DOWNSIDE:

Adverse Effects of Drug Therapy

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Cured yesterday of my disease,
I died last night of my physician.

—Matthew Prior,
"The Remedy Worse than the Disease" (1727)

Probably no one reaches adulthood nowadays without having experienced some kind of adverse effects from medicine: drowsiness from cold and allergy medicines, nausea from pain relievers, a cutaneous rash from antibiotics. Unwanted consequences of taking medicine vary from the trivial (transient and harmless changes in the color of the stools caused by iron or bismuth preparations, and of the urine caused by phenazopyridine or methylene blue) to the lethal (fatal cerebral hemorrhage after thrombolytic therapy of stroke, and anaphylactic shock triggered by certain antibiotics and biologicals).

This topic could be expanded to include adverse reactions to surgical grafts and implants, dressing materials and adhesives, latex gloves and appliances, and diagnostic materials such as injected or ingested contrast materials used in radiography. The present article is limited, however, to a consideration of unwanted consequences of treatment with pharmaceutical agents.

Although severe side effects are more common with certain prescription medicines, over-the-counter (OTC) products can cause serious and even fatal adverse reactions, particularly in persons with sensitivities or allergies. Not only are the adverse effects of treatment objectionable in themselves, but they can dissuade or prevent patients from taking prescribed medicines, or from taking them in adequate dosage. When severe enough to require hospitalization or prolonged treatment, they can add enormously to the cost of treating the original problem.

Untoward drug effects can be particularly treacherous when they go unrecognized, as when one drug blocks the long-term effect of another drug that has been prescribed to retard or modify a chronic or progressive disorder, or when they are not recognized as such, as when OTC skin preparations containing neomycin or diphenhydramine elicit reactions that are indistinguishable from the signs and symptoms of the condition they were meant to relieve. Yet another kind of adverse effect is the masking of disease progression by a drug that merely suppresses signs or symptoms.

It is often difficult or impossible to establish with certainty that a particular unwanted effect has resulted from a particular drug in a particular patient. Medicines are not ordinarily administered to people who are perfectly well. New symptoms or manifestations of the underlying illness, such as fever, weakness, or nausea, are frequently mistaken for side effects of medicines that have recently been administered. And, on the other hand, untoward effects of medicines are often misinterpreted as signs or symptoms of worsening disease.

Before a drug is released for marketing by the U.S. Food and Drug Administration (FDA), it is subjected to clinical trials in a large group of patients, partly to establish a profile of any untoward effects that occur with significant frequency. Clinical trials include control groups to whom inert materials (placebos) are administered instead of the drug under study.

In the standard double-blind trial, neither subjects nor investigators know who is receiving active drug and who is receiving placebo until after all the data have been gathered and analyzed. In any large control group, certain adverse effects are invariably reported. These range from drowsiness and nausea, which may each be reported by at least 5% of subjects receiving placebo, to rashes, headache, and impotence. Since these cannot possibly be side effects of the drug under study, which has not been administered to the subjects in the control group, the most accurate estimate of the incidence of various side effects is the difference between their frequencies in the active drug group and in the control group.

The adverse effects of drug therapy can be categorized in various ways. The following breakdown is a useful working classification.

1. Pharmacologic effects
2. Toxic effects
3. Allergic reactions
4. Idiosyncratic reactions
5. Habituation and addiction
6. Drug use during pregnancy and lactation
7. Drug interactions
8. Medication errors

Pharmacologic vs. Toxic Effects

Despite continuing improvement in the specificity of drugs and in their side-effect profiles, nearly all drugs currently available, including many of those that can be obtained without a prescription, have a significant potential for causing adverse effects, at least in some persons.

The *pharmacologic* effects of a drug are those that result directly from its medicinal properties. These include both its intended effects (e.g., pain relief) and side effects properly so-called (e.g., drowsiness). Although pharmacologic side effects may vary in intensity from person to person, they are likely to occur to some degree in anyone who takes the drug, and to be dose-related (that is, more pronounced at higher doses). Such side effects generally arise from a lack of specificity in the pharmacologic action of the drug.

A common example is the drowsiness that results from taking narcotic analgesics, tranquilizers, antiemetics, antipruritics, and some antidepressants. These drugs work by altering certain functions of the central nervous system (CNS), but their effects are so broad that they can also impair alertness and cognitive acuity.

Conversely, CNS stimulants prescribed for attention-deficit disorder, such as amphetamines and methylphenidate, can cause undesirable CNS side-effects such as anorexia, restlessness, and insomnia. Sympathomimetic agents prescribed for nasal congestion and bronchial spasm can also cause CNS stimulation and insomnia, as well as tachycardia and hypertension.

Anticholinergic drugs prescribed to reduce gastrointestinal hypersecretion often cause dryness of the mouth because they also suppress salivary gland function. Anticoagulants (aspirin, heparin, warfarin) can cause bleeding by various mechanisms, most of which are simply extensions of their intended pharmacologic effects. Some diuretics can lead to electrolyte depletion by performing their intended function on too grand a scale. Chemotherapy agents used in malignant disease can cause bone marrow depression and impairment of immunity as well as other effects (stomatitis, hair loss) related to their role as antimetabolites.

Blocking agents are just that: drugs that prevent or retard pathologic or undesirable physiologic processes. Beta-adrenergic blockers such as propranolol can precipitate cardiac failure by disabling compensatory mechanisms in persons with severely compromised cardiac function. They can also worsen bronchial asthma by interfering with normal adrenergic responses, and can mask the adrenergic manifestations (sweating, tachycardia) of hypoglycemia due to insulin overdose.

Some pharmacologic side effects occur indirectly, or through complex mechanisms. Antibiotics can suppress the normal bacterial flora of the mouth, intestine, or vagina and thus favor the overgrowth of yeasts or other organisms, which can then cause conditions such as thrush or vaginal candidosis. Prolonged administration of adrenocortical steroid can suppress the production of adrenocorticotropic hormone (ACTH) by the pituitary gland. As a result, the output of endogenous corticoids by the adrenal glands declines or

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ceases, and the body's ability to respond to physical stresses may be severely impaired.

Some persons are more susceptible than others to certain pharmacologic side effects. For example, by dilating the pupils, anticholinergics and antihistamines can precipitate acute glaucoma in persons predisposed to it by a narrow ocular drainage angle. Drugs of these two classes can also cause acute urinary retention in elderly men with prostatic hyperplasia by relaxing bladder muscles.

The dosage requirements of some drugs, such as hormones used to treat certain glandular deficiency syndromes (adrenocortical steroids, insulin, thyroid hormone), can vary widely from one patient to another. With such agents, unwanted physiologic effects often occur before dosage has been accurately titrated to the patient's needs.

A *toxic* effect is one that results from some property of a drug other than the one for which it was administered, or at least some property that is not typically exploited in medicine. Many drugs are irritating to the gastrointestinal tract and can cause anorexia, nausea, vomiting, diarrhea, or all of these. Some drugs (carbamazepine, azulfidine) impair the sense of taste and so can lead indirectly to anorexia.

Prolonged use of certain neuroleptics for schizophrenia often results in tardive dyskinesia, a delayed form of CNS toxicity. The usefulness of several otherwise valuable agents is limited by their tendency to cause damage to the bone marrow, liver, or kidneys, which may be severe and irreversible. FDA guidelines mandate frequent laboratory monitoring for various types of toxicity in patients taking certain medicines.

The distinction between the pharmacologic and toxic effects of a drug is sometimes a matter of viewpoint. That is, it may depend on the reason why the drug was prescribed for a particular patient. Incidentally, unexpected side effects of new drugs sometimes prove to be valuable therapeutic properties. After being approved as an antidepressant and put into wide use, bupropion was discovered to have the additional property of facilitating smoking cessation.

Minoxidil, an oral antihypertensive marketed as Loniten, was found to reverse vertex scalp hair thinning in men. Subsequently approved for this indication, it was marketed as Rogaine, and is now available in OTC topical forms, one designed for each sex. Finasteride, a drug designed to improve obstructive symptoms in benign prostatic hyperplasia and marketed as Proscar, not only arrests vertex thinning but corrects male pattern baldness ("tall face" and temporal recession of hairline). Under the brand name Propecia it is now approved for this indication, but only in men.

Drug Allergy

Allergy is an acquired hypersensitivity to some foreign substance. On first exposure, the substance causes no overt ill effects, but elicits an immune reaction, usually involving production of IgE antibody. Later exposure to the substance can result in any of various allergic reactions, including urticaria (hives) or other cutaneous rash, rhinitis, laryngeal edema, bronchospasm, and circulatory collapse. Many allergens (substances capable of causing allergic reactions) are complex organic molecules found in nature, either as components of plant or animal foods or as airborne inhalants (such as pollens, mold spores, and dusts). But many drugs, including antibiotics (which are derived from molds) and other natural and synthetic organic molecules, can also act as potent allergens, and allergic responses of various kinds are among the most frequently observed and most serious adverse reactions to drugs.

An important feature of allergy is that an infinitesimal amount of allergen may suffice to produce a reaction. For example, allergic reactions have been caused by concentrations of penicillin in cow's milk that were too low to be detected by routine chemical testing. Traces of peanut protein left on machinery used to manufacture foods and candies can contaminate batches of non-peanut products in sufficient concentration to cause severe, even fatal, reactions in persons who are allergic to peanuts.

Some persons are much more likely than others to develop allergies. The tendency to develop allergies runs in families, but the type and degree of each person's sensitivities are unique to that person. Generally a person with one allergy will eventually be found to have others.

A history of allergy to a certain drug usually contraindicates the use of other drugs that are closely related to it chemically. For example, a patient who has had an allergic reaction to penicillin V should not take amoxicillin, methicillin, or ticarcillin, all of which share both the thiazolidine and beta-lactam rings of the parent drug. However, drugs that are in the same therapeutic class, but are not chemically related, would not be expected to cause allergic reactions.

When the cephalosporins were first introduced, there was concern about possible cross-reactivity with the penicillins, since both classes of drug contain the beta-lactam ring. Although some cross-reactivity does occur, its incidence is quite low. I have prescribed cephalosporin antibiotics for hundreds of patients who claimed to be allergic to penicillin, and have seldom observed any adverse reactions.

Keeping track of a patient's history of drug allergies and sensitivities is an arduous but essential part of providing medical care and maintaining clinical records. In my own practice, every patient is asked about drug sensitivities at every visit, and notations are accordingly entered or updated on the face sheet of the patient's record envelope.

To many lay persons, the term *allergy* denotes all possible ill effects of medicines, foods, or anything else that can be swallowed, inhaled, injected, or applied to the skin. Patients often erroneously refer to side effects such as nausea and vomiting after taking codeine or erythromycin, or cardiac palpitation after using a bronchodilator, as "allergies." This is a mere mistake in terminology; indeed, even clinical investigators may have difficulty distinguishing between allergic reactions to a drug and reactions due to nonspecific pharmacologic effects or toxicity. But many persons wrongly believe that they have an abnormal sensitivity to "acid," "all fruits," "all food colorings," and so forth, as well as to certain drugs. Over 80% of patients giving a history of penicillin allergy have negative skin tests and can safely receive the drug.

The origins of these misunderstandings are diverse. As mentioned above, symptoms of the underlying illness such as nausea, light-headedness, or weakness are often misinterpreted as adverse effects of medicines that have been taken to treat the illness. Many febrile rashes in children are attributed by parents and physicians to medicines (especially antibiotics) that were administered before the appearance of the rash.

An allergic response can be triggered by inert ingredients of a pharmaceutical product as well as its active ingredient. Such inert ingredients include flavoring and coloring agents, vehicles such as peanut oil, antiseptics such as thimerosal, and egg protein in live or killed vaccines that have been grown in hens' eggs.

Allergic reactions to a given drug can vary widely in type and severity from person to person. Penicillin exemplifies this variability. It can cause acute anaphylaxis, with laryngeal edema, urticaria, and shock, within 30 minutes of administration; or an accelerated allergic reaction consisting of simple urticaria due to IgE antibody and occurring within three days after administration; or a delayed response, usually a macular rash mediated by IgM antibody and occurring still later—often around the time a course of oral penicillin is finished.

Yet another variant of penicillin allergy is the rash that develops in most persons with infectious mononucleosis (IM) who take ampicillin or amoxicillin. This coarse papular rash, which appears about one week after the antibiotic is started, reflects sensitivity to the combination of the Epstein-Barr virus, which causes IM, and a molecular structure found in certain semisynthetic penicillins. After recovery from IM, the patient who is not truly allergic to ampicillin and amoxicillin can take these drugs again without getting a rash.

Not all drug-induced rashes are allergic in origin. For example, the lupus-like rash that occurs after prolonged administration of certain drugs (hydralazine, isoniazid, oral contraceptives, procainamide) is not allergic, and neither is the acne that can occur during treatment with topical or systemic corticosteroids. Some drug rashes are toxic rather than allergic. These include toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome. The latter, fortunately rare, is a severe bullous form of erythema multiforme accompanied by

fever, oral erosions, and conjunctivitis, which sometimes occurs in persons treated with sulfonamides and certain other drugs. Its pathogenesis is poorly understood. The case fatality rate of this condition is 10-25%, and ocular involvement can lead to blindness in survivors.

Drug Idiosyncrasy

An *idiosyncratic* reaction is one that occurs only in isolated instances, affecting just one person or at most a small group. By convention the term excludes allergic reactions. Since, by their nature, idiosyncratic reactions occur only rarely after administration of the drug in question, their causal connection with the drug can be difficult to confirm.

Every medical practice or clinic has a few patients whose records show a history of adverse reactions to ten or more drugs or classes of drugs. While some of these patients also exhibit evidence of hypochondria or somatization disorder, others seem to have genuine sensitivities to a broad variety of therapeutic agents. Some persons experience paradoxic reactions, becoming excited after taking drugs that normally cause CNS depression, or lethargic after taking drugs that normally cause CNS stimulation.

Most idiosyncratic drug reactions are probably due to inherited biochemical deficiencies. For example, persons with glucose-6-phosphate dehydrogenase deficiency, an inborn error of metabolism that affects 10-15% of African-American men, can develop a hemolytic anemia when treated with nitrofurantoin, quinine, or sulfonamides.

Other genetically determined drug idiosyncrasies are neuroleptic malignant syndrome, induced in some persons by psychoactive drugs such as haloperidol (Haldol) and fluphenazine (Prolixin), and malignant hyperthermia, induced in susceptible persons by some inhalation anesthetics and the skeletal muscle relaxant succinylcholine.

In recent years, biochemical research has gradually clarified the role of enzymes belonging to the the cytochrome P-450 system in the metabolism of drugs. An enzyme is a catalyst—a substance that initiates, accelerates, facilitates, or regulates various chemical reactions (such as oxidation or transamination) without being altered or consumed in the process. A material whose chemical alteration is catalyzed by an enzyme is called its substrate.

The cytochrome P-450 system is a heterogeneous group of enzymes that catalyze certain oxidative reactions, particularly in the liver. They are involved in the metabolism of many substrates, including both normal body products (hormones, neurotransmitters, wastes) and materials taken into the body from outside (drugs, foodstuffs, toxins).

Cytochrome P-450 enzymes are classified on the basis of their chemical structure. The designation assigned to each enzyme in the system is CYP followed by a number from 1 to 12 for the family to which it has been assigned, a letter for its subfamily, and usually a second number for the individual enzyme.

Cytochrome P-450 enzymes of families 1, 2, and 3 are the ones principally involved in drug metabolism. Genetic

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defects in these enzymes are responsible for many drug sensitivities and idiosyncrasies. For instance, about 7% of the population are deficient in the expression of CYP2D6, whose substrates include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), beta-blockers, and dextromethorphan. Such persons are poor metabolizers of these substances, and are thus more likely to experience side effects and toxicity at standard dosages.

Drug Habituation and Addiction

Many drugs, particularly those used to treat pain, anxiety, and depression, can temporarily induce pleasant emotional states, varying from carefree serenity to euphoria and exhilaration. Even when such a feeling is not part of the intended therapeutic effect of the drug, it can exercise such an appeal that the patient becomes *habituated* to the drug—that is, craves another dose as soon as the effect of the previous dose begins to wear off.

Narcotic analgesics, barbiturates, amphetamines, and benzodiazepine tranquilizers are among the prescription drugs most commonly associated with habituation, but habituation to alcohol, caffeine, and nicotine is even more prevalent. The nature of habituation is not fully understood. There appears to be a genetic tendency to alcoholism and perhaps to some other types of drug habituation.

Some habituating drugs also produce physical *dependence*. That means that after repeated dosing, the body adapts neurologically or biochemically in such a way that withdrawal of the drug can induce physical symptoms such as diaphoresis, restlessness, dysphoria, and even seizures. The development of withdrawal symptoms reinforces the craving due to psychological habituation. In fact, the victim of drug dependence may keep repeating doses not so much to get "high" over and over as just to reverse withdrawal symptoms and feel normal again.

Drug habituation can be further complicated by the development of *tolerance*—that is, the need to increase dosage continually in order to achieve the desired effect. One type of tolerance occurs when a drug stimulates an increase in the production of a cytochrome P-450 enzyme that is involved in its own breakdown. The more drug taken, the more enzyme produced; and the more enzyme, the less drug effect from a given dose.

Addiction is variously defined; some have advised abandonment of the term (as well as of *drug abuse*) because of acquired judgmental connotations. The usual meaning of addiction is a severe, disabling preoccupation with the use of a drug, involving habituation, dependence, and tolerance. Drug addicts, like alcoholics, often drop out of the work force and

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out of society, and some are driven to crime in order to feed their habits.

Many drugs that were formerly approved for use in this country, such as heroin, γ-hydroxybutyrate (GHB), and phencyclidine ("angel dust"), are now illegal because of their high potential for habituation or addiction, and the use of some other agents, such as amphetamines and cocaine, has been sharply restricted for the same reason.

Commonly abused psychoactive drugs can cause various acute and chronic neurologic and psychiatric disorders. Some also have effects on parts of the body other than the CNS. Cocaine, for example, is a potent coronary vasoconstrictor, and has been responsible for many deaths of young persons from acute myocardial infarction.

Drugs During Pregnancy and Lactation

The familiar term *placental barrier* is something of a misnomer, since nearly all drugs administered to a pregnant woman, except certain large organic molecules such as heparin and insulin, reach the fetal circulation. The developing fetus, besides being subject to many of the pharmacologic and toxic effects of drugs, is particularly vulnerable to certain agents, called teratogens, which are capable of causing developmental anomalies.

The risk of abnormal development is largely confined to the period of organogenesis (organ formation), from the third through the eighth week after conception. (During the first two weeks of pregnancy, teratogens either do no harm at all or cause miscarriage.) Among the types of fetal malformation that are commonly associated with administration of teratogenic drugs during pregnancy may be mentioned cleft lip and palate, heart valve abnormalities, optic atrophy, maldevelopment of the brain with mental retardation, and neural tube defects such as meningomyelocele and spina bifida.

Since all these developmental abnormalities have been occurring for centuries, tracing some instances of them to teratogenic drugs administered during pregnancy demands the laborious accumulation and careful analysis of data. Diethylstilbestrol, a synthetic estrogen, was routinely administered to pregnant women with threatened miscarriage, as evidenced by vaginal bleeding, throughout the 1940s, '50s, and '60s. It was also used, before the development of progesterone-type oral contraceptives, as a birth control pill (with poor success). Only around 1970 was it established that about 20% of female fetuses exposed in utero to diethylstilbestrol develop genital malformations: cervical hood, collar, or pseudopolyps; transverse vaginal ridges; and, less often, deformities of the uterine cavity. A much lower percentage develop clear cell adenocarcinoma of the vagina or cervix.

Thalidomide, a sedative and antiemetic, was administered to many pregnant women in Great Britain, West Germany, and other countries in the late 1950s and early '60s. This drug was soon found to be a major teratogen, causing a very high incidence of phocomelia (rudimentary development of arms, legs, or both).

Long before the period of fetal viability is reached, all the organs have been formed and many of them have even attained functional maturity. A few drugs, however, are capable of causing fetal harm later in pregnancy. For example, angiotensin-converting enzyme (ACE) inhibitors can cause severe fetal damage during the second and third trimesters. Sulfonamides administered during the last trimester can compete with bilirubin for binding sites on serum albumin and lead to jaundice in the newborn. Although the elevation of bilirubin is reversible and does not reflect impairment of liver function, it can cause a form of chemical damage to the basal ganglia of the brain called kernicterus, with lethargy, spasticity, seizures, and often death. Tetracyclines administered late in pregnancy can bind to developing dental enamel and cause discoloration of the deciduous teeth. (Tetracycline given to children under five can discolor the permanent teeth.)

Alcohol, caffeine, nicotine, and cocaine have all been shown to be potentially harmful to the fetus. All are believed to retard fetal growth in some measure. Maternal alcoholism is associated with a syndrome of facial dysmorphism (short palpebral fissures, broad flat nose, hypoplastic upper lip) and cardiac and spinal defects. Maternal cocaine abuse can lead to genitourinary anomalies and central nervous system infarcts in the fetus.

The FDA has often been criticized as being excessively cautious in approving new drugs. However, while the FDA was still gathering and reviewing data on thalidomide, thousands of deformed babies were being born in Europe as a result of intrauterine exposure to this drug. Even though thalidomide was never approved for use in the U.S., the thalidomide experience led to a new consciousness of the risk of drug-induced teratogenesis, and to even more stringent limitations on the use of drugs during pregnancy.

It also led to an epidemic of litigation against pharmaceutical manufacturers for alleged fetal harm due to nearly every drug on the market. The manufacturer of Bendectin, an antimetic once widely used to prevent morning sickness, withdrew the product rather than go bankrupt by defending itself against an endless string of lawsuits, even though no proof was ever adduced that Bendectin had harmed a single fetus.

In order to assist physicians in making decisions about the use of drugs during pregnancy, the FDA has established the following classification of drugs:

Pregnancy Risk Categories
A: Controlled studies show no human risk.
B: Animal studies show no risk, but adequate human studies do not exist.
C: No adequate studies in either animals or humans.
D: Fetal risk is known, but benefits may outweigh risks.
X: Risks outweigh any possible benefits.

The English essayist, poet, and lexicographer Samuel Johnson once boasted that he had memorized an entire chapter of a book on the natural history of Iceland. When challenged to repeat it, he recited: "The Snakes of Iceland. There are no snakes to be met with throughout the whole island." Pretty much the same situation obtains with pregnancy risk category A: There are virtually no drugs in category A—certainly no drugs that have been developed during the past generation.

The reason should be obvious. It would be unethical to perform controlled human studies of a drug whose teratogenic potential has yet to be defined. While studies of the influence of a new drug on fetal development in animals are routinely carried out, these studies often correlate poorly with effects in human beings. For example, when tested in pregnant animals, thalidomide caused no fetal harm. Administration of corticosteroids to pregnant mice can produce cleft lip in the offspring, but no such effect has ever been observed in human beings.

The majority of drugs in current use fall into category C. Virtually all drugs developed in the past 30 years are in this category, unless information resulting from their administration during pregnancy has dictated their placement in category D or X. Category C also includes many long-established drugs such as chlorothiazide, digoxin, nitroglycerin, and propranolol.

Drugs in category D are used in pregnancy only when the benefit to mother or fetus outweighs the risk of fetal harm. Examples would be the continued administration of phenytoin (which can cause microcephaly and physical and mental retardation) to a pregnant patient with an otherwise uncontrollable seizure disorder, and the use of lithium (which causes a high incidence of cardiovascular malformations) to treat bipolar disorder which, if left untreated, might endanger the life of mother, fetus, or both.

Category X includes sex hormones (estrogens, androgens, progesterones, all oral contraceptive formulations), isotretinoin, radiopharmaceuticals, and chemotherapeutic agents used in the treatment of cancer.

Many substances ingested by a nursing mother, including various drugs, find their way into breast milk in sufficient quantity to affect the infant. Here again, ethical concerns prohibit the collection of controlled data on possible harmful effects of new drugs in breast milk. It is an age-old observation that tranquilizers and laxatives taken by a nursing mother often cause sedation and diarrhea respectively in the infant. In addition, some drugs, such as antihistamines, anticholinergics, and levodopa, can diminish milk flow.

Drugs that are contraindicated during lactation because of a high risk of fetal harm are sulfonamides, metronidazole, oral contraceptives, lithium, antithyroid medicines, antimetabolites used in cancer chemotherapy and immunosuppression, and radiopharmaceuticals.

Drug Interactions

Ongoing drug research has led to a steady enrichment of the pharmacopeia, and this in turn has fostered polyphar-

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An Illustration: Aspirin Therapy

Aspirin (acetylsalicylic acid), one of the most valuable and versatile drugs ever synthesized, illustrates the complexity and diversity of drug reactions. A survey of potential adverse consequences of aspirin therapy, some of which are mentioned in the text, provides an epitome or synopsis of the whole topic.

Aspirin can produce bleeding by interfering with various normal coagulation mechanisms. This is an extension or exaggeration of one of its pharmacologic effects, to exploit which it is administered to persons with coronary artery and cerebral vascular disease. The ability of aspirin to induce peptic ulceration arises from another of its pharmacologic properties, an anti-inflammatory effect due to inhibition of prostaglandin synthesis.

In addition, aspirin can cause toxic effects such as reversible tinnitus and, in children with certain febrile diseases, Reye syndrome, a potentially fatal hepatotoxicity.

As an allergen, aspirin can cause acute anaphylaxis, but it is more commonly associated with simple urticaria. Certain persons with an allergic diathesis characterized by nasal polyps and bronchial asthma are highly allergic to aspirin, which can trigger severe urticaria and angioedema. Such persons are usually also sensitive to nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and to the food coloring agent tartrazine (FD&C Yellow No. 5), formerly found in many pharmaceuticals.

Aspirin can also have adverse effects in pregnancy and can interact with other drugs. By various mechanisms, not all of them understood, aspirin increases the duration of pregnancy, the mean duration of spontaneous labor, and perinatal blood loss. It potentiates phenytoin, some hypoglycemic agents, and warfarin by displacing them from serum protein-binding sites, but blocks the uricosuric effect of probenecid. In turn, the effects of aspirin can be blocked by para-aminobenzoic acid (PABA).

Until acetaminophen, ibuprofen, and naproxen displaced it from the family medicine cabinet, aspirin was one of the most common drugs used in suicide attempts, and was by far the leading pharmaceutical involved in accidental childhood poisonings.

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macy—the simultaneous administration of many drugs to the same patient. The older the patient, the greater the likelihood that several chronic conditions coexist, all requiring long-term treatment, and that some of these have complications that also require treatment. For example, many persons over 60 are receiving drug treatment simultaneously for hypertension,

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coronary arteriosclerosis, hyperlipidemia, diabetes mellitus, glaucoma, and osteoarthritis.

In these circumstances, interactions among drugs being taken at the same time are virtually inevitable. According to a study published in 1999, drug interactions are responsible for 3.8% of all emergency department visits, and most of these patients require hospital admission. Another study found that preventable drug interactions account for one half of all costs attributable to adverse events occurring in hospitalized patients. Just as a history of allergy or sensitivity to certain medicines must be an integral part of every patient's medical record, a complete list of all medicines currently being taken, and their dosages, must be available at all times to the treating physician.

Possible interactions include blocking of one drug's effects by another, undesirable enhancement of drug effects (including side effects), and production of a reaction qualitatively unrelated to the properties of the individual reacting drugs. The effects of a drug can be altered not only by other drugs but also by foods. For example, milk and dairy products can impair the absorption of tetracycline and fluoroquinolone antibiotics, while applesauce markedly increases the absorption of phenytoin.

One often hears the criticism by lay persons that doctors don't know about drug interactions, or aren't sufficiently alert to the possibility of their occurrence. Much of this criticism is misdirected. Many patients nowadays have three or more regular physicians (for example, a cardiologist, a diabetologist, an ophthalmologist, and a urologist), who may or may not have been informed by the patient of one another's existence. When queried, patients are seldom able to identify all the medicines they are taking with perfect accuracy. Typically they identify some of them incorrectly and forget others altogether, including particularly prescription eye drops and topical preparations. They don't remember why their medicines were prescribed, or when, or by which physician. They can't accurately describe the shape or color of pills they take every day.

OTC products taken daily, including nutritional supplements, appetite suppressants, analgesics, allergy preparations, and laxatives, are apt to be completely forgotten when the patient is asked to name any current medicines. Women often fail to mention that they are taking oral contraceptives, which they don't regard as medicine. As if all this weren't enough, some patients deliberately conceal the fact that they are taking certain medicines, for a variety of reasons. These obstacles to sound decision-making about drug combinations are not just occasional events in the practice of medicine. They keep occurring all day, every day, even in my own practice, which is virtually limited to college students.

Like other adverse reactions to drugs, drug interactions are sometimes difficult to document and explain. Although modern oral contraceptives (OCs) are highly effective in preventing conception, none has a perfect record of success. When pregnancy occurs in a woman who has been taking an OC, there is a natural tendency to seek an explanation for the drug failure. Often another drug being taken at the same time is blamed for the failure; there are anecdotal accounts of suspected interactions between OCs and dozens, perhaps hundreds, of other drugs. But for only a very few of these drugs is there strong evidence of interference with the efficacy of OCs.

Interactions can occur between two drugs that are chemically related (as when Alka-Seltzer and Pepto-Bismol, both containing salicylates, are taken together and cause ringing in the ears), are in the same therapeutic class (as when two tranquilizers are taken together and cause severe drowsiness), or are wholly unrelated (as when ciprofloxacin causes a rise in the serum level of a tricyclic antidepressant).

Drug interactions can be divided, for purposes of discussion, into two large groups: pharmacologic and pharmacokinetic. Pharmacologic interactions involve an interplay between the medicinal properties of two or more drugs. This interplay can be either additive or subtractive.

The sedative effects of most CNS depressants (tranquilizers, narcotic analgesics, antihistamines, antiemetics, alcohol) are additive, and unwisely combining two or more of these can lead to severe drowsiness, stupor, coma, or even death. Similarly, the CNS stimulant effects of sympathomimetic drugs (such as decongestants or bronchodilators), agents prescribed for attention-deficit disorder (such as methylphenidate or amphetamines), and caffeine consumed medicinally or in beverages can add up to excessive restlessness and insomnia.

To illustrate subtractive or antagonistic interactions with these same agents: caffeine or a decongestant can negate the effect of a bedtime sleeping medicine. Obvious as these examples seem to be, I see patients almost daily who have taken one of these combinations, with exactly the results that might have been expected.

Pharmacologic interactions among cardiovascular drugs used in the treatment of angina pectoris, hypertension, cardiac failure, and peripheral vascular disease are often complex and not fully understood. Beta-adrenergic blocking agents, useful in the treatment of hypertension and angina pectoris because they block the effects of endogenous epinephrine and other sympathomimetic amines on beta-adrenergic receptors in the circulatory system, can also block the effect of epinephrine administered to treat anaphylactic shock or cardiac arrest.

Three antidepressant drugs in current use—isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate)—are known as monoamine oxidase (MAO) inhibitors. MAO is an enzyme that regulates the metabolic degradation of many naturally occurring amines, including the

hormonal neurotransmitters epinephrine, norepinephrine, and serotonin. It performs the same function with certain sympathomimetic (epinephrine-like) drugs and with tyramine, a substance found in aged cheese and other foods. The mechanism whereby MAO inhibitors relieve depression is believed to be related to their effect on serotonin metabolism.

The usefulness of these drugs is limited by their tendency to interact with other drugs and with many foods. Administration of sympathomimetic amines (decongestants, bronchodilators), antihistamines, other antidepressants, narcotics, certain anesthetics, or alcohol to a person taking an MAO inhibitor can lead to an accumulation of pressors (blood pressure-raising substances) in the circulation and thus trigger a hypertensive crisis, which can culminate in seizures, coma, and death. Similar reactions have been observed after the ingestion of cheese, beer, wine, yeast, salami, pickled herring, chocolate, and other foods.

Still more numerous and more complex than these interactions between pharmacologic effects are pharmacokinetic interactions. *Pharmacokinetics* is the branch of pharmacology that studies the absorption, transport, distribution, metabolism, and excretion of drugs. Any of these steps in the processing of a drug by the body can be influenced by the presence of another drug, which may enhance, prolong, diminish, delay, or shorten the action of the first drug.

Some drugs can form insoluble complexes with other drugs in the digestive system and so reduce their absorption and bioavailability. Common examples include antacids, iron, sucralfate (Carafate), cholesterol-binding agents such as cholestyramine (Questran) and colestipol (Colestid), and the osteoporosis drug alendronate (Fosamax). Among drugs that are vulnerable to such effects may be mentioned tetracyclines, fluoroquinolones, nitrofurantoin, isoniazid, ranitidine (Zantac), indomethacin (Indocin), propranolol (Inderal), and digitalis. Some antibiotics can reduce the effectiveness of oral contraceptives, apparently by suppressing the normal bacterial flora of the intestine and thus altering the absorption of hormones.

The transport and distribution of drugs depend on a number of intricate mechanisms. Many drugs, upon entering the circulation, form loose chemical complexes with plasma proteins, and are transported chiefly in the bound form. Competition between two or more drugs for binding sites on plasma proteins can result in higher concentrations of the unbound, active form of one or both of the drugs. Phenytoin, sulfonamides, and warfarin are particularly likely to compete with each other, and with other drugs, for protein binding sites.

Some drugs can affect the excretion of other drugs. For example, antacids reduce the renal excretion of pseudoephedrine and tricyclic antidepressants. Probenecid (Benemid) is useful in the treatment of gout because it is uricosuric—that is, it increases the clearance of uric acid by the kidneys. But it also delays the excretion of some other drugs. This property of probenecid is sometimes exploited to augment and prolong the effects of a single dose of penicillin, but it can

> *Drug metabolism—the chemical alterations undergone by a drug in the living body between administration and excretion—provides the most fertile field for pharmacokinetic interactions with other drugs.*

also increase the risk of side effects and toxicity of drugs such as indomethacin and methotrexate.

Drug metabolism—the chemical alterations undergone by a drug in the living body between administration and excretion—provides the most fertile field for pharmacokinetic interactions with other drugs. Although most drugs, and all synthetic ones, are foreign substances, the body handles them in various ways. Some are so similar to natural substances that they are metabolized and excreted by existing biochemical pathways. Others may elicit one or more impromptu detoxification responses in which the foreign substance is rendered less harmful or more readily disposed of by being conjugated with a natural substance. These detoxification processes usually take place in the liver and include acetylation, alkylation, sulfonation, and conjugation with benzoic and glucuronic acids.

Disturbances in the functioning of the cytochrome P-450 system are responsible for many kinds of undesirable drug interaction. Such disturbances can come about in either of two ways. Some drugs and other substances *induce* specific cytochrome P-450 enzymes; that is, they stimulate the formation of more enzyme than is normally present. When this occurs, drugs that are substrates of that enzyme are eliminated more rapidly and may fail to produce the desired therapeutic effects.

For example, the most abundant of human cytochrome P-450 enzymes, CYP3A, is induced by carbamazepine (Tegretol), phenobarbital, phenytoin (Dilantin), and rifampin (Rifadin). The substrates of CYP3A include erythromycin, ketoconazole (Nizoral), protease inhibitors used in the treatment of AIDS, and many psychoactive medicines.

In contrast, a drug that *inhibits* cytochrome P-450 enzyme activity can retard the metabolism of substrate drugs, with resultant increases in serum and tissue levels and in drug effects, including side effects. A temporary inhibition of enzyme function, usually involving competition between drugs for the same binding site on an enzyme molecule, is the commonest type of drug interaction involving the P-450 system. CYP3A is inhibited in this way by some antidepressants, azole antifungals, cimetidine (Tagamet), erythromycin, and other drugs.

Some kinds of drug interaction are not fully understood. Dexfenfluramine (Redux), an appetite suppressant that alters serotonin metabolism, occasionally causes potentially lethal cardiac valvular lesions and pulmonary hypertension. For reasons that are not clear, the incidence of such effects appears to be heightened when dexfenfluramine is taken in combination with another appetite suppressant, phentermine

(Ionamin). Because of increasing reports of adverse effects from this combination, known colloquially as "phen-fen," dexfenfluramine was removed from the market by the FDA in 1997.

As noted earlier, the effects of some medicines can be altered by certain foods as well as by other medicines. Indeed, the presence of almost any food in the stomach reduces the bioavailability of certain drugs, such as azithromycin (Zithromax), norfloxacin (Noroxin), and zafirlukast (Accolate). Consumption of a diet high in vitamin K can counteract the anticoagulant effect of warfarin (Coumadin). Grapefruit juice (as well as cimetidine and erythromycin) inhibits the action of CYP1A2, whose substrates include acetaminophen, caffeine, and theophylline. On the other hand, charcoal-broiled beef, radishes, and broccoli (as well as phenytoin and rifampin) can induce increased production of this enzyme.

Caffeine, a staple element in the diet of many persons, can have additive effects with other CNS stimulants and with caffeine derived from medicinal sources. Caffeine is present in coffee, tea, many soft drinks (Coca-Cola, Dr. Pepper, Edge, Mountain Dew, Surge, Pepsi-Cola), and several OTC analgesics and pep pills (Anacin, Coricidin, Excedrin, NoDoz, Vanquish, Vivarin).

Daily alcohol consumption is also common. The FDA now requires products containing acetaminophen or ibuprofen to carry a warning that these OTC analgesics should not be used by persons who habitually consume more than three alcoholic drinks daily, because of the risk of cumulative toxicity. The alcohol content of liquid pharmaceuticals, particularly cough syrups, can be as high as 15% or more.

Disulfiram (Antabuse), a drug that inhibits the action of aldehyde dehydrogenase, has been used in the treatment of alcoholism. If a person who is taking this drug regularly consumes alcohol, the result is an accumulation of acetaldehyde, a breakdown product of ethyl alcohol, which causes an "instant hangover"—a distressing but harmless and reversible syndrome of flushing, tachycardia, headache, nausea, vomiting. Many substances besides disulfiram, including ceftriaxone (Rocephin), metronidazole (Flagyl), and sulfonylurea agents used in the treatment of type 2 diabetes mellitus, can cause a similar reaction when taken with alcohol.

Medication Error

Medication errors can be committed by physicians, caregivers, or patients themselves. The term *iatrogenic* refers to diseases and abnormal conditions that are induced by the medical treatment of some other disease. It is estimated that, in the United States, 300,000 hospital admissions a year and 30,000 deaths a year are attributable to iatrogenic illness. Although by no means all of these adverse results of treatment are due to physician error, many of them do result from a wrong choice of medicine, a mistake in dosage, or failure to observe some necessary precautions in drug use.

Adverse effects of drugs and known interactions are listed in professional product literature (package inserts) and other reference sources, including whole books devoted to this one subject. Warning systems built into many medical software programs prevent a physician from ordering a medicine to which the patient is known to be sensitive or allergic, or that might interact adversely with another medicine the patient is already taking.

But such systems cannot detect diagnostic errors or lapses of medical judgment. The authors of one study concluded that physicians prescribe potentially inappropriate medicines for nearly one-fourth of all older persons not living in nursing homes, thus placing them at risk of adverse drug effects such as cognitive impairment and sedation.

The prescribing of drugs by physicians for indications not approved by the FDA (called "off-label use," although approved indications are listed on package inserts, not labels) is exceedingly common. While not illegal, this practice goes against the body of informed medical opinion and incurs the risk of successful malpractice litigation in the event of an unfortunate outcome. The Centers for Disease Control and Prevention estimates that U.S. physicians write 50 million unnecessary antibiotic prescriptions annually, including 17 million to treat the common cold.

Errors made by pharmacists in filling prescriptions and by nurses in administering medicines in hospitals account for an enormous number of adverse drug consequences and deaths each year. It has been estimated that the medication-related error rate in intensive care units (ICUs) is about 15% of all doses ordered.

But patients themselves no doubt make the largest number of medication errors, by misreading, misunderstanding, or forgetting directions, confusing one medicine with another, omitting doses, taking extra doses, and failing to observe dosage schedules and related procedures and precautions.

The continuing development of new drugs is spurred on by the desire of medical researchers to expand the horizons of medicinal therapy as well as by the eagerness of pharmaceutical manufacturers to exploit the enormous potential for profit from drug sales. But it often happens that the first drug developed in a new class has pharmacologic, toxic, or allergic effects that severely limit its usefulness, and may lead to its removal from the market.

For example, troglitazone (Rezulin), the first of a new line of drugs that combat insulin resistance in type 2 diabetes mellitus, caused an unacceptably high incidence of liver damage, and for that reason was withdrawn from the market in March 2000. Newer members of the class, such as

pioglitazone (Actos) and rosiglitazone (Avandia), have not displayed this form of toxicity.

The first antihistamines, released in the 1940s, revolutionized the treatment of allergy, but caused undesirable sedation. In the 1980s a new generation of antihistamines lacking this side effect was inaugurated with terfenadine (Seldane), followed soon after by astemizole (Hismanal). But these agents were eventually found to be toxic to the conduction system of the heart, at serum levels only slightly above the therapeutic range. Moreover, they are metabolized by CYP3A4, and inhibition of this enzyme by concomitant administration of clarithromycin (Biaxin), erythromycin, ketoconazole, itraconazole (Sporanox), or troleandomycin (Tao) can elevate serum levels into the toxic range. Terfenadine and astemizole have now been withdrawn from the market. Antihistamines currently in use include fexofenidine (Allegra), which lacks cardiac toxicity and is comparable to the active molecule of terfenadine after cytochrome enzyme degradation.

Thus, while one kind of research looks for ways to control or mitigate diseases and conditions that are currently untreatable, or to improve on the effectiveness of currently available agents, an equally aggressive line of study seeks to modify or supplant existing drugs so as to reduce or eliminate dangerous or distressing side effects and toxicity.

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