapy or when theophylline is initiated in patients being treated with phenytoin. This report is of additional interest because phenobarbital, which is thought to stimulate the same drug-metabolizing enzymes as does phenytoin, has no effect on theophylline metabolism.

Phenobarbital. This barbiturate has been the most extensively studied enzyme-inducing agent; it is a potent inducer in most species. Phenobarbital can stimulate a wide range of metabolic pathways and has been shown to reduce the effects of many drugs in man.

Probably the most widely studied interaction of barbiturates is with oral anticoagulants. Figure 14–8 shows plasma warfarin levels and anticoagulant effect before, during, and after phenobarbital treatment. A significant decline in warfarin levels and anticoagulant effect is evident within 6 days; the maximum effect is usually seen after 2 to 3 weeks.[110]

Phenobarbital administration has also been shown to stimulate the metabolism of dicumarol. Patients who had been on dicumarol for an average of about 4 years were found to require an average increase of 33% in their daily dose to maintain adequate anticoagulation when phenobarbital therapy was initiated.[111]

The barbiturate-oral anticoagulant interaction is clinically significant. A physician may respond to the reduced anticoagulant effect by increasing the dose of warfarin or dicumarol. No problems ensue as long as both the barbiturate and the anticoagulant are continued. The patient is at risk, however, when the barbiturate is stopped, because the rate of drug metabolism will return to normal levels over a week or two and the plasma concentrations of the anticoagulant will increase. Unless the dose is reduced, serious or fatal hemorrhage may occur.

An additional complication of the interaction between barbiturates and oral anticoagulants is the considerable interpatient variability in the degree of induction. Whenever possible this drug combination should be avoided because, even with careful monitoring, optimal anticoagulant control will be difficult.

Few reports have considered the effects of hepatic enzyme induction with phenobarbital on the disposition of high clearance drugs. To this end, Rutledge et al.[112] studied the kinetics of verapamil before and after 21 days of phenobarbital (180 mg/day) in healthy subjects. The mean apparent clearance of unbound drug after an oral dose of verapamil was increased after treatment with phenobarbital from 950 to 3600 ml/min/kg, but the systemic clearance of unbound verapamil, determined after an iv dose, was about the same before and after phenobarbital. The findings suggest that much larger oral doses of verapamil may be required in patients regularly receiving phenobarbital. The lack of effect on the systemic clearance of verapamil suggests that phenobarbital has little effect on hepatic blood flow rate in humans.

Phenobarbital and other barbiturates are known to induce enzymes involved in the metabolism of steroids, including those used in oral contraceptive products. Pregnancies have been reported in patients taking phenobarbital in conjunction with oral contraceptives,[113] but it has not been established whether the interaction is with the estrogen or the progestogen. The clinical implications of drug-stimulated biotransformation of hormonal steroid contraceptives has been reviewed by Hempel and Klinger.[114]

The ability of phenobarbital to stimulate liver enzymes has been used to advantage in the treatment of unconjugated hyperbilirubinemia in neonates.[115] In some infants, the induction of glucuronyl transferase results in a significant decrease in bilirubin levels. The induction of this enzyme has also been used as a method of minimizing the hazard of Rh-incompatibility and neonatal jaundice by dosing a mother who has developed rhesus antibodies with phenobarbital to induce the enzymes in the liver of her unborn child.[116]

Other Barbiturates. Enzyme induction appears to be a characteristic shared by most if not all barbiturates. Differences in potency may exist but their importance is not known. Human investigations indicate that phenobarbital reduces the anticoagulant effect of warfarin to a slightly greater extent than does secobarbital.[117]

When the metabolism of a drug is rate-limited by the rate of hepatic blow flow, changes in the activity of hepatic drug metabolizing enzymes may have little effect on systemic clearance. This has been demonstrated with verapamil[112] and with alprenolol.[118] The systemic clearance of alprenolol,

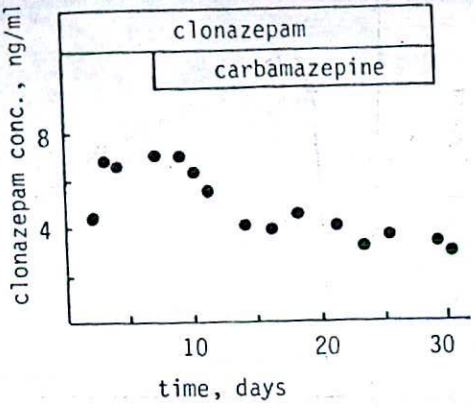

Fig. 14–9. Effect of carbamazepine on clonazepam levels in plasma. (Data from Lai, A.A., Levy, R.H., and Cutler, R.E.[119])

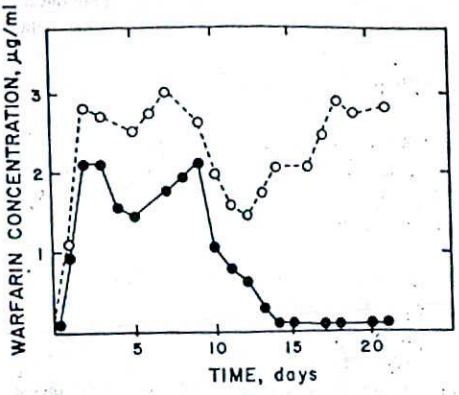

Fig. 14–10. Warfarin concentrations in plasma after daily doses of warfarin alone (○) or daily doses of warfarin and rifampin (●) in a healthy subject. The daily dose of warfarin was the same in both studies, the studies were 4 wk apart, and the daily dose of rifampin was 600 mg. (Data from O'Reilly, R.A.[123])

a β-blocking drug widely used in Europe, was determined after intravenous administration before and during treatment with pentobarbital. Clearance was not significantly different, averaging 1.2 L/min in the control period and 1.5 L/min in the barbiturate period. One might incorrectly conclude from these results that pentobarbital interacts little or not at all with alprenolol. The effect of pentobarbital on the metabolism of alprenolol is clearly evident, however, after oral administration of the β-blocker. The bioavailability decreases from 26% of the dose during the control phase to only 7% during the pentobarbital period because of a large increase in presystemic metabolism of alprenolol, secondary to induction of drug metabolizing enzymes.[118] If one wishes to determine whether or not a compound is an inducer or inhibitor of drug metabolizing enzymes, it is better to study its effects after oral rather than intravenous administration of a test drug.

Carbamazepine. The clearance of many drugs given with carbamazepine is increased because carbamazepine, like phenytoin, is a potent inducer of drug metabolizing enzymes. As noted above, discontinuing carbamazepine in patients with epilepsy who were also treated with either valproic acid or ethosuximide resulted in a nearly 50% decrease in antipyrine clearance.[98] Removal of carbamazine also resulted in increased levels of valproic acid and ethosuximide in these patients.

Carbamazepine has also been reported to increase the elimination of phenytoin, warfarin, and clonazepam.[95] The effect of carbamazepine on steady-state levels of clonazepam are shown in Figure 14–9.[119]

Autoinduction

There are many examples of changes in pharmacokinetics during repeated dosing of a drug compared with a single dose. In a very small number of cases, changes appear to be related to a slow induction of drug-metabolizing enzymes involved in the biotransformation of the inducer itself. This has been called autoinduction.

Carbamazepine is the principal example of a drug that displays autoinduction. It is now well established that during long-term therapy, carbamazepine induces its own metabolism.[120] During repeated dosing, the clearance of carbamazepine increases at least 2-fold and blood levels decline by 50%. Induction occurs over 3 to 4 weeks; thereafter, blood levels are relatively stable. Concomitant treatment with phenobarbital or phenytoin at this time further induces the metabolism of carbamazepine.

A recent report suggests that cyclophosphamide may also induce its own metabolism. Moore et al.[121] studied the disposition of cyclophosphamide and its active metabolite phosphoramide mustard in patients receiving high-dose intravenous cyclophosphamide daily for 2 days before bone marrow transplantation.

Total clearance of cyclophosphamide increased from 93 ml/min on the first day of treatment to 178

ml/min on the second day. An increased rate of formation of phosphoramide mustard with higher peak concentrations was also seen. Peak levels were 19 μmol/L on day 1 and 36.5 μmol/L on day 2.

Moore et al. gave an iv test dose of dexamethasone each day, hypothesizing that, if increased cyclophosphamide clearance was due to microsomal enzyme induction, increased clearance of dexamethasone should also be observed on day 2. Dexamethasone, like antipyrine, is metabolized by hepatic mixed-function oxidases and exhibits increased clearance in the presence of hepatic enzyme induction. Dexamethasone clearance was 369 ml/min on day 1 and 526 ml/min on day 2. The investigators concluded that "high-dose cyclophosphamide causes an increase in its own clearance and that of dexamethasone through an apparent induction of hepatic-metabolizing enzymes detectable 24 hours after initial exposure to cyclophosphamide."

Rifampin. Since the introduction of rifampin into clinical practice for the treatment of tuberculosis, there have been many reports of interactions with other drugs, most of which relate to rifampin being a potent enzyme-inducing agent. Drug interactions with rifampin have been reviewed by Zilly and co-workers.[122]

The interaction between rifampin and warfarin is a particularly dramatic example of rifampin's ability to stimulate drug metabolism. Administration of 600 mg daily doses of rifampin to subjects on warfarin abolishes the anticoagulant effect and reduces plasma warfarin levels to near zero (Fig. 14–10).[123]

Clinical reports indicate menstrual disturbances and an unusually high incidence of pregnancy in patients with tuberculosis treated with rifampin and also on oral contraceptives. These findings suggest stimulated elimination of one or both of the components of oral contraceptive products.[122] Back and co-workers found a 50% decrease in blood levels and half-life of norethindrone, a commonly used progestin in oral contraceptives, during rifampin treatment compared to that found during a control period.[124]

Rifampin also stimulates the metabolism of glucocorticoids, hexobarbital, diazepam, metoprolol, quinidine, and other drugs.[122] Increased clearance and decreased effects of glucocorticoids, resulting from treatment with rifampin, may lead to rejection episodes in renal transplant patients.[125] Rifampin

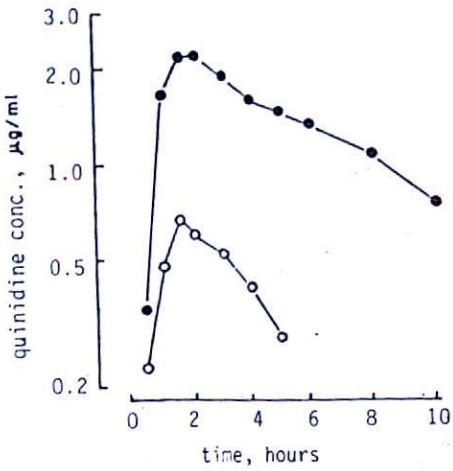

Fig. 14–11. Plasma quinidine concentrations (log scale) after a single 6 mg/kg oral dose of quinidine sulfate before (●) or after oral rifampin, 600 mg daily for 7 days (○). (Data from Twum-Barima, Y., and Carruthers, S.G.[129])

was found to decrease the half-life of hexobarbital from 407 min to 171 min and increase its clearance 3-fold.[126] The half-life of diazepam in tuberculosis patients treated with several drugs including rifampin was only 14 hr compared to a value of 58 hr in age- and sex-matched control subjects.[127] Metoprolol concentrations after an oral dose are decreased about one third from control levels during treatment with rifampin.[128] Rifampin markedly increases the clearance and presystemic metabolism of oral quinidine and virtually abolishes the clinical effect of standard dosages of the drug (Fig. 14–11).[129]

More recent drug interaction studies with rifampin have demonstrated a two-fold increase in the clearance of phenytoin[130] and a decrease in steady-state levels of sulfapyridine, from 17 to 7 μg/ml, following sulfasalazine administration.[131] Peak levels of chloramphenicol at steady state in 2 patients with *Hemophilus influenzae* fell from 21.5 and 38.5 μg/L before rifampin to 3.1 and 8 μg/L, respectively, after initiation of rifampin therapy.[132] These investigators concluded that "if the American Academy of Pediatrics' recommendation is followed and index patients receive rifampin during treatment of serious *H influenza* Type b infections, there is a risk that serum concentrations of chloramphenicol will be reduced to subtherapeutic levels, resulting in treatment failure."

Although enzyme-inducing drugs like rifampin ordinarily decrease the efficacy of coadministered drugs, enhanced toxicity may be found if stimulation of drug metabolizing enzymes leads to the production of active or toxic metabolites. A higher than expected number of cases of isoniazid-related hepatitis have been described in patients treated with isoniazid and rifampin.[133] Hepatitis may be the result of a hepatotoxic metabolite of isoniazid, the production of which is stimulated by the enzyme-inducing effects of rifampin.

Inhibition of Drug Metabolizing Enzymes

Much of the research in drug metabolism during the past decade has been concerned with enzyme inhibition. A surprisingly large number of drugs have been found to inhibit the metabolism of other drugs in man. Inhibition mechanisms include substrate competition, interference with drug transport, depletion of hepatic glycogen, and functional impairment of enzyme activity by hepatotoxicity. Competition for the same substrate-binding site is probably the most prevalent mechanism for drug interactions in man.

Interactions between drugs that lead to impaired metabolism are probably more important than those that result from stimulated metabolism. The clinical consequence of enzyme induction is usually a decrease in the efficacy of the drug. This is undesirable but usually not life-threatening. Inhibition of drug metabolism may lead to serious adverse effects because of accumulation of drugs to toxic concentrations. The therapeutic problems associated with enzyme inhibition have been reviewed by Park and Breckenridge.[95] A more recent, comprehensive review article that should be noted is a survey of the pharmacokinetic interactions of cimetidine.[134]

Chloramphenicol. Chloramphenicol has been shown to be a potent inhibitor of the metabolism of tolbutamide, phenytoin, and dicumarol in man.[135] Treatment with chloramphenicol for several days results in a marked rise in the steady-state serum concentrations of tolbutamide and phenytoin. A case of chloramphenicol-induced nystagmus in a phenytoin-treated patient has also been reported.[136] Another case report documents a serious phenytoin intoxication resulting from the simultaneous administration of chloramphenicol; blood levels of phenytoin as high as 50 μg/ml were observed (Fig. 14–12).[137]

Disulfiram. Disulfiram is used to treat chronic alcoholism; it acts by inhibiting the enzyme aldehyde dehydrogenase, which is involved in the conversion of ethanol to acetic acid. When alcohol is taken by a patient receiving disulfiram there is an accumulation of acetaldehyde, which produces undesirable central effects. Disulfiram also inhibits other drug metabolizing enzymes.

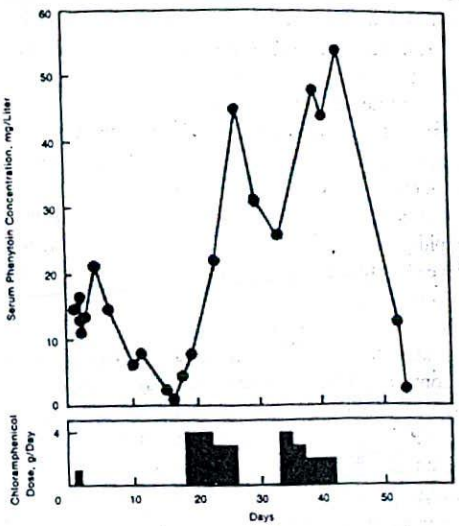

Fig. 14–12. Changes in serum phenytoin concentrations associated with intermittent administration of chloramphenicol during hospitalization of a patient receiving 300 mg/day phenytoin until day 43. (From Rose, J.Q., et al.: JAMA, 237:2630, 1977. Copyright 1977, American Medical Association.)

Disulfiram impairs the metabolism of antipyrine,[138] warfarin,[139] and phenytoin.[140] It also increases the anticoagulant effect of warfarin. Disulfiram decreases the plasma clearance of chlordiazepoxide by 50% and of diazepam by 40%.[141] This interaction is important because benzodiazepines are frequently used with disulfiram in the treatment of chronic alcoholics. Disulfiram has little effect on the elimination of oxazepam, which is metabolized by glucuronide conjugation rather than by oxidation.[141]

Allopurinol. Allpurinol and its metabolite oxypurinol decrease the production of uric acid by inhibiting xanthine oxidase, the enzyme that converts hypoxanthine to xanthine and xanthine to uric acid. It is indicated in the treatment of gout. Xanthine oxidase is also involved in the metabolism of mercaptopurine, an antineoplastic drug. Concurrent use of allopurinol and mercaptopurine may

result in greatly increased mercaptopurine activity and toxicity.

Although the interaction between mercaptopurine (MP) and allopurinol is well known, it has not been studied in much detail. In light of this, Zimm et al.[142] considered the effects of allopurinol on the pharmacokinetics of oral and iv mercaptopurine in patients with acute lymphoblastic leukemia.

After an iv dose, plasma levels of MP decline rapidly; mean clearance is about 750 ml/min. MP levels were slightly elevated when the drug was given intravenously after allopurinol pretreatment, but there were no significant changes in clearance or half-life. On the other hand, pretreatment with allopurinol profoundly affected the kinetics of MP after oral administration.

MP is subject to considerable first-pass metabolism after oral administration. Pretreatment with allopurinol increased oral bioavailability from 12 to 59%, producing a 500% increase in the plasma levels of MP compared with those observed during the control period. Zimm et al. ascribe the results to inhibition of first-pass metabolism of oral MP related to the effects of allopurinol on liver and intestinal xanthine oxidase.

They suggested that "the interaction between 6-MP and allopurinol appears to represent a unique example of inhibition of first-pass metabolism in cancer chemotherapy." When oral MP is given with allopurinol, dosage reduction is appropriate but changes in dose do not appear to be needed when MP is given intravenously.

Allopurinol also inhibits drug metabolizing enzymes other than xanthine oxidase. It decreases the elimination of antipyrine and dicumarol,[143] phenprocoumon,[144] and theophylline.[145] Administration of an oral dose of allopurinol, 300 mg every 12 hr, decreased the clearance and increased the half-life of theophylline by about 25%.

Phenylbutazone. Although the use of phenylbutazone has declined a great deal in recent years, the interaction between warfarin and phenylbutazone is a classic one because it was one of the earliest examples of inhibition of metabolism, albeit unrecognized, and because of its complexity. The anticoagulant effect of warfarin is greatly enhanced when phenylbutazone is given to patients stabilized on warfarin; unless the dosage of warfarin is reduced, bleeding and hemorrhage can result. For many years, this interaction was thought to be the result of displacement of warfarin from plasma protein binding sites by phenylbutazone. We now recognize that the mechanism is much more complex.[146,147]

Warfarin is a racemic mixture of two enantiomers, R- and S-warfarin, which are really two different drugs. S-warfarin is 5 times more potent than R-warfarin and the metabolism of the two enantiomers is quite different. In man, phenylbutazone either has no effect or slightly increases the metabolism of R-warfarin, but it significantly inhibits the metabolism of the S-isomer. The accumulation of the more potent S-warfarin is believed to account for the toxicity observed when warfarin and phenylbutazone are given at the same time. Confusion arose initially because accumulation was limited to the S-isomer and was masked by the plasma binding displacement effect of phenylbutazone.

Sulfinpyrazone. Sulfinpyrazone is a derivative of phenylbutazone. It was originally used to lower elevated uric acid levels but is now of interest for its effects on platelets. Several drug interactions have been reported with sulfinpyrazone, involving displacement from plasma protein, inhibition and induction of hepatic microsomal metabolism, and effects on renal tubular secretion. Clinically, the most important interactions are potentiation of the effects of oral anticoagulants, phenytoin, and tolbutamide probably resulting from enzyme inhibition.[148]

Toon et al.[149] determined that sulfinpyrazone increases the anticoagulant effect of racemic warfarin primarily by inhibiting the cytochrome P-450-mediated oxidation of S-warfarin, the biologically more potent enantiomer. Curiously, the clearance of R-warfarin was greater when sulfinpyrazone was given concurrently. The increased clearance of R-warfarin, however, arises not from induction of drug metabolizing enzymes but from competitive displacement of warfarin from plasma protein binding sites.

These investigators also reported that sulfinpyrazone treatment did not affect the anticoagulant response to phenprocoumon, an agent which is widely used outside the U.S., and did not appear to change the pharmacokinetics of the racemic drug or of its two enantiomers.[150] Inhibition of 7-hydroxylation of S-phenprocoumon by sulfinpyrazone occurred, but was masked by an increase in the free fraction in plasma of both enantiomers. This interaction, however, was not sufficient to measurably change the anticoagulant effect of phenprocoumon.

Sulfonamides. Certain sulfa drugs also inhibit drug metabolizing enzymes. Severe hypoglycemia has been observed in patients receiving tolbutamide and sulfaphenazole, because of an unusual accumulation of tolbutamide. Sulfaphenazole increased the half-life of tolbutamide from the usual 4 to 8 hr to values ranging from 24 to 70 hr.[151] Sulfamethizole has similar, though less pronounced, inhibitory effects on the metabolism of several drugs, including tolbutamide, phenytoin, and warfarin.[152]

Coadministration of warfarin and trimethoprim-sulfamethoxazole (TMP-SMZ) results in a marked increase in the anticoagulant effect but little change in the plasma concentration of warfarin. This finding might suggest a pharmacodynamic rather than a pharmacokinetic basis for the interaction. A complex mechanism like that found in the phenylbutazone-warfarin interaction, however, masks the underlying basis for this interaction.

Trimethoprim-sulfamethoxazole displaces warfarin from plasma proteins, which tends to lower blood levels, but also inhibits the metabolism of warfarin, which tends to elevate blood levels; the net effect is little change in steady-state levels of total warfarin in plasma. The inhibition of warfarin metabolism is stereoselective; TMP-SMZ has no effect on the clearance or anticoagulant effect of R-warfarin, but it decreases the clearance of the S-isomer by about 20% and increases the anticoagulant effect by about 65%.[153]

Metronidazole. A stereoselective interaction in man has also been observed between warfarin and metronidazole, a widely used drug indicated for the treatment of anaerobic infections, amebiasis, trichomoniasis, and other protozoal infections. Metronidazole increases the apparent half-life of racemic warfarin from 35 to 46 hr and increases its anticoagulant effect by 40%. This effect is almost completely the result of inhibition of the metabolism of S-warfarin. Metronidazole has no effect on the half-life or anticoagulant activity of R-warfarin.[154]

Isoniazid. In vitro studies suggest that isoniazid is a noncompetitive inhibitor of drug metabolism. Some patients receiving isoniazid show an impaired capacity to metabolize phenytoin and may become intoxicated.[155] In one study, 6 of 32 patients receiving both drugs developed phenytoin toxicity; all were slow inactivators of isoniazid.[156] No cases of phenytoin intoxication were found among the 18 fast inactivators of isoniazid. Animal experiments indicate that the rate of phenytoin metabolism is inversely related to isoniazid concentrations.

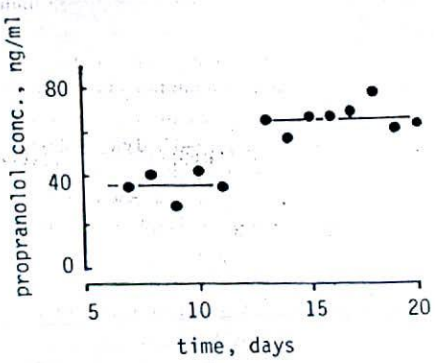

Fig. 14–13. Effect of chlorpromazine on steady-state concentrations of propranolol in plasma. The subject was maintained on 80-mg oral propranolol every 8 hr. On day 11, chlorpromazine, 50 mg every 8 hr was initiated and maintained. (Data from Vestal, R.E., et al.[160])

The clinical problem of phenytoin toxicity induced by isoniazid appears to be prevalent in patients who are slow inactivators of isoniazid. Most of these patients show significant impairment in phenytoin metabolism when these drugs are given together.

The clinical importance of the interaction between phenytoin and isoniazid has been documented in a more recent report.[157] Of 22 hospitalized medical patients who received phenytoin and isoniazid for at least 5 days, 6 (27%) experienced central nervous system (CNS) toxicity. In contrast, only 30 of 1093 patients (3%) who received phenytoin without isoniazid had CNS toxicity. The risk of adverse effects from phenytoin is greatly increased in patients also receiving isoniazid, probably because of isoniazid-induced impairment of phenytoin metabolism. A recent report suggests that isoniazid also inhibits the metabolism of carbamazepine; coadministration can result in carbamazepine intoxication.[158]

Wright et al.[159] also studied the isoniazid-carbamazepine interaction in a patient with neurologic disorders. Addition of isoniazid to long-term, stable carbamazepine therapy resulted in a rapid and considerable (about 50%) decrease in the metabolic clearance of carbamazepine, leading to carbamazepine toxicity and requiring discontinuation of both drugs. It was later found that the patient was ge-

netically a slow acetylator and probably had high serum levels of isoniazid.

On reinitiating drug therapy with more conservative doses, the apparent inhibition of carbamazepine metabolism by isoniazid was confirmed. About 3 weeks later, the patient had elevated serum levels of liver enzymes suggestive of isoniazid hepatotoxicity. The investigators proposed that carbamazepine stimulated the metabolism of isoniazid to form hepatotoxic reactive intermediates.

Neuroleptics. Recent investigations indicate that phenothiazines and other neuroleptic drugs inhibit the elimination of a wide variety of drugs including propranolol, phenytoin, and perhaps some tricyclic antidepressants. The effects of chlorpromazine, 50 mg every 8 hr, on the disposition and effectiveness of propranolol was studied in healthy subjects.[160] Chlorpromazine decreased the presystemic metabolism of propranolol and increased steady-state plasma propranolol levels by 70% (Fig. 14–13). Elevated levels of propranolol in plasma resulted in increased isoproterenol antagonism and lower plasma renin activity.

Phenytoin toxicity has been reported in 2 patients during concurrent administration of thioridazine, another phenothiazine drug.[161] More than 2-fold increases in steady-state plasma desipramine concentrations have been found in patients also receiving antipsychotic agents, including perphenazine, haloperidol, or thiothixene.[162] High plasma concentrations of imipramine and desipramine have been observed in patients simultaneously treated with oral imipramine and intramuscular fluphenazine decanoate.[163]

β-Blockers. There is evidence that β-blockers may be inhibitors of drug metabolizing enzymes. This is of interest because of the widespread use of these drugs.

Propranolol has been found to inhibit the metabolism of antipyrine; antipyrine half-life is increased from 11 to 14 hr and clearance is decreased from 0.7 to 0.5 ml/min per kg.[164] Another group of investigators reported that both propranolol and metoprolol inhibit antipyrine metabolism, but propranolol has a greater effect.[165] Studies with rat liver microsomes suggest that inhibition of oxidative drug metabolism by β-blockers is related to their lipid solubility; propranolol was the most potent of the drugs studied; timolol, oxprenolol, and labetalol were slightly less potent than propranolol.[166]

Propranolol lowers the systemic clearance of lidocaine by about 40%. Since lidocaine is highly extracted by the liver, its systemic clearance is dependent on hepatic blood flow. Therefore, the effects of propranolol might be due to a decrease in hepatic blood flow, inhibition of hepatic microsomal enzymes, or both. To answer this question, Bax et al.[167] administered oral lidocaine to healthy subjects with and without propranolol pretreatment (80 mg twice daily for 3 days).

Propranolol increased the mean peak lidocaine concentration in plasma from 502 to 875 ng/ml and increased the area under the lidocaine curve (AUC) from 58 to 117 μg-min/ml. Propranolol pretreatment decreased iv indocyanine green clearance, an index of hepatic blood flow, by 11% but this change was not statistically significant. Based on these data, the investigators concluded that propranolol lowers the systemic clearance of lidocaine mainly by direct inhibition of its hepatic metabolism rather than by lowering hepatic blood flow.

Other investigators have reported that propranolol decreases the systemic clearance of bupivicaine by 35%, an effect that could result in the accumulation of this local anesthetic to toxic levels.[168] These investigators also ascribed the effects of propranolol to inhibition of hepatic metabolism, rather than to changes in hepatic blood flow.

Miners et al.[169] studied the effects of propranolol at two dose levels, 120 mg/day and 720 mg/day, on the disposition of theophylline. The low dose of propranolol decreased theophylline by 30%, whereas the high dose resulted in a 52% decrease in clearance. Low-dose propranolol decreased the formation clearances of the two demethylated metabolites of theophylline, 1-methyluric acid and 3-methylxanthine, by 40 to 45% and the formation clearance of the 8-hydroxylated metabolite, dimethyluric acid, by 27%. High-dose propranolol had a greater effect. The formation clearances of the demethylated metabolites decreased by 70 to 75% and the formation clearance of the hydroxylated metabolite decreased by 44%. The investigators concluded that the results were "consistent with a dose-dependent and selective inhibitory effect of propranolol on the separate forms of cytochrome P-450 involved in theophylline demethylation and 8-hydroxylation."

Oral Contraceptives. Oral contraceptive steroids decrease the plasma clearance of antipyrine[170] and inhibit N-demethylation of aminopyrine.[171] In another study, women using low-dose estrogen oral contraceptive steroids (OCS) on a long-term basis

were matched for age and weight with female control subjects not using OCS. Subjects on OCS had a longer antipyrine half-life than control subjects (17 hr vs 10.5 hr). Both estrogens and progestins are competitive inhibitors of cytochrome P-450 and both probably contribute to this interaction.

Plasma metoprolol concentrations after an oral dose are about 70% higher in young women using oral contraceptives than in matched control subjects not using oral contraceptive steroids.[172] The half-life of diazepam is considerably longer (69 hr vs 47 hr) and its plasma clearance much lower (0.27 ml/min per kg vs 0.45 ml/min per kg) in women using oral contraceptive steroids than in control subjects.[173] The clinical significance of these interactions is probably small, but the widespread use of oral contraceptives warrants caution in patients receiving the combination of potent drugs and oral contraceptive steroids.

Other studies have shown that oral contraceptives markedly decrease the plasma clearance of unbound prednisolone in healthy women subjects, from 576 to 214 ml/min.[174] The investigators proposed "very careful monitoring of women taking birth control pills who are concurrently undergoing prednisolone therapy . . [and] expect lower doses of prednisolone to yield clinical efficacy in these subjects."

Valproic Acid. Although valproic acid is a relatively recent addition to the treatment of convulsive disorders and epilepsy, its capacity for interacting with other drugs is well documented. Valproic acid displaces drugs from plasma proteins and inhibits drug metabolism.

The phenobarbital-valproic acid interaction has been carefully studied. Elevated blood levels of phenobarbital and sedation are seen when valproic acid is given to patients treated with phenobarbital.[175] Dosage reductions of phenobarbital of 40 to 50% are required to avoid these effects. Patel and associates report that when a single dose of phenobarbital was given before and during treatment with valproic acid (250 mg twice a day), the half-life of phenobarbital rose from 96 to 142 hr and its clearance fell from 4.2 to 3.0 ml/hr per kg; renal clearance was unchanged but metabolic clearance fell from 3.3 to 2.0 ml/hr per kg; the percentage of the phenobarbital dose excreted unchanged in the urine rose from 22 to 33%.[176] These findings indicate that valproic acid inhibits phenobarbital metabolism.

Valproic acid also inhibits the elimination of ethosuximide. The addition of valproic acid to an ethosuximide dosage regimen in patients treated for seizures resulted in increased serum concentrations of ethosuximide in 4 of 5 patients (Table 14–3).[177] All patients felt sedated and the average initial dose of 27 mg/kg was lowered to 20 mg/kg.

Table 14–3. Effect of Valproic Acid (VPA) Treatment on Ethosuximide Concentrations in Serum*

Patient	Ethosuximide serum concentration (μg/ml)	
	Before VPA	With VPA
1	91	115
2	84	126
3	46	53
4	59	138
5	87	130
Mean	73	112

*Data from Mattson, R.H., and Cramer, J.A.[177]

The teratogenic effects of valproic acid on the human fetus, particularly when combined with other anticonvulsants, may also be related to valproic acid's ability to inhibit enzymes involved in the detoxification of active agents. Kerr and Levy[178] proposed that valproic acid inhibits epoxide hydrolase, a microsomal enzyme required to detoxify unstable reactive arene oxide metabolites that are formed by the oxidative metabolism of phenytoin and carbamazepine.

They found that therapeutic concentrations of valproic acid inhibit the metabolism of carbamazepine epoxide by human liver microsomal epoxide hydrolase and strongly recommended that combination drug therapy with valproic acid should be avoided during pregnancy. This preliminary communication was followed by a more detailed report.[179]

Cimetidine. This histamine H_2-receptor antagonist is an effective drug in the treatment of peptic ulcer and certain other gastrointestinal disorders. It is among the most widely prescribed drugs in the world.

Cimetidine has been shown to inhibit microsomal drug metabolizing enzymes in animals and man, mostly likely through binding of the imidazole ring of cimetidine to cytochrome P-450. Related drugs, like ranitidine, without the imidazole ring do not appear to inhibit drug metabolizing enzymes. Because of the widespread use of cimetidine, there is considerable potential for interactions to occur with other drugs.[180]

The single dose pharmacokinetics of warfarin

were studied in healthy subjects before and after 2 weeks of repeated dosing (1.6 g/day) with cimetidine.[181] Cimetidine reduced the clearance of warfarin from 3.4 to 2.5 ml/min. In an additional 7 subjects maintained on a daily warfarin dose, administration of cimetidine caused a significant increase in plasma warfarin concentrations and anticoagulant effect.[181] Cimetidine also increased the anticoagulant effects of nicoumalone and phenindione.[181] This interaction is clinically relevant; physicians should take care when prescribing cimetidine for patients on anticoagulant therapy.

The effects of cimetidine on the clearance of several benzodiazepines are shown in Table 14–4.[180] Cimetidine inhibited the elimination of diazepam, desmethyldiazepam, and chlordiazepoxide by 30 to 60% but had no effect on the elimination of oxazepam or lorazepam. During chronic dosing with oral diazepam, concomitant administration of cimetidine increased steady-state diazepam concentrations by 30 to 80%, a consequence of reduced diazepam plasma clearance.[182]

Cimetidine also inhibits the metabolism of theophylline and phenytoin. Table 14–5 shows the half-lives and clearances of theophylline during a control period and after 1 and 8 days of cimetidine treatment.[183] Cimetidine significantly inhibits theophylline clearance even on the first day of cimetidine administration. This effect persists or increases as cimetidine is continued in usual therapeutic doses.

The effects of cimetidine on serum phenytoin concentrations were studied in patients requiring the anticonvulsant drug for various neurologic or cardiovascular indications.[184] Steady-state levels rose from 5.7 to 9.1 μg/ml after 3 weeks on cimetidine, then fell to 5.8 μg/ml within 2 weeks after withdrawal of cimetidine. In another study, steady-state serum levels of phenytoin in epileptic patients increased from 13.6 μg/ml before cimetidine to 17.2 μg/ml after 6 days of cimetidine.[185] Patients with relatively high serum phenytoin concentrations, in the order of 15 to 20 μg/ml, are at risk of phenytoin toxicity when cimetidine is added to the treatment regimen.

Other investigators studied the effects of cimetidine, 300 mg 4 times daily for 7 days, on the pharmacokinetics and pharmacodynamics of quinidine.[186] Cimetidine increased the average plasma levels of quinidine by almost 60% and increased the effect of quinidine on several electrocardiographic parameters, including QT intervals. The interaction between cimetidine and quinidine may lead to quinidine toxicity. ECG monitoring and/or dosage reduction of quinidine may be appropriate in patients treated with both drugs.

In another study,[187] patients receiving lidocaine were divided into two groups. About two-thirds of the patients were given cimetidine, 300 mg every 6 hours, in addition to lidocaine, and the rest of the patients received only lidocaine. In all but one of the patients receiving both drugs, lidocaine serum levels were higher than any of those found in the control group. The average difference between the two groups was 75% at steady state. Nearly half of the patients given both drugs were found to have lidocaine levels above 5 μg/ml, a warning point, and 2 patients had symptoms of lethargy and confusion, attributed to lidocaine. No patient in the control group had excess levels. The investigators recommended careful monitoring of serum lidocaine during cimetidine administration.

Cimetidine inhibits hepatic microsomal oxidative drug metabolism but has little effect on conjugation. This distinction was clearly demonstrated by Abernethy et al.,[188] who found that cimetidine impaired the elimination of antipyrine and diazepam, drugs subject to hepatic cytochrome P-450-mediated oxidation, but had no effect on lorazepam, which is glucuronidated, or acetaminophen (APAP), which is predominantly metabolized by glucuronidation and sulfation.

The small fraction of an acetaminophen dose subject to oxidative metabolism and inhibition by

Table 14–4. Effect of Cimetidine on the Half-Life and Clearance of Several Benzodiazepines*

Benzodiazepine	Half-Life, hr		Clearance, ml/min	
	Control	Cimetidine	Control	Cimetidine
Diazepam	34	51	20	11
Desmethyldiazepam	52	73	12	9
Chlordiazepoxide	10	24	0.38	0.14
Oxazepam	13	11	107	93
Lorazepam	21	19	—	—

*Data from Somogyi, A., and Gugler, R.[180]

Table 14–5. Effects of Cimetidine on Theophylline Pharmacokinetics after 1 Day or 8 Days of Cimetidine Administration*

Theophylline variable	Control	Cimetidine administration (1 day)	Cimetidine administration (8 days)
Half-life, hr	7.6	10.0	11.7
Clearance, ml/min	46.0	37.2	31.5

*Data from Reitberg, D.P., Bernhard, H., and Schentag, J.J.[183]

cimetidine is of little consequence after therapeutic doses of APAP, but may be important following an overdose. Ordinarily, the reactive metabolites resulting from oxidation of APAP are quickly conjugated with glutathione and excreted. When large amounts of acetaminophen are ingested, however, the amount of reactive material formed overwhelms the availability of the glutathione pool and hepatotoxicity may result. Cimetidine inhibits the formation of reactive metabolites and may be useful in APAP overdose. Studies in mice have shown that the average lethal dose of acetaminophen is increased about twofold when it is given with cimetidine.[188] More recently, it hs become clear that too high a dose of cimetidine is needed in man to protect against APAP toxicity.

Several studies have compared cimetidine and ranitidine with respect to drug interactions. For example, Schwartz et al.[189] found that pretreatment with cimetidine decreased the oral clearance of nifedipine following a single dose of the calcium antagonist from 66 to 33 L/hr, whereas ranitidine had no effect. Sambol et al.[190] compared the influence of famotidine and cimetidine on phenytoin elimination. Cimetidine decreased the plasma clearance of phenytoin by 16%, but famotidine had no effect.

Cimetidine is known to cause gynecomastia and sexual dysfunction in some men. This may be related to inhibition of the cytochrome P-450-dependent metabolism of estradiol. Galbraith and Michnovicz[191] found that cimetidine reduced the extent of 2-hydroxylation of estradiol in male subjects from a mean of about 30 to 20% after 2 weeks of oral treatment (800 mg twice daily). At the same time, the urinary excretion of 2-hydroxyestrone decreased by about 25% and the serum levels of estradiol increased by about 20%.

Another male subject, given cimetidine at a lower dose, 400 mg twice a day, showed a reduction in the 2-hydroxylation of estradiol from 37 to 24%. In a separate study, ranitidine, 150 mg twice daily, was found to have no effect on the 2-hydroxylation of estradiol. The investigators suggested that "this mechanism may help to account for the signs and symptoms of estrogen excess reported with the long-term use of cimetidine."

Calcium Channel Blockers. Many reports have been published concerning interactions of various drugs with calcium channel blockers. Both diltiazem[192] and verapamil[193] decrease the nonrenal clearance of digoxin and may elevate steady-state digoxin concentrations by 20 to 30%. Nifedipine, on the other hand, has no effect on the elimination of digoxin.

To better understand the effects of calcium antagonists on the disposition of other drugs, Bauer et al.[194] studied antipyrine and indocyanine green (ICG) kinetics in healthy subjects before and after pretreatment with nifedipine (10 mg 3 times daily), diltiazem (30 mg 4 times daily), and verapamil (80 mg 3 times daily).

Diltiazem and verapamil, but not nifedipine, significantly decreased the clearance of antipyrine by about 25%. ICG clearance was about 700 ml/min during the control period but increased to about 900 ml/min when either nifedipine or verapamil was given. These results suggest that nifedipine primarily increases liver blood flow with little effect on hepatic oxidative metabolism, whereas diltiazem has only a modest effect on liver blood flow but significantly inhibits oxidative metabolism. Interactions of verapamil with other drugs may involve either or both of these mechanisms.

Other investigators have determined that diltiazem also inhibits the metabolism of theophylline.[195] The calcium antagonist decreased the clearance of theophylline from 52 to 42 ml/min/1.73 m^2 in nonsmokers, and from 65 to 51 ml/min/1.73 m^2 in cigarette smokers.

Both verapamil and diltiazem present a clinical problem when given with carbamazepine. Verapamil, 120 mg 3 times daily, when given to patients with epilepsy, treated with carbamazepine, resulted in elevated plasma levels of carbamazepine and neurotoxicity.[196] Two patients, rechallenged with a lower dose of verapamil, 120 mg twice daily, again showed signs of carbamazepine toxicity. Withdrawal of verapamil was associated with a decline in plasma carbamazepine from 12 to 7 μg/ml. A case report concerning a patient on carbamazepine also described elevated blood levels of the anticonvulsant and neurotoxicity when diltiazem was

given concurrently but not when nifedipine was administered.[197]

Quinolone Antibiotics. A large group of synthetic fluroquinolones, related chemically to nalidixic acid, are under investigation. At this time, two compounds, norfloxacin and ciprofloxacin, are approved for use in the United States. Several others are in clinical trials, awaiting approval.

A potential disadvantage of some of the quinolones is their ability to inhibit the metabolism of drugs given concurrently.[198] The earliest reports indicated that enoxacin increased blood levels of theophylline when the drugs were given concomitantly. Beckmann et al.[199] reported that enoxacin inhibited the formation of all three primary metabolites of theophylline.

In another study, Wijnands et al.[200] found that pefloxacin and ciprofloxacin also inhibited the metabolism of theophylline but much less so than enoxacin. These investigators suggested that the inhibition involved the 4-oxo metabolite of the quinolones, which is formed in larger amounts after enoxacin than after pefloxacin or ciprofloxacin.

The ciprofloxacin-theophylline interaction was also studied by Schwartz et al.[201] Theophylline clearance after 2 days of ciprofloxacin, 750 mg twice daily, was decreased in 8 of 9 subjects; clearance was decreased by an average of 31%, after 4 days of ciprofloxacin. Theophylline clearance returned to baseline 2 days after discontinuing ciprofloxacin. Norfloxacin also inhibits theophylline metabolism but to a smaller extent than does ciprofloxacin.[202] Mean theophylline clearance decreased by 15% after a course of norfloxacin.

Clearly, the quinolones inhibit theophylline metabolism but they differ widely in the magnitude of their effects, perhaps related to the ease of formation of a particular metabolite. Ofloxacin and lomefloxacin appear to have a negligible effect on theophylline metabolism.

Most likely, quinolones will also be found to inhibit the metabolism of other drugs. One report indicates that enoxacin decreases the mean clearance of R-warfarin by about 30% but has no effect on the clearance of the more potent S-enantiomer. Consequently, enoxacin may be given with racemic warfarin without seeing any effect on anticoagulant response.[203]

Propoxyphene. A case study concerning a massive overdose of acetaminophen reported, unexpectedly, little liver damage.[204] The authors speculated that this outcome may have resulted because large quantities of propoxyphene were also ingested with acetaminophen. In vitro studies have shown that propoxyphene is an inhibitor of cytochrome P-450 hepatic oxidative drug metabolism. Recent reports have provided clinical evidence of this.

An elderly man stabilized on doxepin for depression was given propoxyphene 65 mg every 6 hours for relief of arthritic pain. The addition of propoxyphene produced a more than 2-fold increase in doxepin levels and progressive lethargy. Doxepin levels declined and attentiveness improved when propoxyphene was discontinued.[205] As a follow-up to this observation, the effects of propoxyphene on the metabolism of antipyrine were studied. A short course of propoxyphene, 65 mg every 4 hours, decreased antipyrine clearance by 20%.

Other investigators concerned with the clearance of benzodiazepines during regular administration of propoxyphene reported that propoxyphene decreased the clearance of alprazolam and diazepam by 40% and 13%, respectively, but had no effect on the elimination of lorazepam.[206] To summarize, propoxyphene significantly impairs the clearance of alprazolam, metabolized mainly by aliphatic hydroxylation, has far less effect on the oxidation of diazepam via an N-demethylation pathway, and has no effect on the conjugation of lorazepam with glucuronic acid.

Erythromycin. The most widely known interaction of erythromycin is with theophylline; concurrent administration for at least 5 days increases serum theophylline levels about 2-fold, requiring a theophylline dosage reduction.[207] More recently, other investigators have reported several case studies of a carbamazepine-erythromycin interaction.[208] In 4 patients with head trauma, serum levels of carbamazepine doubled or tripled when erythromycin treatment, 1 g/day in divided doses, was initiated.

Another report suggests that erythromycin may also have a significant effect on the elimination of cyclosporine.[209] Cylosporine levels in a woman receiving the drug after renal transplantation rose from 122 to 666 ng/ml within a few days of starting erythromycin treatment for a urinary tract infection. Five days after discontinuing erythromycin, the patient's cyclosporine levels declined to 222 ng/ml.

Other Interactions. A wide range of other drugs have been reported to inhibit the metabolism of

certain drugs given concurrently. Ketoconazole, like several other related antifungal drugs and like cimetidine, has an imidazole ring and is a likely candidate to inhibit oxidative metabolism. Clinical evidence of this has been presented by Brown et al.[210]

Methoxsalen (8-methoxypsoralen), a natural product used in the treatment of psoriasis, is a potent inhibitor of caffeine metabolism.[211] Methoxsalen increased the mean area under the concentration-time curve after a single oral dose of caffeine from 34 to 106 mg-hr/ml. Assuming caffeine is completely bioavailable after oral administration, methoxsalen decreased caffeine clearance from 110 to 34 ml/min. The investigators pointed out that "patients receiving methoxsalen . . . are often treated with other drugs, such as sulindac, indomethacin, and analogs of retinoic acid. Our results suggest that elimination of these or other microsomally metabolized drugs may be altered by methoxsalen."

Omeprazole, a selective inhibitor of gastric acid secretion, is still another imidazole derivative. Treatment over 6 days with a single daily dose of 40 mg omeprazole decreased diazepam clearance by more than 50%. Plasma levels of desmethyldiazepam, diazepam's major metabolite, were smaller after omeprazole indicating reduced metabolite formation. Omeprazole has also been found to cause a small (15%) but consistent reduction in phenytoin clearance but appears to have no effect on theophylline clearance.[212]

Propafenone, a class Ic antiarrhythmic agent under active investigation, also appears to be a potent inhibitor of drug metabolism. After a case report suggesting that propafenone potentiates the anticoagulant effects of phenprocoumon, Kates et al.[213] set out to determine if there was an interaction between propafenone and warfarin. Propafenone increased mean steady-state levels of warfarin nearly 40% and significantly prolonged prothrombin time compared with the effects of warfarin alone.

Propafenone also inhibits the metabolism of metoprolol.[214] The investigators pointed out that although the therapeutic index of metoprolol is large, the marked rise in plasma metoprolol levels when propafenone is added might cause serious adverse effects in susceptible patients. "It seems necessary therefore to reduce the dose of metoprolol when propafenone is administered simultaneously."

A life-threatening interaction has been reported between tamoxifen, an adjuvant used in the treatment of breast cancer, and warfarin.[215] A 43-year-old woman was stabilized on a daily warfarin dose of 5 mg and a prothrombin time of 19 seconds. Seven weeks later, tamoxifen 40 mg daily was added to her treatment. The next day her prothrombin time was 38 seconds. Eventually, she was restabilized on 1 mg warfarin daily to maintain a prothrombin time of 20 to 25 seconds.

A review of medical records suggested that this problem had occurred in 5 other patients who received tamoxifen and warfarin concurrently. It is likely that tamoxifen inhibits the metabolism of warfarin, but further studies are needed to firmly nail down the mechanism of this interaction.

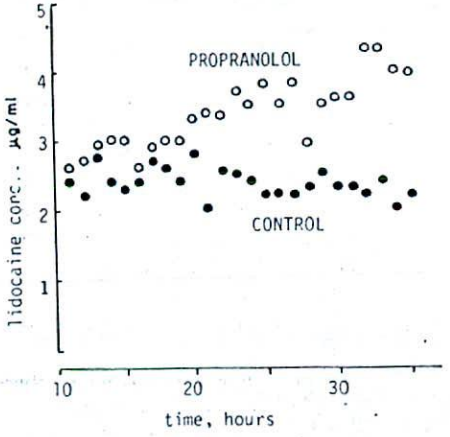

Fig. 14–14. Effect of coadministered propranolol on serum lidocaine levels during a continuous intravenous infusion of lidocaine. (Data from Ochs, H.R., Carstens, G., and Greenblatt, D.J.[216])

Changes in Hepatic Blood Flow

The clearance of drugs such as lidocaine and propranolol, that have a high hepatic extraction (> 0.5), will be sensitive to changes in the blood flow rate to the liver. Interactions may occur when they are given with other drugs that affect cardiac output or directly affect hepatic blood flow (HBF).

Propranolol-induced β-blockade results in a reduction in cardiac output and HBF. Consistent with this effect, propranolol also reduces the elimination of lidocaine because the clearance of lidocaine is HBF rate-limited.[216] Single dose studies indicate that the clearance of iv lidocaine falls from 18 ml/min per kg during a control period to 11 ml/min

per kg during a propranolol treatment period. Propranolol also causes a 30% increase in steady-state serum lidocaine levels during continuous intravenous infusion (Fig. 14–14).[216] This difference may be clinically important because the therapeutic index of lidocaine is narrow. A lower dosage of lidocaine may be required in patients who are also being treated with β-blockers. It is also important to note that propranolol not only reduces HBF, but also inhibits hepatic metabolism. Increases in lidocaine levels are probably related to both effects of propranolol.

A single dose of cimetidine significantly reduces the clearance of indocyanine green in man;[217] this is consistent with the known effect of cimetidine on HBF in the dog, an effect related to its histamine blocking action. Therefore, cimetidine can affect the clearance of drugs with high hepatic excretion ratios in two ways, by decreasing the HBF rate and by inhibiting hepatic drug metabolizing enzymes.

Cimetidine decreased the systemic clearance of intravenous propranolol by about 25%.[217] Steady-state levels of propranolol on oral dosing were increased from 23 to 45 ng/ml during treatment with cimetidine.[218] Cimetidine also reduced the systemic clearance of lidocaine from 766 ml/min to 576 ml/min.[219] Lidocaine toxicity was noted in 5 of 6 subjects during the cimetidine infusion but in only 1 of 6 subjects during a placebo infusion. Lidocaine concentrations were 50% higher when subjects received cimetidine.

Whether or not changes in the rate of liver blood flow play an important role in these interactions with cimetidine is difficult to say in light of the inhibitory effects of cimetidine on the intrinsic hepatic clearance of propranolol and lidocaine.

Low concentrations of caffeine and theophylline block the vasodilatory effects of adenosine and, in this manner, may modulate hepatic blood flow. To test this hypothesis, Onrot et al.[220] studied the effects of these xanthines on liver perfusion using ICG clearance as an index of hepatic blood flow.

Thirty min after dosing with 250 mg oral caffeine, ICG clearance was reduced by an average of 19%, from 630 to 510 ml/min. Dosing with theophylline, 4.3 mg/kg iv infused over 1 hr, also resulted in a fall in ICG clearance from 550 to 470 ml/min. The investigators suggested that "the observed fall . . . may affect the disposition of concomitantly administered drugs or absorbed nutrients that are highly extractable." They concluded that "because of their widespread use in Western society, caffeine and theophylline may be major determinants of liver blood flow in the general population."

In principle, blood levels of a drug subject to presystemic hepatic metabolism on oral administration are independent of HBF. Elevated blood levels, however, may be observed if HBF rate is transiently increased during absorption but thereafter declines to baseline.[221] This phenomenon may explain the elevated blood levels of propranolol when it is given with food[222] or with hydralazine,[223] a potent vasodilator. A 25-mg oral dose of hydralazine given simultaneously with oral propranolol increased plasma propranolol levels by 60%; a 50-mg oral dose of hydralazine increased plasma propranolol concentrations by about 80%.[223]

An alternative mechanism to explain the interaction between hydralazine and propranolol is inhibition of the first-pass metabolism of the beta-blocker by hydralazine. To select between these mechanisms, Schneck and Vary[224] measured the urinary excretion rate and profile of propranolol metabolites after oral administration of radiolabeled propranolol 40 mg, alone or with 25 or 50 mg hydralazine.

The investigators reasoned that if hydralazine inhibits the metabolism of propranolol, the urinary excretion rate of propranolol metabolites would be expected to decrease and, if there were selective inhibition of the propranolol metabolic pathways, there would be a change in the composition of propranolol metabolites in urine. On the other hand, if hydralazine affects only liver blood flow, there would be no change in the profile of propranolol metabolites in urine.

Coadministration of hydralazine substantially increased the plasma levels of propranolol, by 60% after the 25 mg dose and by 120% after the 50 mg dose, but hydralazine had no effect on the fraction of the propranolol dose recovered in the urine as basic, acidic, or polar metabolites; these fractions accounted for 99% of the dose.

Furthermore, hydralazine did not alter the pattern of metabolites measurable by high-performance liquid chromatography (i.e., naphthoxylactic aid, propranolol glucuronide, and 4-hydroxypropranolol) and did not decrease the urinary excretion rates of propranolol metabolites. These results support an interaction mechanism involving an increase in hepatic blood flow during the absorption of propranolol when it is given with hydralazine.

Other investigators have reported that hydrala-

zine also increases blood levels of metoprolol, another drug highly extracted by the liver.[225] Steady-state concentrations of metoprolol in plasma increased nearly 40% and peak levels of metoprolol increased by about 90% in hypertensive pregnant women when hydralazine 25 mg twice daily was added to a regimen of metoprolol 50 mg twice daily.

Stereochemical Considerations in Drug Interactions

Most investigators now agree that effects on individual enantiomers must be considered when studying an interaction involving a racemic drug. As noted above, the interaction between enoxacin and warfarin is not clinically important because only the R-form of warfarin is inhibited, not the more potent S-enantiomer.[203] Considering only the effects on racemic warfarin, we would arrive at the implausible conclusion that the interaction results in an increase in warfarin serum levels but no change in anticoagulant activity.

Stereoselective interactions have also been reported with cimetidine. Toon et al.[226] discovered that cimetidine, like enoxacin, inhibits the metabolism of R-warfarin, but not that of S-warfarin, and has little effect on the anticoagulant activity of a dose of racemic warfarin. These investigators also found that although cimetidine had no effect on beta-blockade after a single dose of metoprolol, it did increase the bioavailability of oral metoprolol through inhibition of first-pass metabolism.[227] The interaction was stereoselective, with the major effect being on the less pharmacologically active enantiomer of metoprolol.

Drug Interactions as a Probe to Identify Metabolic Pathways Regulated by the Debrisoquin Phenotype

Poor metabolizers (PMs) of debrisoquin may be at risk of adverse effects during treatment with drugs that share its genetic polymorphism. Patients at risk have usually been identified by phenotyping with debrisoquin or sparteine, which displays the same genetic polymorphism as debrisoquin. Drugs that cosegregate with debrisoquin or sparteine have been identified by pharmacokinetic studies in panels of phenotyped subjects.

The low frequency of PMs in the U.S. population (less than 10%) has made it difficult to identify, early in the course of development, those drugs likely to cause adverse effects in patients with impaired oxidative metabolism. Few centers have available panels of phenotyped subjects and in those that do, very few PMs are included in the panel. The development of an alternative screening method not requiring the preselection of PMs would be an important contribution.

An agent that could be given safely and acted as a potent and selective inhibitor of debrisoquin 4-hydroxylase activity might be useful in this regard. Ideally, this agent would inhibit the elimination of only those drugs significantly metabolized by the cytochrome P-450 isozyme regulating debrisoquin hydroxylation. One compound that may be suitable for this purpose is quinidine.

Speirs et al.[228] reported that quinidine was a potent inhibitor of the 4-hydroxylation of debrisoquin and the 1′-hydroxylation of bufuralol by human liver microsomes. Quinidine was about 100 times more potent in this respect than quinine, its diastereoisomer. Quinidine also inhibited the *O*-deethylation of phenacetin but 1000-fold higher concentrations were required than those needed to inhibit the aforementioned hydroxylation processes.

Other studies have shown that the polymorphic isozyme directing debrisoquin hydroxylation is important in the metabolism of bufuralol. The dealkylation of phenacetin, on the other hand, is known to be catalyzed by an isozyme other than that involved in the hydroxylation of debrisoquin. Other oxidation pathways that do not appear to be associated with the debrisoquin/sparteine isozyme are the hydroxylation of mephenytoin and tolbutamide, and the N-demethylation of aminopyrine.

Speirs and his colleagues concluded that "quinidine at subpharmacological doses may be used to investigate the contribution of the isozyme of cytochrome P-450 catalysing the 4-hydroxylation of debrisoquin in the elimination of a new drug. If the elimination of such a compound is significantly impaired following the co-administration of quinidine then it could be concluded that this isozyme is likely to catalyse a quantitatively important proportion of the elimination of the drug and would indicate that its elimination may well be impaired in PM subjects." This conclusion has been supported by a report showing that quinidine nearly abolished the oxidation of sparteine.[229]

The debrisoquin/sparteine isozyme is known to be involved in the metabolism of more than 30 drugs. The metabolism of all that have been studied, including metoprolol, propafenone, encainide,

and dextromethorphan is inhibited by quinidine.[230] A great deal more must be done, however, before we can be sure that quinidine will interact only with a drug having a metabolic pathway that cosegregates with debrisoquin hydroxylation. In the meantime, it would make sense to study the interaction between quinidine and new compounds subject to oxidative metabolism, at least at the level of human liver microsomes. If an interaction is observed, it might be prudent to set up a panel of EMs and PMs for further study.

ENVIRONMENTAL CHEMICALS

Although genetic factors contribute substantially to the large degree of intersubject variability found in apparently healthy, drug-free individuals, certain environmental factors also contribute to this variability. Relatively few of these factors have been isolated, but during the past 2 decades a lot has been learned about the effects of excessive or chronic alcohol consumption, cigarette smoking, and diet on drug metabolism.

Alcohol

The damaging effects of chronic alcoholism on the human liver are well documented. The hepatic metabolism of many drugs is impaired in patients with alcoholic cirrhosis. Excessive or chronic alcohol consumption, however, also affects drug metabolism in people who have no signs of liver disease.

Acute ethanol intoxication inhibits drug metabolism.[231] This effect is clearly seen in studies with chlordiazepoxide.[232] The elimination of chlordiazepoxide after intravenous administration was determined before and after acute ingestion of ethanol, 0.8 g/kg followed by 0.5 g/kg every 5 hr for 30 hr. Plasma clearance of chlordiazepoxide fell about one third, from 27 ml/min in the control period to 17 ml/min during ethanol intoxication. Plasma ethanol concentrations were maintained in a range of 50 to 150 mg/dl during the study. Ethanol also decreased the plasma protein binding of chlordiazepoxide; percentage unbound rose from 5.3 to 6.6%. Therefore, plasma clearance of unbound chlordiazepoxide decreased almost 50%, from 468 ml/min to 264 ml/min. The results suggest that pharmacokinetic as well as pharmacologic factors contribute to the more profound sedation observed when chlordiazepoxide is taken with ethanol.

Drug metabolism studies with alcohol are complicated by the fact that ethanol not only inhibits drug metabolism but also stimulates drug metabolism, at least on chronic administration.[233] Regular administration of ethanol for one month to alcoholic and nonalcoholic subjects resulted in an enhanced elimination of meprobamate, phenobarbital, and ethanol itself. The half-life of meprobamate was reduced from 17 to 7 hr in alcoholic subjects and from 14 to 8 hr in nonalcoholic subjects. The half-life of pentobarbital in nonalcoholic subjects decreased from 35 to 26 hr. Approximately 4 to 8 weeks after the end of the ethanol treatment, the rate of elimination of ethanol and meprobamate had returned to normal.

Cigarette Smoking

Tobacco smoke is a complex mixture composed primarily of gases, but it also contains particulate matter. The particulate matter consists of water-soluble compounds, including nicotine, and fat-soluble compounds, including polycyclic aromatic hydrocarbons.

Polycyclic aromatic hydrocarbons, and perhaps other constituents of tobacco smoke, are potent inducers of certain drug metabolizing enzymes, particularly the enzyme aryl hydrocarbon hydroxylase. The enzymes affected by tobacco smoke are involved in the metabolism of many drugs; chronic smoking has been reported to increase the metabolism of nicotine, phenacetin, antipyrine, theophylline, imipramine, pentazocine, and propranolol. The effects of smoking on drug metabolism and actions have been reviewed by Miller,[234] Jusko,[235] and Dawson and Vestal.[236]

Propoxyphene was rated ineffective for the relief of mild to moderate pain or headache in 10% of nonsmokers, 15% of light smokers, and 20% of heavy smokers.[237] Of the 7 reported adverse reactions to propoxyphene, 6 occurred in nonsmokers. The reduced efficacy of propoxyphene in smokers is consistent with enhanced metabolism and suggests the need for higher dosage in these patients.

The incidence of drowsiness in patients receiving diazepam or chlordiazepoxide is also related to smoking history.[234] About 8% of nonsmokers or light smokers but only 3% of heavy smokers reported drowsiness with diazepam. The incidence of drowsiness with chlordiazepoxide was 10% in nonsmokers, 6% in light smokers, and 3.5% in heavy smokers. No heavy smoker experienced drowsiness with doses of diazepam up to 20 mg/day. Whether these results are related to stimulated

Table 14–6. Phenacetin Concentrations in the Plasma after Oral Administration of a 900-mg Dose to Cigarette Smokers and Nonsmokers*

Time after administration (hr)	Plasma phenacetin levels (μg/ml)	
	Nonsmokers	Smokers
1	0.81	0.33
2	2.24	0.48
3.5	0.39	0.09
5	0.12	0.02

*Data from Pantuck, E.J., Kuntzman, R., and Conney, A.H.[239]

metabolism or increased tolerance to benzodiazepines in smokers is not established.

Clinically, the dosage requirements for pentazocine as a supplement to nitrous oxide anesthesia are greater in smokers than nonsmokers. Studies in healthy subjects suggest that stimulated metabolism is the reason for differences in dosage requirements because smokers metabolize pentazocine more efficiently than nonsmokers.[238]

The metabolism of phenacetin is also accelerated in smokers.[239] Plasma phenacetin levels after oral administration are much lower in smokers than in nonsmokers (Table 14–6). The low plasma concentrations of phenacetin in smokers are probably the results of increased presystemic gastrointestinal or hepatic metabolism.

The interaction between theophylline and tobacco smoke is one of the most clinically important effects of smoking because of the low therapeutic index of theophylline. The half-life of theophylline is short in smokers, averaging about 4 hr, compared to nonsmokers, who show values of about 7 hr.[240] The clearance of theophylline was 44.5 ml/min per 1.73 m^2 in nonsmokers and 100 ml/min in smokers.[241] These differences suggest a 2-fold difference in theophylline dosage requirements in smokers and nonsmokers to achieve comparable blood levels, the smokers requiring more theophylline.

The increased metabolism of theophylline in smokers seems to be associated with reduced toxicity during clinical use of this bronchodilator. There is a significant relationship between the incidence of adverse reactions to theophylline and smoking history.[242] The incidence of theophylline toxicity was 13% in nonsmokers, 11% in light smokers, and 7% in smokers.

Vestal and his colleagues[243,244] determined that the effects of smoking on theophylline disposition are independent of age and persist even when the metabolism of theophylline is inhibited by cimetidine or accelerated by phenytoin. Their study group consisted of young (19 to 31 years) and elderly (65 to 75 years) smokers and nonsmokers.

Theophylline clearance was 68 ml/hr/kg in young smokers and 46 ml/hr/kg in young nonsmokers. Similar differences were observed in the elderly panel: 55 ml/hr/kg in smokers and 31 ml/hr/kg in nonsmokers. Young smokers treated with cimetidine also had a higher theophylline clearance than young nonsmokers similarly treated: 48 vs 32 ml/hr/kg. The same was true in the old subjects. Theophylline clearance in subjects treated with phenytoin was again consistently higher in smokers than in nonsmokers. Old and young smokers had values of 106 and 120 ml/hr/kg, respectively; corresponding values in nonsmokers were 49 and 78 ml/hr/kg.

In a related study, Crowley[245] again found that phenytoin enhanced the metabolism of theophylline in both smokers and nonsmokers. In a panel of young adults, before treatment with phenytoin, theophylline clearance was 48 ml/hr/kg in nonsmokers and 90 ml/hr/kg in smokers. Phenytoin increased theophylline clearance by 40% in nonsmokers and by 48% in smokers.

In spite of the pronounced increase in theophylline clearance as a result of smoking, the drug metabolizing enzymes concerned with theophylline metabolism can be induced further. The investigators concluded that "the induction of theophylline clearance by phenytoin is additive to that caused by cigarette smoking and provides support for the suggestion that theophylline metabolism is influenced by multiple polymorphisms."

When cigarette smokers are hospitalized, they are often forced to stop smoking. With this in mind, Lee et al.[246] studied the effects of brief abstinence from tobacco on theophylline elimination in healthy subjects. Abstinence from smoking for 1 week resulted in a 38% decrease in the clearance of theophylline. The results indicate that at least partial normalization of the enzyme-inducing effects of smoking may be realized in a short time after stopping. The investigations recommended that "for smokers who are taking theophylline chronically, their dose of theophylline will need to be reduced by one fourth to one third after brief tobacco abstinence."

Smoking also accelerates the metabolism of caffeine. This may explain the higher coffee consumption in smokers than in nonsmokers. To better understand the implications of this interaction, Benowitz et al.[247] investigated the effects of smok-

ing and short-term abstinence from smoking on the rate and pattern of caffeine metabolism in habitual smokers who were regular coffee drinkers. Participants were heavy smokers whose habit ranged from 30 to 50 cigarettes per day and who regularly consumed 3 to 8 cups of coffee per day.

Blood levels of caffeine following a series of 6 test doses given every 2 hr were about 50% higher 3 to 4 days after smoking was stopped than just before stopping. The mean peak caffeine concentrations during the smoking and abstinence phases were 2.9 and 3.8 μg/ml, respectively. Cessation also resulted in a significant decrease in the urinary recovery of two metabolites of caffeine. The urinary excretion patterns found in this study suggest that smoking accelerated the demethylation pathways of caffeine metabolism but had little effect on the xanthine oxidase pathway.

In another study,[248] caffeine consumption and plasma caffeine concentrations were measured before and for 6 months after a panel of subjects gave up smoking. Volunteers were recruited for a stop smoking program and evaluated before and at 12 and 26 weeks afterward. Of the 95 subjects who started the program, 64 were available for evaluation at 12 weeks; 30 of these subjects had resumed smoking during this period.

Although coffee consumption was unchanged from baseline, both in those who resumed smoking and those who remained abstinent, plasma levels of caffeine increased markedly after 12 weeks in the former smokers, from 6.6 to 17.9 μmol/L, but hardly at all in those who resumed smoking. The findings were almost identical at 26 weeks. Mean plasma caffeine levels increased by nearly 300% in those who remained abstinent, whereas caffeine consumption during this period actually decreased by about 25%. Caffeine levels in plasma were unchanged in those who did not succeed in their efforts to quit smoking.

The investigators recommended that "doctors offering antismoking treatment should advise patients that continued consumption of coffee at the same level may exacerbate the tobacco withdrawal syndrome and contribute to increased health risks; these patients should reduce their consumption."

Epidemiologic data have linked smoking to earlier menopause and increased osteoporosis, both of which are associated with a relative deficiency of estrogen. Michnovitz et al.[249] have considered the possibility that the apparent anti-estrogen effects of smoking may be related to increased hepatic metabolism of natural estrogens. They found a significant increase in estradiol 2-hydroxylation, on the order of 50%, in premenopausal women who smoked compared with those who did not smoke. The investigators concluded that "smoking exerts a powerful inducing effect on the 2-hydroxylation pathway of estradiol metabolism, which is likely to lead to decreased bioavailability at estrogen target tissues."

Diet

Dietary factors have been shown to be determinants of drug-metabolizing enzyme activity in laboratory animals, but little is known of the effects of diet or specific foods on drug metabolism in man. When the diets of healthy subjects were changed from their usual diets to a low carbohydrate-high protein diet, the half-life of antipyrine decreased from 16 to 10 hr and that of theophylline decreased from 8 to 5 hr. When diets were again changed from low carbohydrate-high protein to high carbohydrate-low protein, the mean antipyrine half-life increased from 10 to 16 hr and the mean theophylline half-life increased from 5 to 8 hr. Supplementing standard diets with carbohydrate caused an increase in drug half-life, whereas a protein supplement caused a decrease in drug half-life.[250]

Certain vegetables, including brussels sprouts, cabbage, turnips, broccoli, cauliflower, and spinach, contain chemicals that induce aryl hydrocarbon hydroxylase enzyme activity. A test diet containing brussels sprouts and cabbage reduced plasma phenacetin concentrations after oral administration to healthy subjects by 50% compared to those observed in the same subjects maintained on a control diet containing no enzyme-inducing vegetables.[251]

Charcoal-broiled beef also enhances drug metabolism. The average peak concentration of phenacetin in plasma after a 900-mg oral dose fell from 1630 ng/ml when healthy subjects were fed a control diet to 350 ng/ml after they were maintained on a diet containing charcoal-broiled beef.[252] Charcoal-broiled beef also induces the metabolism of antipyrine and theophylline; the half-lives of these 2 drugs were each decreased about 20% when healthy subjects were fed a diet containing charcoal-broiled beef.[253] These effects are probably related to the fact that charcoal-broiled beef contains large quantities of polycyclic aromatic hydrocarbons.

In 1984, Nutt and his colleagues[254] presented evidence suggesting that competition between large neutral amino acids (resulting from the administration of phenylalanine, leucine, or isoleucine) and levodopa for transport from plasma to brain may be partly responsible for the fluctuating clinical response, called the 'on-off phenomenon,' frequently seen in patients with Parkinson's disease treated with levodopa.

More recently, these investigators considered the use of a low-protein diet as a therapeutic strategy for treating parkinsonian patients handicapped by a fluctuating response to levodopa.[255] A diet containing 1.6 g/kg protein was compared with a 0.8 g/kg diet with protein evenly distributed between meals, and a 0.8 g/kg diet with protein restricted to the evening meal.

The mean percent of the time patients were responding satisfactorily to levodopa (i.e., 'on' time) was 51% for the high-protein diet, 67% for the low-protein diet distributed over three meals, and 77% for the low-protein diet restricted to the evening meal. The mean plasma levels of large neutral amino acids were 732 nmol/ml for the high-protein diet, 640 for the distributed low-protein diet, and 542 for the restricted low-protein diet.

Nutt et al. concluded that "for patients with a fluctuating response who have not responded to dosage adjustment, lower protein intake will augment the effects of levodopa. The low-protein distributed diet is effective and easiest to implement."

A decrease in diet protein depresses creatinine clearance and renal plasma flow. Dietary protein also affects the renal tubular transport of certain endogenous compounds, but there is little understanding of the role of diet in the renal excretion of drugs. Studies with allopurinol suggest that this kind of interaction merits more attention.[256]

The pharmacokinetics of allopurinol and oxypurinol, its active metabolite, were studied in healthy subjects. Each subject received, in random order, a low-protein (19 g/day) or high-protein (268 g/day) diet for 14 days. Before the study and on day 12 of each diet, 24-hour urine and plasma samples were obtained to determine creatinine clearance. On day 13 of each diet, each subject received a 600-mg oral dose of allopurinol.

Compared with baseline values, renal function was decreased by the low-protein diet and increased by the high-protein diet. Creatinine clearance increased from 96 ml/min on the low-protein diet to 138 ml/min on the high-protein diet. The same was true of urea and uric acid renal clearance.

Small differences were observed in the kinetics of allopurinol. Consistent with the difference in creatinine clearance, the renal clearance of allopurinol was about 30% smaller, compared with control values, when protein was restricted. The area under the curve (AUC) for allopurinol was about 45% greater during the low-protein diet than during the high-protein diet. Since the renal clearance of allopurinol accounts for only a small percentage of its total body clearance, the increase in allopurinol AUC may reflect a decrease in the xanthine-oxidase dependent metabolism of allopurinol to oxypurinol during protein restriction.

In contrast to the relatively small effect of dietary protein on allopurinol, a pronounced effect was observed on the pharmacokinetics of oxypurinol. Renal clearance of the metabolite during protein restriction was only one-third that observed during the high-protein diet; the AUC and half-life of oxypurinol were three times greater.

The decrease in the renal clearance of oxypurinol during protein restriction was about twice as large as the change in creatinine clearance. Based on the size of this difference, the investigators proposed that the mechanism of the interaction must also involve a change in tubular function associated with protein restriction.

They hypothesized that oxypurinol, a weak acid chemically similar to uric acid, may be reabsorbed by the uric acid system in the renal tubules. A high-protein diet, which is similar to the typical American diet, inhibits reabsorption and produces the characteristic pharmacokinetic profile of oxypurinol. Protein restriction, on the other hand, allows extensive tubular reabsorption of oxypurinol, which would result in a decreased renal clearance and more persistent oxypurinol levels in plasma.

In support of this hypothesis, urea and uric acid renal clearances were about 60% smaller during protein restriction than during the high-protein diet, whereas creatinine clearance was only 30% smaller. If this hypothesis is correct, it adds a new mechanism to the ways in which dietary factors can alter clinical pharmacokinetics.

Other Chemicals

Certain chemicals found in the work environment can stimulate drug metabolizing enzymes.[257] The half-life of antipyrine in men occupationally exposed to a mixture of insecticides (mainly Lin-

dane and DDT) was significantly shorter than in 33 control subjects (8 hr vs 12 hr).[258] Others have shown a decrease in the half-life of phenylbutazone in workers exposed to chlorinated pesticides.[259]

Other chemicals in the work environment may inhibit drug metabolism. Plasma warfarin half-life and anticoagulant effect were determined in anesthesiology residents at the start of their training period. Average warfarin half-life in these subjects was 32 hr and average prothrombin response was 1340 U. After 4 months in the operating room, average warfarin half-life had increased to 49 hr and prothrombin response to 1550 U.[260] The change in warfarin kinetics and effect appears to be the result of inhibition of warfarin metabolism, related to the repeated exposure of these subjects to an operating room environment.

CONCLUSIONS

In view of the effects of age, sex, body size, genetic factors, disease, and interactions on drug blood levels resulting from usual dosage regimens, one cannot be surprised that a wide range of individual responses to therapy is found with all drugs. One can also understand the need for and interest in individualization of dosage regimens.

REFERENCES

1. Tatro, D.S.: Drug Interaction Facts. Philadelphia, Facts and Comparisons Division, J.B. Lippincott Co., 1988.
2. Hansten P.D., and Horn, J.R.: Drug Interaction Newsletter. Spokane, WA, Applied Therapeutics, Inc.
3. Somogyi, A., and Muirhead, M.: Pharmacokinetic interactions of cimetidine 1987. Clin. Pharmacokin., *12*:321, 1987.
4. Gugler, R., and Jensen, J.C.: Drugs other than H_2-receptor antagonists as clinically important inhibitors of drug metabolism *in vivo*. Pharmac. Ther., *33*:133, 1987.
5. Anon.: Drug interactions update. Med. Lett. Drugs Ther., *26*:11, 1984.
6. Shinn, A.F.: Evaluation of Drug Interactions. 1988/89 Ed. Washington, DC, American Pharmaceutical Association, 1988.
7. Hansten, P.D.: Drug Interactions. Decision Support Tables. Spokane, WA, Applied Therapeutics Inc., 1987.
8. Hansten, P.D. and Horn, J. R.: Drug Interactions. 6th Ed. Philadelphia, Lea & Febiger, 1989.
9. Koch-Weser, J., and Greenblatt, D.J.: Drug interactions in clinical perspective. Eur. J. Clin. Pharmacol., *11*:405, 1977.
10. Smith, J.W., Seidl, L.G., and Cluff, L.E.: Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility. Ann. Intern. Med., *65*:629, 1966.
11. May, F.E., Stewart, R.B., and Cluff, L.E.: Drug interactions and multiple drug administration. Clin. Pharmacol. Ther., *22*:323, 1977.
12. Kunin, C.M., and Finland, M.: Clinical pharmacology of the tetracycline antibiotics. Clin. Pharmacol. Ther., *2*:51, 1961.
13. Neuvonen, P.J., et al.: Interference of iron with absorption of tetracyclines in man. Br. Med. J., 1:532, 1970.
14. Gothoni, G., et al.: Iron-tetracycline interactions: Effect of time interval between the drugs. Acta Med. Scand., *191*:409, 1972.
15. Galeazzi, R.L.: The effect of an antacid on the bioavailability of indomethacin. Eur. J. Clin. Pharmacol., *12*:65, 1977.
16. Naggar, V.F., and Khalil, S.A.: Effect of magnesium trisilicate on nitrofurantoin absorption. Clin. Pharmacol. Ther., *25*:857, 1979.
17. Verbeeck, R., et al.: Effect of aluminum hydroxide on diflusinal absorption. Br. J. Clin. Pharmacol., *7*:519, 1979.
18. Spencer, H., et al.: Effect of aluminum hydroxide on fluoride metabolism. Clin. Pharmacol. Ther., *28*:529, 1980.
19. Carter, B.L., et al.: Effects of antacids on phenytoin bioavailability. Ther. Drug. Monit., *3*:333, 1981.
20. Gugler, R., Brand. M., and Somogyi, A.: Impaired cimetidine absorption due to antacids and metoclopramide. Eur. J. Clin. Pharmacol., *20*:225, 1980.
21. Smart, H.L., et al.: The effects of sucralfate upon phenytoin absorption in man. Br. J. Clin. Pharmacol., *20*:238, 1985.
22. Parpia, S.H., et al.: Sucralfate reduces the gastrointestinal absorption of norfloxacin. Antimicrob. Agents Chemother., *33*:99, 1989.
23. Wagner, J.G.: Biopharmaceutics: Absorption aspects. J. Pharm. Sci., *50*:539, 1961.
24. Sorby, D.L., and Liu, G.: Effects of adsorbents on drug absorption. II. Effect of an antidiarrhea mixture in promazine absorption. J. Pharm. Sci., *55*:504, 1966.
25. Brown, D.B., and Juhl, R.P.: Decreased bioavailability of digoxin due to antacids and kaolin-pectin. N. Engl. J. Med., *295*:1034, 1976.
26. Albert, K.S., et al.: Decreased tetracycline bioavailability caused by a bismuth subsalicylate antidiarrheal mixture. J. Pharm. Sci., *68*:586, 1979.
27. Ericsson, C.D., et al.: Influence of subsalicylate bismuth on absorption of doxycycline. JAMA, *247*:2266, 1982.
28. Robinson, D.S., Benjamin, D.M., and McCormack, J.J.: Interaction of warfarin and nonsystemic gastrointestinal drugs. Clin. Pharmacol. Ther., *12*:491, 1971.
29. Northcutt, R.C., et al.: The influence of cholestyramine on thyroxine absorption. JAMA, *208*:1857, 1969.
30. Brown, D.D., et al.: A steady-state evaluation of the effects of propantheline bromide and cholestyramine on the bioavailability of digoxin when administered as tablets or capsules. J. Clin. Pharmacol., *25*:360, 1985.
31. Morgan, J.P., et al.: Impramine-medicated interference with levodopa absorption from the gastrointestinal tract in man. Neurology, *25*:1029, 1975.
32. Algeri, S., et al.: Effect of anticholinergic drugs on gastrointestinal absorption of L-dopa in rats and in man. Eur. J. Clin. Pharmacol., *35*:293, 1976.
33. Lindenbaum, J., et al.: Inactivation of digoxin by the gut flora; Reversal by antibiotic therapy. N. Engl. J. Med., *305*:789, 1981.
34. Lindenbaum, J., Maulitz, R.M., and Butler, V.P., Jr.: Inhibition of digoxin absorption by neomycin. Gastroenterology, *71*:399, 1976.
35. Juhl, R.P., et al.: Effect of sulfasalazine on digoxin bioavailability. Clin. Pharmacol. Ther., *20*:387, 1976.
36. Riegelman, S., Rowland, M., and Epstein, W.L.: Griseofulvin-phenobarbital interaction in man. JAMA, *213*:426, 1970.
37. Aggeler, P.M., and O'Reilly, R.A.: Effect of heptabar-

bital on the response to bishydroxycoumarin in man. J. Lab. Clin. Med., *74*:229, 1969.
38. Gibaldi, M., and Grundhofer, B.: Biopharmaceutical influences on the anticholinergic effects of propantheline. Clin. Pharmacol. Ther., *18*:457, 1975.
39. McCall, C.E., Steigbigel, N.H., and Finland, M.: Lincomycin: Activity in vitro and absorption and excretion in normal young men. Am. J. Med. Sci., *254*:144, 1967.
40. Singhvi, S.M., et al.: Effect of food on the bioavailability of captopril in healthy subjects. J. Clin. Pharmacol., *22*:135, 1982.
41. Johnson, P.C., Braun, G.A., and Cressman, W.A.: Nonfasting state and the absorption of a hypnotic. Arch. Intern. Med., *131*:199, 1973.
42. Shepherd, A.M.M., Irvine, N.A., and Ludden, T.M.: Effect of food on blood hydralazine levels and response in hypertension. Clin. Pharmacol. Ther., *36*:14, 1984.
43. Hendeles, L., et al.: Food-induced dose-dumping from a once-a-day theophylline product as a cause of theophylline toxicity. Chest, *87*:758, 1985.
44. Pedersen, S., and Moller-Petersen, J.: Erratic absorption of a slow-release theophylline sprinkle product caused by food. Pediatrics, *74*:534, 1984.
45. Jonkman, J.H.G.: Food interactions with sustained-release theophylline preparations. Clin. Pharmacokin., *16*:162, 1989.
46. Mojaverian, P., et al.: Effect of food on the absorption of enteric coated aspirin: correlation with gastric residence time. Clin. Pharmacol. Ther., *41*:11, 1987.
47. Mojaverian, P., et al.: Effects of gender, posture, and age on gastric residence time of an indigestible solid: pharmaceutical considerations. Pharm. Res., *5*:639, 1988.
48. Sellers, E.M., and Koch-Weser, J.: Displacement of warfarin from human albumin by diazoxide and ethacrynic, mefenamic, and nalidixic acids. Clin. Pharmacol. Ther., *11*:524, 1970.
49. Solomon, H.M., and Schrogie, J.J.: The effect of various drugs on the binding of warfarin-^{14}C to human albumin. Biochem. Pharmacol., *16*:1219, 1967.
50. Solomon, H.M., Schrogie, J.J., and Williams, D.: The displacement of phenylbutazone-^{14}C and warfarin-^{14}C from human albumin by various drugs and fatty acids. Biochem. Pharmacol., *17*:143, 1968.
51. Lunde, P.K.M., et al.: Plasma protein binding of diphenylhydantoin in man. Clin. Pharmacol. Ther., *11*:846, 1970.
52. MacKichan, J.J.: Protein binding drug displacement interactions, fact or fiction? Clin. Pharmacokin., *16*:65, 1989.
53. Friel, P.N., Leal, K.W., and Wilensky, A.J.: Valproic acid-phenytoin interactions. Ther. Drug. Monit., *1*:243, 1979.
54. Frigo, G.M., et al.: Modification of phenytoin clearance by valproic acid in normal subjects. Br. J. Clin. Pharmacol., *8*:553, 1979.
55. Perucca, E., et al.: Interaction between phenytoin and valproic acid: Plasma protein binding and metabolic effects. Clin. Pharmacol. Ther., *28*:779, 1980.
56. Sansom, L.N., Beran, R.C., and Schapel, G.J.: Interaction between phenytoin and valproate. Med. J. Aust., *2*:212, 1980.
57. Day, R.O., et al.: The effect of concurrent aspirin upon plasma concentrations of tenoxicam. Br. J. Clin. Pharmacol., *26*:455, 1988.
58. Sellers, E.M., and Koch-Weser, J.: Potentiation of warfarin-induced hypoprothrombinemia by chloral hydrate. N. Engl. J. Med., *283*:827, 1970.
59. Sellers, E.M., Lang, M., and Koch-Weser, J.: Enhancement of warfarin-induced hypoprothrombinemia by triclofos. Clin. Pharmacol. Ther., *13*:911, 1972.
60. Boston Collaborative Drug Surveillance Program. Interaction between chloral hydrate and warfarin. N. Engl. J. Med., *286*:53, 1972.
61. Gibaldi, M., Grundhofer, B., and Levy, G.: Effect of antacids on pH of urine. Clin. Pharmacol. Ther., *16*:520, 1974.
62. Levy, G., and Leonards, J.R.: Urine pH and salicylate therapy. JAMA, *217*:81, 1971.
63. Levy, G., et al.: Decreased serum salicylate concentrations in children with rheumatic fever treated with antacid. N. Engl. J. Med., *293*:323, 1975.
64. Anggard, E., et al.: Pharmacokinetic and clinical studies on amphetamine dependent patients. Eur. J. Clin. Pharmacol., *3*:3, 1970.
65. Offerhaus, L.: Drug interactions at excretory mechanisms. Pharmacol. Ther., *15*:69, 1981.
66. Aherne, G.W., et al.: Prolongation and enhancement of serum methotrexate concentrations by probenecid. Br. J. Clin. Pharmacol., *1*:1097, 1978.
67. Stoeckel K., et al.: Effect of probenecid on the elimination and protein binding of ceftriaxone. Eur. J. Clin. Pharmacol., *34*:151, 1988.
68. Somogyi, A., McLean, A., and Heinzow, B.: Cimetidine-procainamide pharmacokinetic interaction in man: evidence of competition for tubular secretion of basic drugs. Eur. J. Clin. Pharmacol., *25*:339, 1983.
69. van Crugten J., et al.: Selectivity of the cimetidine-induced alterations in the renal handling of organic substrates in humans. Studies with anionic, cationic and zwitterionic drugs. J. Pharmacol. Exp. Ther., *236*:481, 1986.
70. Frölich, J.C., et al.: Indomethacin increases plasma lithium. Br. Med. J., *1*:1115, 1979.
71. Reimann, I.W., and Frolich, J.C.: Effects of diclofenac on lithium kinetics. Clin. Pharmacol. Ther., *30*:348, 1981.
72. McGiff, J.C.: Interactions of nonsteroidal anti-inflammatory drugs and antihypertensives. JAMA, *260*:850, 1988.
73. Thyss, A., et al.: Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. Lancet, *1*:256, 1986.
74. Tilstone, W.J., et al.: Effects of furosemide on glomerular filtration rate and clearance of practolol, digoxin, cephaloridine, and gentamicin. Clin. Pharmacol. Ther., *22*:389, 1977.
75. Ejvinsson, G.: Effect of quinidine on plasma concentrations of digoxin. Br. Med. J., *1*:279, 1978.
76. Leahey, E.B., Jr., et al.: Interaction between quinidine and digoxin. JAMA, *240*:533, 1978.
77. Doering, W.: Quinidine-digoxin interaction. Pharmacokinetics, underlying mechanism and clinical implications. N. Engl. J. Med., *301*:400, 1979.
78. Doherty, J.E.: The digoxin-quinidine interaction. Annu. Rev. Med., *33*:163, 1982.
79. Hager, W.D., et al.: Digoxin-quinidine interaction. Pharmacokinetic evaluation. N. Engl. J. Med., *300*:1238, 1979.
80. Schenck-Gustafsson, K., and Dahlquist, R.: Pharmacokinetics of digoxin in patients subjected to the quinidine-digoxin interaction. Br. J. Clin. Pharmacol., *11*:181, 1981.
81. Mungall, D.R., et al.: Effects of quinidine on serum digoxin concentration. A prospective study. Ann. Intern. Med., *93*:689, 1980.
82. Leahey, E.B., et al.: Quinidine-digoxin interaction: Time course and pharmacokinetics. Am. J. Cardiol., *48*:1141, 1981.

83. Fenster, P., et al.: Digoxin-quinidine interaction in patients with chronic renal failure. Circulation, *66*:1277, 1982.
84. Chapron, D.J., Mumford, D., and Pitegoff, G.I.: Apparent quinidine-induced digoxin toxicity after withdrawal of pentobarbital. Arch. Intern. Med., *139*:363, 1979.
85. Schenck-Gustafsson, K., et al.: Effect of quinidine on digoxin concentration in skeletal muscle and serum in patients with atrial fibrillation. N. Engl. J. Med., *305*:209, 1981.
86. Das, G., Barr, C.E., and Carlson, J.: Reduction of digoxin effect during the digoxin-quinidine interaction. Clin. Pharmacol. Ther., *35*:317, 1984.
87. Walker, A.M., et al.: Drug toxicity in patients receiving digoxin and quinidine. Am. Heart J., *105*:1025, 1983.
88. Warner, N.J., et al.: Myocardial monovalent cation transport during the quinidine-digoxin interaction in dogs. Circ. Res., *54*:453, 1984.
89. Leahey, E.B., et al.: The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. Ann. Intern. Med., *92*:605, 1980.
90. Pedersen, K.E., et al.: Digoxin-verapamil interaction. Clin. Pharmacol. Ther., *30*:311, 1981.
91. Moysey, J.O., et al.: Amiodarone increases plasma digoxin concentrations. Br. Med. J., *282*:272, 1981.
92. Cogan, J.J., et al.: Acute vasodilator therapy increases renal clearance of digoxin in patients with congestive heart failure. Circulation, *64*:973, 1981.
93. Baber, N., et al.: The interaction between indomethacin and probenecid. A clinical and pharmacokinetic study. Clin. Pharmacol. Ther., *24*:298, 1978.
94. Meinertz, T., et al.: Interruption of the enterohepatic circulation of phenprocoumon by cholestyramine. Clin. Pharmacol. Ther., *21*:731, 1977.
95. Park, B.K., and Breckenridge, A.M.: Clinical implications of enzyme induction and inhibition. Clin. Pharmacokinet., *6*:1, 1981.
96. Perucca, E.: Pharmacokinetic interactions with antiepileptic drugs. Clin. Pharmacokinet., *7*:57, 1982.
97. Sotaniemi, E.A., et al.: Drug metabolism in epileptics: in vivo and in vitro correlations. Br. J. Clin. Pharmacol., *5*:71, 1978.
98. Patsalos, P.N., Duncan, J.S., and Shorvon, S.D.: Effect of removal of individual antiepileptic drugs on antipyrine kinetics, in patients taking polytherapy. Br. J. Clin. Pharmacol., *26*:253, 1988.
99. Chiba, K., et al.: Comparison of steady-state pharmacokinetics of valproic acid in children between monotherapy and multiple antiepileptic drug treatment. J. Pediatrics, *106*:653, 1985.
100. Data, J.L., Wilkinson, G.R., and Nies, A.S.: Interaction of quinidine with anticonvulsant drugs. N. Engl. J. Med., *294*:699, 1976.
101. Dhillon, S., and Richens, A.: Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. Br. J. Clin. Pharmacol., *12*:841, 1981.
102. Mattson, R.H., et al.: Use of oral contraceptives by women with epilepsy. JAMA, *256*:238, 1986.
103. Capewell, S., et al.: Reduced felodipine bioavailability in patients taking anticonvulsants. Lancet, *2*:480, 1988.
104. Khoo, K., et al.: Influence of phenytoin and phenobarbital on the disposition of a single oral dose of clonazepam. Clin. Pharmacol. Ther., *28*:368, 1980.
105. Reynolds, E.H., et al.: Interaction of phenytoin and primidone. Br. Med. J., *2*:594, 1975.
106. Porro, M.G., et al.: Phenytoin: An inhibitor and inducer of primidone metabolism in an epileptic patient. Br. J. Clin. Pharmacol., *14*:294, 1982.
107. Petereit, L.B., and Meikle, A.W.: Effectiveness of prednisolone during phenytoin therapy. Clin. Pharmacol. Ther., *22*:912, 1977.
108. Pond, S.M., and Kretschzmar, K.M.: Effect of phenytoin on meperidine clearance and normeperidine formation. Clin. Pharmacol. Ther., *30*:680, 1981.
109. Marquis, J.F., et al.: Phenytoin-theophylline interaction. N. Engl. J. Med., *307*:1189, 1982.
110. Breckenridge, A.M., and Orme, M.L'E.: Clinical implications of enzyme induction. Ann. NY Acad. Sci., *179*:421, 1971.
111. Goss, J.E., and Dickhaus, D.W.: Increased bishydroxycoumarin requirements in patients receiving phenobarbital. N. Engl. J. Med., *273*:1094, 1965.
112. Rutledge, D.R., Pieper, J.A., and Mirvis, D.M.: Effects of chronic phenobarbital on verapamil disposition in humans. J. Pharmacol. Exp. Ther., *246*:7, 1988.
113. Hempel, E., et al.: Medikamentose enzymindaktion und hormonale kontrazeption. Zentralbl. Gynaekol., *95*:1451, 1973.
114. Hempel, E., and Klinger, W.: Drug stimulated biotransformation of hormonal steroid contraceptives: Clinical implications. Drugs, *12*:442, 1976.
115. Yaffe, S.J., et al.: Enhancement of glucuronide-conjugating capacity in hyperbilirubinemic infants due to apparent enzyme induction by phenobarbital. N. Engl. J. Med., *275*:1461, 1966.
116. Maurier, H.M., et al.: Reduction in concentration of total serum bilirubin in offspring of women treated with phenobarbitone during pregnancy. Lancet, *2*:122, 1968.
117. Udall, J.A.: Clinical implications of warfarin interactions with five sedatives. Am. J. Cardiol., *35*:67, 1975.
118. Alván, G., et al.: Effect of pentobarbital on the disposition of alprenolol. Clin. Pharmacol. Ther., *22*:316, 1977.
119. Lai, A.A., Levy, R.H., and Cutler, R.E.: Time course of interaction between carbamazepine and clonazepam in normal man. Clin. Pharmacol. Ther., *24*:316, 1978.
120. Bertilsson, L., and Tomson, T.: Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide. An update. Clin. Pharmacokin., *11*:177, 1986.
121. Moore, M.J., et al.: Rapid development of enhanced clearance after high-dose cyclophosphamide. Clin. Pharmacol. Ther., *44*:622, 1988.
122. Zilly, W., Breimer, D.D., and Richter, E.: Pharmacokinetic interactions with rifampin. Clin. Pharmacokinet., *2*:61, 1977.
123. O'Reilly, R.A.: Interaction of chronic daily warfarin therapy and rifampin. Ann. Intern. Med., *83*:506, 1975.
124. Back, D.J., et al.: The effect of rifampicin on norethisterone pharmacokinetics. Eur. J. Clin. Pharmacol., *15*:193, 1979.
125. Buffington, G.A., et al.: Interaction of rifampin and glucocorticoids. Adverse effect on renal allograft function. JAMA, *236*:1958, 1976.
126. Breimer, D.D., Zilly, W., and Richter, E.: Influence of rifampicin on drug metabolism: Differences between hexobarbital and antipyrine. Clin. Pharmacol. Ther., *21*:470, 1977.
127. Ochs, H.R., et al.: Diazepam interaction with antituberculosis drugs. Clin. Pharmacol. Ther., *29*:671, 1981.
128. Bennett, P.N., John, V.A., and Whitmarsh, V.B.: Effect of rifampicin on metoprolol and antipyrine kinetics. Br. J. Clin. Pharmacol., *13*:387, 1982.
129. Twum-Barima, Y., and Carruthers, S.G.: Quinidine-rifampin interaction. N. Engl. J. Med., *304*:1466, 1981.
130. Kay, L., et al.: Influence of rifampicin and isoniazid on the kinetics of phenytoin. Br. J. Clin. Pharmacol., *20*:323, 1985.

131. Shaffer, J.L., and Houston, J.B.: The effect of rifampin on sulphapyridine plasma concentrations following sulphasalazine administration. Br. J. Clin. Pharmacol., *19*:526, 1985.
132. Prober, C.G.: Effect of rifampin on chloramphenicol levels. N. Engl. J. Med., *312*:788, 1985.
133. Pessayre, D., et al.: Isoniazid-rifampin fulminant hepatitis. A possible consequence of the enhancement of isoniazid hepatotoxicity by enzyme induction. Gastroenterology, *72*:284, 1977.
134. Somogyi, A., and Muirhead, M.: Pharmacokinetic interactions of cimetidine 1987. Clin. Pharmacokin., *12*:321, 1987.
135. Christensen, L.K., and Skovsted, L.: Inhibition of drug metabolism by chloramphenicol. Lancet, *2*:1397, 1969.
136. Ballek, R.E., Reidenberg, M.M., and Orr, L.: Inhibition of diphenylhydantoin metabolism by chloramphenicol. Lancet, *1*:150, 1973.
137. Rosé, J.Q., et al.: Intoxication caused by interaction of chloramphenicol and phenytoin. JAMA, *237*:2630, 1977.
138. Vesell, E.S., Passananti, G.T., and Lee, C.H.: Impairment of drug metabolism by disulfiram in man. Clin. Pharmacol. Ther., *12*:785, 1971.
139. O'Reilly, R.A.: Interaction of disulfiram (Antabuse) in man. Ann. Intern. Med., *78*:73, 1973.
140. Svendsen, T.L., et al.: The influence of disulfiram on the half-life and metabolic clearance rate of diphenylhydantoin and tolbutamide in man. Eur. J. Clin. Pharmacol., *9*:439, 1976.
141. MacLeod, S.M., et al.: Interaction of disulfiram with benzodiazepines. Clin. Pharmacol. Ther., *24*:583, 1978.
142. Zimm, Z., et al.: Inhibition of first-pass metabolism in cancer chemotherapy: interaction of 6-mercaptopurine and allopurinol. Clin. Pharmacol. Ther., *34*:810, 1983.
143. Vesell, E.S., Passananti, G.T., and Greene, F.E.: Impairment of drug metabolism in man by allopurinol and nortriptyline. N. Engl. J. Med., *283*:1484, 1970.
144. Janhnchen, E., Meinertz, T., and Gilfrich, N.J.: Interaction of allopurinol with phenprocoumon in man. Klin. Wochenschr., *55*:759, 1977.
145. Manfredi, R.L., and Vessell, E.S.: Inhibition of theophylline metabolism by long-term allopurinol administration. Clin. Pharmacol. Ther., *29*:224, 1981.
146. Lewis, R.J., et al.: Warfarin. Stereochemical aspects of its metabolism and the interaction with phenylbutazone. J. Clin. Invest., *53*:1607, 1974.
147. Schary, W.L., Lewis, R.J., and Rowland, M.: Warfarin-phenylbutazone interaction in man: A long term multiple dose study. Res. Commun. Chem. Pathol. Pharmacol., *10*:663, 1975.
148. Pedersen, A.K., et al.: Clinical pharmacokinetics and potentially important drug interactions of sulphinpyrazone. Clin. Pharmacokinet., *7*:42, 1982.
149. Toon, S., et al.: The warfarin-sulfinpyrazone interaction: stereochemical considerations. Clin. Pharmacol. Ther., *39*:15, 1986.
150. Heimark, L.K., et al.: The effect of sulfinpyrazone on the disposition of pseudoracemic phenprocoumon in humans. Clin. Pharmacol. Ther., *42*:312, 1987.
151. Rowland, M., and Matin, S.B.: Kinetics of drug-drug interactions. J. Pharmacokinet. Biopharm., *1*:553, 1973.
152. Lumholtz, B., et al.: Sulfamethizole-induced inhibition of diphenylhydantoin, tolbutamide, and warfarin metabolism. Clin. Pharmacol. Ther., *17*:731, 1975.
153. O'Reilly, R.A.: Stereoselective interaction of trimethoprim-sulfamethoxazole with the separated enantiomorphs of racemic warfarin in man. N. Engl. J. Med., *302*:33, 1980.
154. O'Reilly, R.A.: The stereoselective interaction of warfarin and metronidazole in man. N. Engl. J. Med., *295*:354, 1976.
155. Kutt, H., et al.: Diphenylhydantoin intoxication: a complication of isoniazid therapy. Am. Rev. Respir. Dis., *101*:377, 1970.
156. Brennan, R.W., et al.: Diphenylhydantoin intoxication attendant to slow inactivation of isoniazid. Neurology, *20*:687, 1970.
157. Miller, R.R., Porter, J., and Greenblatt, D.J.: Clinical importance of the interaction of phenytoin and isoniazid. A report from the Boston Collaborative Surveillance Program. Chest, *75*:356, 1979.
158. Valsalan, V.C., and Cooper, G.L.: Carbamazepine intoxication caused by interaction with isoniazid. Br. Med. J., *285*:261, 1982.
159. Wright, J.M., Stokes, E.F., and Sweeney, V.P.: Isoniazid-induced carbamazepine toxicity and vice versa. A double drug interaction. N. Engl. J. Med., *307*:1325, 1982.
160. Vestal, R.E., et al.: Inhibition of propranolol metabolism by chlorpromazine. Clin. Pharmacol. Ther., *25*:19, 1979.
161. Vincent, F.M.: Phenothiazine-induced phenytoin intoxication. Ann. Intern. Med., *93*:56, 1980.
162. Nelson, J.C., and Jatlow, P.I.: Neuroleptic effect on desipramine steady-state plasma concentrations. Am. J. Psychiatry, *137*:1232, 1980.
163. Siris, S.G., et al.: Plasma imipramine concentrations in patients receiving concomitant fluphenazine decanoate. Am. J. Psychiatry, *139*:104, 1982.
164. Greenblatt, D.J., Franke, K., and Huffman, D.H.: Impairment of antipyrine clearance in humans by propranolol. Circulation, *57*:1161, 1978.
165. Bax, N.D.S., Lennard, M.S., and Tucker, G.T.: Inhibition of antipyrine metabolism by β-adrenoceptor antagonists. Br. J. Clin. Pharmacol., *12*:779, 1981.
166. Deacon, C.S., et al.: Inhibition of oxidative drug metabolism by β-adrenoceptor antagonists is related to their lipid solubility. Br. J. Clin. Pharmacol., *12*:429, 1981.
167. Bax, N.D.S., et al.: The impairment of lignocaine clearance by propranolol—major contribution from enzyme inhibition. Br. J. Clin. Pharmacol., *19*:597, 1985.
168. Bowdle, T.A., Freund, P.R., and Slattery J.T.: Propranolol reduces bupivicaine clearance. Anesthesiol., *66*:36, 1987.
169. Miners, J.O., et al.: Selectivity and dose-dependency of the inhibitory effect of propranolol on theophylline metabolism in man. Br. J. Clin. Pharmacol., *20*:219, 1985.
170. Abernethy, D.R., and Greenblatt, D.J.: Impairment of antipyrine metabolism by low-dose oral contraceptive steroids. Clin. Pharmacol. Ther., *29*:106, 1981.
171. Field, B., Lu, C., and Hepner, G.W.: Inhibition of hepatic drug metabolism by norethindrone. Clin. Pharmacol. Ther., *25*:196, 1979.
172. Kendall, M.J., et al.: Metoprolol pharmacokinetics and the oral contraceptive pill. Br. J. Clin. Pharmacol., *14*:120, 1982.
173. Abernethy, D.R., et al.: Impairment of diazepam metabolism by low-dose estrogen-containing oral-contraceptive steroids. N. Engl. J. Med., *306*:791, 1982.
174. Legler, U.F., and Benet, L.Z.: Marked alterations in dose-dependent prednisolone kinetics in women taking oral contraceptives. Clin. Pharmacol. Ther., *39*:425, 1986.
175. Wilder, B.J., et al.: Valproic acid: Interaction with other anticonvulsant drugs. Neurology, *28*:892, 1978.
176. Patel, I.H., Levy, R.H., and Cutler, R.E.: Phenobarbital-valproic acid interaction. Clin. Pharmacol. Ther., *27*:515, 1980.

177. Mattson, R.H., and Cramer, J.A.: Valproic acid and ethosuximide interaction. Ann. Neurol., *7*:583, 1980.
178. Kerr, B.M., and Levy, R.H.: Inhibition of epoxide hydrolase by anticonvulsants and risk of teratogenicity. Lancet, *1*:610, 1989.
179. Kerr, B.M., et al.: Inhibition of human liver microsomal epoxide hydrolase by valproate and valpromide: in vitro/in vivo correlation. Clin. Pharmacol. Ther., *46*:82, 1989.
180. Somogyi, A., and Gugler, R.: Drug interactions with cimetidine. Clin. Pharmacokinet., *7*:23, 1982.
181. Serlin, M.J., et al.: Cimetidine interactions with oral anticoagulants in man. Lancet, *2*:317, 1979.
182. Klotz, U., and Reimann, I.: Elevation of steady-state diazepam levels by cimetidine. Clin. Pharmacol. Ther., *30*:513, 1981.
183. Reitberg, D.P., Bernhard, H., and Schentag, J.J.: Alteration of theophylline clearance and half-life by cimetidine. Ann. Intern. Med., *95*:582, 1981.
184. Neuvonen, P.J., Tokola, R.A., and Kaste, M.: Cimetidine-phenytoin interaction: Effect on serum phenytoin concentration and antipyrine test. Eur. J. Clin. Pharmacol., *21*:215, 1981.
185. Hetzel, D.J., et al.: Cimetidine interaction with phenytoin. Br. J. Clin. Pharmacol., *282*:1512, 1981.
186. Hardy, B.G., et al.: Effect of cimetidine on the pharmacokinetics and pharmacodynamics of quinidine. Am. J. Cardiol., *52*:172, 1983.
187. Knapp, A.B., et al.: The cimetidine-lidocaine interaction. Ann. Intern. Med., *98*:174, 1983.
188. Abernethy, D.R., et al.: Differential effect of cimetidine on drug oxidation (antipyrine and diazepam) vs conjugation (acetaminophen and lorazepam): prevention of acetaminophen toxicity by cimetidine. J. Pharmacol. Exp. Ther., *224*:508, 1983.
189. Schwartz, J.B., et al.: Effect of cimetidine or ranitidine administration on nifedipine pharmacokinetics and pharmacodynamics. Clin. Pharmacol. Ther., *43*:673, 1988.
190. Sambol, N.C., et al.: A comparison of the influence of famotidine and cimetidine on phenytoin elimination and hepatic blood flow. Br. J. Clin. Pharmacol., *27*:83, 1989.
191. Galbraith, R.A., and Michnovicz, J.J.: The effects of cimetidine on the oxidative metabolism of estradiol. N. Engl. J. Med., *321*:269, 1989.
192. Rameis, H., Magometschnigg, D., and Ganzinger, U.: The diltiazem-digoxin interaction. Clin. Pharmacol. Ther., *36*:183, 1984.
193. Pedersen, K.E., et al.: Digoxin-verapamil interaction. Clin. Pharmacol. Ther., *30*:311, 1981.
194. Bauer, L.A., et al.: Changes in antipyrine and indocyanine green kinetics during nifedipine, verapamil, and diltiazem therapy. Clin. Pharmacol. Ther., *40*:239, 1986.
195. Nafziger, A.N., May, J.J., and Bertino, J.S., Jr.: Inhibition of theophylline elimination by diltiazem therapy. J. Clin. Pharmacol., *27*:862, 1987.
196. Macphee, G.J.A., et al.: Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. Lancet, *1*:700, 1986.
197. Brodie, M.J., and Macphee, G.J.A.: Carbamazepine neurotoxicity precipitated by diltiazem. Br. Med. J., *292*:1170, 1986.
198. Edwards, D.J., et al.: Inhibition of drug metabolism by quinolone antibiotics. Clin. Pharmacokin., *15*:194, 1988.
199. Beckman, J., et al.: Enoxacin—a potent inhibitor of theophylline metabolism. Eur. J. Clin. Pharmacol., *33*:227, 1987.
200. Wijnands, W.J.A., Vree, T.B., and van Herwaarden, C.L.A.: The influence of quinolone derivatives on theophylline clearance. Br. J. Clin. Pharmacol., *22*:687, 1986.
201. Schwartz, J., et al.: Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. Antimicrob. Agents Chemother., *32*:75, 1988.
202. Ho, G., Tierney, M.G., and Dales, R.E.: Evaluation of the effect of norfloxacin on the pharmacokinetics of theophylline. Clin. Pharmacol. Ther., *44*:35, 1988.
203. Toon, S., et al.: Enoxacin-warfarin interaction: pharmacokinetic and stereochemical aspects. Clin. Pharmacol. Ther., *42*:33, 1987.
204. Pond, S.M., et al.: Massive intoxication with acetaminophen and propoxyphene: unexpected survival and unusual pharmacokinetics of acetaminophen. J. Toxicol. Clin. Toxicol., *19*:1, 1982.
205. Abernethy, D.R., et al.: Impairment of hepatic drug oxidation by propoxyphene. Ann. Intern. Med., *97*:223, 1982.
206. Abernethy, D.R., et al.: Interaction of propoxyphene with diazepam, alprazolam and lorazepam. Br. J. Clin. Pharmacol., *19*:51, 1985.
207. Shinn, A.F., and Shrewsbury, R.P.: Evaluation of Drug Interactions, 3rd ed, St. Louis, C.V. Mosby Co., 1985.
208. Wroblewski, B.A., Singer, W.D., and Whyte, J.: Carbamazepine-erythromycin interaction. Case studies and clinical significance. JAMA, *255*:1165, 1986.
209. Ptachcinski, R.J., et al.: Effect of erythromycin on cyclosporine levels. N. Engl. J. Med., *313*:1416, 1985.
210. Brown, M.W., et al.: Effect of ketoconazole on hepatic oxidative drug metabolism. Clin. Pharmacol. Ther., *37*:297, 1985.
211. Mays, D.C., et al.: Methoxsalen is a potent inhibitor of the metabolism of caffeine. Clin. Pharmacol. Ther., *42*:621, 1987.
212. Gugler, R., and Jensen, J.C.: Drugs other than H_2-receptor antagonists as clinically important inhibitors of drug metabolism *in vivo*. Pharmacol. Ther., *33*:133, 1987.
213. Kates, R.E., Yee, Y.-G., and Kirsten, E.: Interaction between warfarin and propafenone in healthy volunteer subjects. Clin. Pharmacol. Ther., *42*:305, 1987.
214. Wagner, F., et al.: Drug interaction between propafenone and metoprolol. Br. J. Clin. Pharmacol., *24*:213, 1987.
215. Tenni P., Lalich, D.L., and Byrne, M.J.: Life threatening interaction between tamoxifen and warfarin. Br. Med. J., *298*:93, 1989.
216. Ochs, H.R., Carstens, G., and Greenblatt, D.J.: Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. N. Engl. J. Med., *303*:373, 1980.
217. Feely, J., Wilkinson, G.R., and Wood, A.J.J.: Reduction of liver blood flow and propranolol metabolism by cimetidine. N. Engl. J. Med., *304*:692, 1981.
218. Reimann, I.W., Klotz, U., and Frolich, F.C.: Cimetidine increases propranolol steady-state plasma levels in man (abstr.). Eighth International Congress of Pharmacology, Tokyo, 1981.
219. Feely, J., et al.: Increased toxicity and reduced clearance of lidocaine by cimetidine. Ann. Intern. Med., *96*:592, 1982.
220. Ontrot, J., et al.: Reduction of liver plasma flow by caffeine and theophylline. Clin. Pharmacol. Ther., *40*:506, 1986.
221. McLean, A.J., et al.: Food, splanchnic blood flow, and bioavailability of drugs subject to first-pass metabolism. Clin. Pharmacol. Ther., *24*:5, 1978.
222. Melander, A., et al.: Enhancement of the bioavailability of propranolol and metoprolol by food. Clin. Pharmacol. Ther., *22*:108, 1977.
223. McLean, A.J., et al.: Interaction between oral propranolol and hydralazine. Clin. Pharmacol. Ther., *27*:726, 1980.
224. Schneck, D.W., and Vary, J.E.: Mechanism by which

hydralazine increases propranolol bioavailability. Clin. Pharmacol. Ther., *35*:447, 1984.
225. Lindeberg, S., et al.: The effect of hydralazine on steady-state plasma concentrations of metoprolol in pregnant hypertensive women. Eur. J. Clin. Pharmacol., *35*:131, 1988.
226. Toon, S., et al.: Comparative effects of ranitidine and cimetidine on the pharmacokinetics and pharmacodynamics of warfarin in man. Eur. J. Clin. Pharmacol., *32*:165, 1987.
227. Toon, S., et al.: The racemic metoprolol H_2-antagonist interaction. Clin. Pharmacol. Ther., *43*:283, 1988.
228. Speirs, C.J., et al.: Quinidine and the identification of drugs whose elimination is impaired in subjects classified as poor metabolizers of debrisoquine. Br. J. Clin. Pharmacol., 22:739, 1986.
229. Brinn, R., et al.: Sparteine oxidation is practically abolished in quinidine-treated patients. Br. J. Clin. Pharmacol., *22*:194, 1986.
230. Gibaldi, M.: Drug interactions—a probe to identify drug metabolism pathways controlled by the debrisoquine phenotype. Perspect. Clin. Pharmacol., 7:89, 1989
231. Rubin, E., et al.: Inhibition of drug metabolism by acute ethanol intoxication: A hepatic microsomal mechanism. Am. J. Med., *49*:801, 1970.
232. Desmond, P.V., et al.: Short-term ethanol administration impairs the elimination of chlordiazepoxide (Librium) in man. Eur. J. Clin. Pharmacol., *18*:275, 1980.
233. Misra, P.S., et al.: Increase of ethanol, meprobamate and pentobarbital metabolism after chronic ethanol administration in man and rats. Am. J. Med., *51*:346, 1971.
234. Miller, R.R.: Effects of smoking on drug action. Clin. Pharmacol. Ther., *22*:749, 1977.
235. Jusko, W.J.: Role of tobacco smoking in pharmacokinetics. J. Pharmacokinet. Biopharm., *6*:7, 1978.
236. Dawson, G.W., and Vestal, R.E.: Smoking and drug metabolism. Pharmacol. Ther., *15*:207, 1982.
237. Boston Collaborative Drug Surveillance Program: Decreased clinical efficacy of propoxyphene in cigarette smokers. Clin. Pharmacol. Ther., *14*:259, 1973.
238. Vaughan, D.P., Beckett, A.H., and Robbie, D.S.: The influence of smoking on the intersubject variation in pentazocine elimination. Br. J. Clin. Pharmacol., *3*:279, 1976.
239. Pantuck, E.J., Kuntzman, R., and Conney, A.H.: Decreased concentration of phenacetin in plasma. Science, *175*:1248, 1972.
240. Jenne, J., et al.: Decreased theophylline half-life in cigarette smokers. Life Sci., *17*:195, 1975.
241. Hunt, S.N., Jusko, W.J., and Yurchak, A.M.: Effect of smoking on theophylline disposition. Clin. Pharmacol. Ther., *19*:546, 1976.
242. Pfeifer, H.J., and Greenblatt, D.V.: Clinical toxicity of theophylline in relation to cigarette smoking. Chest, *73*:455, 1978.
243. Vestal, R.E., et al.: Aging and drug interactions I. Effect of cimetidine and smoking on the oxidation of theophylline and cortisol in healthy men. J. Pharmacol. Exp. Ther., *241*:488, 1987.
244. Crowley, J.J., et al.: Aging and drug interactions II. Effect of phenytoin and smoking on the oxidation of theophylline and cortisol in healthy men. J. Pharmacol. Exp. Ther., *245*:513, 1988.
245. Crowley, J.J., et al.: Cigarette smoking and theophylline metabolism: effects of phenytoin. Clin. Pharmacol. Ther., *42*:334, 1987.
246. Lee, B.L., Benowitz, N.L., and Jacob, P., III: Cigarette abstinence, nicotine gum, and theophylline disposition. Ann. Intern. Med., *106*:553, 1987.
247. Brown, C.R., et al.: Changes in rate and pattern of caffeine metabolism after cigarette abstinence. Clin. Pharmacol. Ther., *43*:488, 1988.
248. Benowitz, N.L., Hall, S.M., and Modin, G.: Persistent increase in caffeine concentrations in people who stop smoking. Br. Med. J., *298*:1075, 1989.
249. Michnovicz, J.J., et al.: Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. N. Engl. J. Med., *315*:1305, 1986.
250. Kappas, A., et al.: Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism. Clin. Pharmacol. Ther., *20*:643, 1976.
251. Pantuck, E.J., et al.: Stimulatory effect of bussels sprouts and cabbage in human drug metabolism. Clin. Pharmacol. Ther., *25*:88, 1979.
252. Conney, A.H., et al.: Enhanced phenacetin metabolism in human subjects fed charcoal-broiled beef. Clin. Pharmacol. Ther., *20*:633, 1976.
253. Kappas, A., et al.: Effect of charcoal-broiled beef on antipyrine and theophylline metabolism. Clin. Pharmacol. Ther., *23*:445, 1978.
254. Nutt, J.G., et al.: The "on-off" phenomenon in Parkinson's disease. Relation to levodopa absorption and transport. N. Engl. J. Med., *310*:483, 1984.
255. Carter, J.H., et al.: Amount and distribution of dietary protein affects clinical response to levodopa in Parkinson's disease. Neurol., *39*:55, 1989.
256. Berlinger, W.G., Park, G.D., and Spector, R.: The effect of dietary protein on the clearance of allopurinol and oxypurinol. N. Engl. J. Med., *313*:771, 1985.
257. Alvares, A.P.: Interactions between environmental chemicals and drug biotransformation in man. Clin. Pharmacokinet., *3*:462, 1978.
258. Kolmodin, B., Azarnoff, D.L., and Sjöqvist, F.: Effect of environmental factors on drug metabolism: Decreased plasma half-life of antipyrine in workers exposed to chlorinated hydrocarbon insecticides. Clin. Pharmacol. Ther., *10*:638, 1969.
259. Kolmodin-Hedman, B.: Decreased plasma half-life of phenylbutazone in workers exposed to chlorinated pesticides. Eur. J. Clin. Pharmacol., *5*:195, 1973.
260. Ghoneim, M.M., et al.: Alteration of warfarin kinetics in man associated with exposure to an operating-room environment. Anesthesiology, *43*:333, 1975.