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Specialty Conference

Complications of Antibiotic Therapy

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FOR THE PURPOSES OF THIS SYMPOSIUM the term *antibiotic* will not be strictly defined, but will embrace the commonly administered antimicrobial drugs—that is, the systemic antibacterial agents, the tuberculostatic agents, the sulfonamides, the "urinary disinfectants," and the major antifungal agents. We will be employing the commonly accepted loose interpretation of the word, and we will avoid committing ourselves to a strict pharmacological definition.

Thousands of naturally-occurring antimicrobial agents have been isolated and studied, but the vast majority are far too toxic for therapeutic use. Fewer than 50 agents have general clinical application, and only the more important will be considered in this symposium.

Antibiotics differ from other powerful pharmacological agents in their limited therapeutic range of application; they rarely have any practical beneficial medical properties apart from their specific antimicrobial activity. The clinical use of antibiotics is always accompanied by the risk of complications, which range from minor discomfort to fatal reactions. Antibiotics probably have a greater propensity to cause hypersensitivity reactions than any other class of drugs.

Although the penicillins are among the safest and most effective antibiotics in usual dosage, they cause more hypersensitivity reactions than any other agent. The widespread use of the penicillins coupled with an estimated 5 to 10 percent incidence of reactions, including 100 to 300 deaths per year in the United States,[1] accounts for considerable overall toxicity. Drugs of the antituberculosis group cause the greatest variety of hypersensitivity reactions, as well as direct toxic effects; paraminosalicylic acid (PAS) is perhaps responsible for the most protean toxic side effects, but it rarely causes anaphylaxis. Most of the other groups of antibiotics have more direct

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toxicity, and the agents with a Gram-negative spectrum are mostly very toxic, causing serious complications if administered in excessive dosage. Although the modes of action of most antimicrobial agents have been elucidated in considerable detail, understanding of the mechanisms of their toxic effects is relatively incomplete.

In this symposium we will cover the major complications of antibiotic therapy with relation to specific organ-systems rather than by considering the drugs individually. A very extensive catalogue of the complications of all the microbial agents is provided in Meyler's book.[1] The topic of allergic reactions to antibiotics from a general point of view is covered by Kasik and Thompson in their recent article.[2] A useful general discussion of drug toxicity is provided by Cluff.[3] The participants in this review will be more selective and discursive and will not attempt to mention every known complication.

The complications of antibiotic therapy can be divided into five categories (Table 1):

1. Irritative reactions related to the method of administration of the drug, such as pain and erythema at the site of intramuscular injection, or phlebitis from intravenous administration.

2. Direct toxic actions of many antibiotics occur mainly as a result of excessive accumulation of an agent. The damage may be extremely severe, particularly in the kidney, the inner ear and nervous system, the bone marrow and the liver.

3. Superinfection primarily affects the mouth, the gastrointestinal tract, the respiratory tract and the skin. Broad-spectrum antibiotics admin-

TABLE 1.—*Complications of Antibiotic Therapy*

Complication	*Mechanisms*	*Susceptible Organs*	*Examples*
1. Local effects	Irritation at site of administration.	Muscle	Polymyxin, cephalothin, penicillin, tetracyclines, erythromycin, streptomycin, chloramphenicol, kanamycin, carbenicillin
		Vein	Amphotericin, cephalothin, erythromycin, tetracyclines, nafcillin, carbenicillin
2. Direct Toxicity	Pharmacologic side-effects, or from accumulation due to excessive dosage or decreased excretion.	Kidney	Kanamycin, polymyxin, vancomycin, viomycin, amphotericin, gentamicin, cephaloridine, neomycin, streptomycin, sulfonamides, tetracyclines, nitrofurantoin, capreomycin
		Ear	Kanamycin, gentamicin, streptomycin, neomycin, vancomycin, viomycin, capreomycin
		Bone Marrow	Chloramphenicol, nitrofurantoin, sulfonamides, methicillin, rifampin
		Liver	Erythromycin (estolate), isoniazid, PAS, ethionamide, pyrazinamide, tetracyclines, rifampin, capreomycin, lincomycin
		Bowel	PAS, pyrazinamide, ethionamide, tetracyclines, lincomycins, ampicillin, erythromycin, chloramphenicol, nitrofurantoin, nystatin, griseofulvin, cephalosporins
		Eye	Ethambutol, chloramphenicol, isoniazid, streptomycin, ethionamide, nalidixic acid
		Skin	Tetracyclines, penicillin, sulfonamides, isoniazid, griseofulvin
		Nervous System (A) central	Penicillin, carbenicillin, cycloserine, cephalothin, cephaloridine, tetracycline, isoniazid, nalidixic acid, polymyxins, streptomycin, kanamycin, sulfonamides, nitrofurantoin, griseofulvin, amphotericin

(Continued next page)

Table 1, continued

		(B) peripheral	Polymyxins, neomycin, kanamycin, isoniazid, nitrofurantoin, streptomycin, sulfonamides, amphotericin, griseofulvin, ethionamide, ethambutol
3. Superinfection	Alteration of normal flora.	Gastro-intestinal tract	Tetracyclines, ampicillin, chloramphenicol, penicillin + streptomycin, oral neomycin, oral kanamycin, oral cephalosporins
		Respiratory tract	All broad-spectrum agents
		Skin	Broad-spectrum topical and systemic agents
4. Hypersensitivity	(A) Antigen-antibody reactions.	Whole body— anaphylaxis serum sickness drug fever	Most agents
		Specific organs— dermatitis nephritis pneumonitis hematologic reactions vasculitis	Most agents can affect several organs
	(B) Immunologic phenomena	Serologic (anti-nuclear factor)	Isoniazid
		Collagen-vascular (systemic lupus erythematosus)	Isoniazid, griseofulvin, sulfonamides, penicillin, tetracyclines, PAS
5. Miscellaneous	(A) Genetic abnormality	Blood (various enzyme deficiencies)	Nitrofurantoin, sulfonamides, nalidixic acid, chloramphenicol, PAS
		Bone marrow	Chloramphenicol, sulfonamides, amphotericin
	(B) Fetus	Ear	(?) Streptomycin
		Teeth	Tetracyclines
		Teratogenic effects	Tetracyclines
	(C) Immaturity (neonates)	Brain (kernicterus)	Sulfonamides
		General (gray syndrome)	Chloramphenicol
		Teeth (staining)	Tetracyclines
	(D) Pregnancy	Liver (hepatic necrosis)	Tetracyclines
	(E) Abnormal laboratory finding, without definite organ damage	Abnormal liver function test	Newer penicillins, cephalosporins, lincomycins, gentamicin, nitrofurantoin, nalidixic acid, isoniazid, cycloserine, rifampin
		Increased prothrombin time	Broad-spectrum antibiotics, sulfonamides, PAS
		Decreased prothrombin time	Griseofulvin, rifampin
		Positive Coombs test	Cephalosporins, penicillins
		Hypokalemia	Amphotericin, para-aminosalicylic acid, viomycin
		Hypocalcemia	Viomycin
		Methemoglobinemia	Sulfonamides
		Increased porphyrin excretion	Griseofulvin, sulfonamides
		Interference with chemical tests	Various (for details see section on Alterations of Laboratory Tests, by Dr. Lubran)

istered to a debilitated host are particularly dangerous in this respect, since they may pave the way for unusual opportunistic organisms.

4. Hypersensitivity reactions of various types are some of the most common complications of antibiotic administration. These reactions may involve the body generally, or may affect a single organ. Drug fever is a fairly common side effect, and may occur in the absence of other clinical signs of hypersensitivity. Various patterns of fever may occur, but resolve within a few days of discontinuing the drug. Immunologic disturbances are being recognized with increasing frequency. Thus the development of systemic lupus erythematosus has been attributed to the administration of at least seven antibacterial agents.

5. Certain drug reactions are related to the particular susceptibility of the individual. Unusual reactions may occur as a result of genetic defects leading to enzyme deficiencies, such as glucose-6-phosphate dehydrogenase deficiency. Neonates are susceptible to special side effects of tetracyclines, chloramphenicol and sulfonamides. In pregnancy, women are liable to severe hepatic damage if given tetracyclines, whereas this rarely occurs in the non-pregnant.

Any classification is convenient as a summary, but it will be inadequate in that it fails to provide for the full range of antimicrobial drug side effects, and it will imply a greater understanding of the mechanisms than is at present available. Dr. Beall will enlarge on this theme in the following section where the nature of the allergic reaction will be detailed.

Complications of Antibiotic Therapy—An Overview

GILDON N. BEALL, M.D.*

THE MECHANISMS underlying the occurrence of most adverse drug reactions are not well understood. Many are thought to be allergic, either because some immunological changes have been found or because the drug-induced disease is clinically similar to an allergic disease of man or animals. Such clinical criteria for classification of reactions as "allergic" are unreliable. In addition, allergic reactions to drugs may take unanticipated forms. Several of the organ-specific reactions considered in this review demonstrate that unusual patterns of disease do not rule out an immunological cause. These considerations attest the importance of careful immunological investigations in these patients. With rapid advances taking place in immunology, it is almost certain that the fundamental mechanisms involved in many drug reactions will be clarified in the near future.

In this section, I will offer a classification of drug reactions. This will be followed by some discussion of their frequency and the factors that control individual susceptibility. Then, a more specific discussion of adverse drug reactions which mimic disease usually associated with hypersensitivity mechanisms will precede consideration of the diagnosis, prevention and treatment.

Classification of Drug Reactions

A large proportion of drug reactions involves a pharmacological effect of the drug. Such reactions may be further categorized as *overdosage, intolerance,* or *side effects,* depending largely on the aims and point of view of the physician. The overdosage can be due to an error in dosage or an abnormality in the absorption, distribution, catabolism or excretion of the drug. Identifiable genetic defects account for some of these abnormalities, and more will certainly be found. Disease of organs such as the liver or the kidney may predispose the patient to overdosage or intolerance because of failure to detoxify, catabolize or excrete the drug. Side effects are pharmacologic effects of the drug which are unwanted in the situation at hand. The pattern of pharmacological effects of a drug vary from one patient to the next so that ordinarily unimportant side effects represent severe problems in some patients.

Reactions which are unanticipated from knowledge of the pharmacological actions of the drug are called *idiosyncratic* reactions. The cause of most of these reactions is obscure. Some may be due to enzymic defects, such as the idiosyncratic reactions that occur in patients with glucose-6-phosphate dehydrogenase deficiency. Finally, there are *allergic* reactions to drugs. In these in-

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stances, immunological phenomena can be discovered, providing evidence that the adverse drug reactions are due to hypersensitivity.

Hypersensitivity reactions have been conveniently classified by Coombs and Gell.[4] Type I reactions involve skin sensitizing antibodies or reagins (such as IgE), and include asthma, allergic rhinitis and probably anaphylaxis. The reactions are the result of the release of mediators (such as histamine and the slow reacting substance of anaphylaxis). Serum complement is probably not involved in these reactions. Type II reactions (cytotoxic) involve antigens which are part of or are attached to a cell surface. Interaction of these antigens with specific antibodies with or without the participation of serum complement can damage the cell. Penicillin-induced hemolytic anemia is an example of this type of allergic reaction. Type III hypersensitivity involves antigen-antibody complexes. Such complexes may be deposited far from their site of production or entry into the body. Where they are deposited they excite inflammatory processes, often, but not exclusively, with the participation of serum complement. Serum sickness reactions are usually Type III allergic reactions, but some of the serum sickness-like urticarial reactions induced by drugs are probably Type I allergy.

Type IV hypersensitivity involves sensitized cells (small lymphocytes) which react specifically with antigen without the participation of detectable antibody. The reaction releases substances (lymphokines) capable of producing such effects as cytotoxicity, blastogenesis, and inhibition of macrophage migration. Contact dermatitis due to medicinals falls into this category. The recent development of methods for studying delayed hypersensitivity *in vitro* should clarify the role of this mechanism of hypersensitivity in other drug reactions.

Rates of Reactions to Drugs

An epidemiologic study of adverse drug reactions was made by Smith et al.[5] In 900 patients they found an overall incidence of adverse drug reactions of 10.8 percent. The incidence was much greater in patients who received many drugs than in those who received few. For example, of 35 patients who received from 16 to 20 drugs, 40 percent had some adverse drug reactions. The incidence of adverse drug reactions was also increased in patients with abnormal hepatic or renal function. In patients with blood urea nitrogen over 40 mg per 100 ml, 25 percent had adverse drug reactions. Although Smith et al were able to show that the frequency of adverse drug reactions was greater in patients who had given a history of a previous reaction, they did not find an increased rate of adverse drug reactions in patients with an atopic history (for example, asthma or hay fever). With specific reference to Type I allergy, however, Levine has collected evidence indicating that a reaginic response to penicillin is much more frequent in atopic than non-atopic patients. These patients are also the ones who are more likely to have anaphylactic or urticarial reactions to penicillin.[6]

TABLE 2.—*Rates of Reactions to Antibiotics*

Drug	*Main Adverse Effects*	*Rate %*	*Ref.*
Tetracycline	Nausea, vomiting, diarrhea	6.1	7
Streptomycin	Tinnitus, vertigo, rash	12.5	7
Colistimethate	Renal toxicity, neurologic symptoms	25.1	8
Ampicillin	Erythematous rash	9.5	9-11
Other penicillins	Urticaria	4.5	9
Penicillin G	anaphylaxis	0.004-0.015	12

Rates of Reaction to Antibiotics

Table 2 shows some reaction rates (incidence of unwanted effects) for drugs in which this has been studied carefully. Most agents have not been studied sufficiently to make this data available. It is notable that the reaction rates to ampicillin are not as great as with some other drugs although the total number of penicillin-related reactions is large. It has been reported that the incidence of erythematous eruptions with penicillin is 9.5 percent and this incidence climbs almost to 100 percent if the patient has infectious mononucleosis.[9-11] This interesting association is not well understood at present. The incidence of anaphylaxis from penicillin administration has been estimated at 0.004-0.015 percent and it is said that 9 percent of such reactions are fatal.[12]

Antibiotic Reactions Resembling Diseases Known to be Due to Allergy (Table 3)

Anaphylaxis. The antibiotics listed in Table 3 have all been reported to produce anaphylaxis.

TABLE 3.—*Hypersensitivity Diseases Due to Antibiotics*

Anaphylaxis
- amphotericin
- cephalothin
- demethylchlortetracycline
- methicillin
- nitrofurantoin
- para-aminosalicylic acid
- penicillin
- streptomycin
- sulfonamides (several)
- tetracycline

Asthma
- penicillin inhalation

Serum sickness
- penicillin
- cephalothin
- chlortetracycline
- novobiocin
- streptomycin
- sulfonamides

Stevens-Johnson syndrome
- sulfonamides
  - sulfamethoxypyridazine
  - sulfadimethoxine
- penicillin

SLE *(or* SLE*-like) syndrome*
- griseofulvin
- penicillin
- isoniazid
- para-aminosalicylic acid
- sulfonamides
- tetracycline
- streptomycin

Allergic vasculitis
- sulfonamides
- penicillin
- chloramphenicol
- streptomycin

Penicillin is, of course, the most important because of the frequency of its administration. It is suspected that these reactions are Type I hypersensitivity since positive immediate wheal and flare skin tests can be produced with appropriate antigens, and anaphylaxis is more frequent in atopic than nonatopic persons. Asthma seems to be an uncommon complication; it has been described following inhalation of penicillin in sensitive patients. Presumably, this could happen following inhalation of other antibiotics as well.

Serum sickness reactions have been associated with all the different penicillins and with many other antibiotics. Animal studies of serum sickness have indicated it is a Type III (complex mediated) disease. IgE, IgG and IgM antibody formation has been described in drug-induced serum sickness but there has not been a clear demonstration of antigen-antibody complex deposition in vessels. Some reports have indicated a depression of serum complement in serum sickness which would support the idea that complexes are involved. It is possible that both Type I and Type III hypersensitivity can produce a drug-induced serum sickness. Further studies are needed to clarify this situation.

The Stevens-Johnson syndrome has been repeatedly ascribed to long-acting sulfonamides although some questions about this association still exist. Stevens-Johnson syndrome has been reported following treatment with other sulfonamides and penicillin as well. Nothing is known about the possible immunological basis of Stevens-Johnson syndrome.

A syndrome resembling *systemic lupus erythematosus* (SLE) has been reported after administration of several drugs, including such antimicrobials as penicillin, isoniazid and griseofulvin. Some insight into the mechanism of this phenomenon is provided with the knowledge that isoniazid can denature DNA and the antinuclear factors produced in patients taking isoniazid bind more specifically to isoniazid-denatured than native DNA. The renal pathology in SLE is characterized by deposits in the glomerular basement membrane, at least some of which are DNA-anti-DNA antigen-antibody complexes (Type III allergy). It is likely that the drug-induced SLE syndromes will be found to have similar mechanisms of pathogenesis when appropriate investigations are performed.

Allergic vasculitis or polyarteritis nodosa has been described in patients receiving penicillin and sulfonamides and attributed to those agents. Chloramphenicol and streptomycin have also been implicated as causes of polyarteritis. The acute vasculitis of experimental serum sickness (a Type III reaction) has been put forward as a possible model of polyarteritis. However, drug-anti-drug complexes have not yet been demonstrated in the human vascular lesions of polyarteritis.

Diagnosis of Adverse Drug Reactions—Immunological Test Procedures

Where reaginic or IgE mediated allergic reactions (Type I reactions) are involved, a skin test using an appropriate antigen will produce a

wheal and flare reaction in 15 minutes. Many adverse drug reactions, however, almost certainly do not involve IgE antibodies and skin tests are not helpful. In addition, the choice of an appropriate antigen or hapten is critical. Skin testing for penicillin allergy requires the use of two different kinds of materials, penicillolyl-polylysine and a minor determinant mixture. Neither of these materials is readily available. The penicillolyl hapten is apparently the major antigenic determinant of penicillin G, but a group of haptens apparently including benzylpenicillin itself are also important. Levine's studies indicate that one can predict anaphylactic sensitivity in patients who have positive skin test reactions to both mixtures.[13] It is hoped that these materials will be generally available in the near future.

Skin testing can be hazardous; preliminary scratch testing and adequate dilution of the suspected material are mandatory, particularly if the testing is being done to determine the cause of an anaphylactic reaction. If no personal experience or published information exists about the material for which skin testing is being contemplated, then the procedure should be regarded as a clinical experiment and subjected to the kinds of scrutiny reserved for experimentation.

It would be desirable if the biologic phenomenon of skin testing could somehow be transplanted to a test tube. An approach to this has been made by the use of techniques in which leucocytes from sensitized patients are challenged with antigen *in vitro* and the release of histamine into the supernatant fluid is measured. This system detects reaginic antibodies. There is some evidence that it is useful in penicillin hypersensitivity. Some workers have used mast cells or basophils from animals in similar *in vitro* tests which have been monitored either by histamine release or by observation of degranulation of the amine-containing cells. To date, the results of these procedures have not been sufficiently reliable to make them useful as diagnostic tests. Another technique which has been investigated depends upon the transformation and blastogenic change of leucocytes *in vitro* following exposure to drugs which have produced reactions *in vivo*. Further study of this reaction is definitely needed.

Patch tests are an easy and reasonably reliable way of detecting contact allergens. If the material is a liquid it should be used undiluted. If a solid, it should be dissolved in propylene glycol in order to give a nontoxic concentration. The skin is then cleansed with acetone, and the drug, on a patch, is put on the skin and left for two or three days to see if it produces a miniature reaction of the contact dermatitis type from which the patient is suffering. A similar patch using only the solvent is placed on a nearby area of skin to serve as a control.

Some drugs can be fixed to red cells and the resulting combination used for a hemagglutination test. Such studies usually demonstrate either IgG or IgM type antibodies. These antibodies may have great significance in certain types of hemolytic anemias but their titers may be unrelated to the occurrence of adverse drug reactions in other tissues.

Clot retraction tests are useful in patients suspected of having drug-induced thrombocytopenic purpura. The blood of the thrombocytopenic patient is combined with normal blood (containing a supply of platelets) in two different tubes. A saline solution of the drug is added to one and saline solution only to the other tube. Clot retraction is then examined. Inhibition of clot retraction serves as evidence of an antiplatelet-drug factor in the patient's serum. This test seems to work nicely with quinidine-induced thrombocytopenia. It is not completely reliable in other instances of apparently drug-induced thrombocytopenia, possibly because not all such thrombocytopenic reactions are immunologic in nature.

If no *in vitro* or *in vivo* test procedure is available to verify sensitivity to a drug, it may be desirable, under certain circumstances, to give the patient a test dose. Such test doses are very dangerous. Testing should only be done for a vitally needed drug where there is no substitute, and testing should be postponed until the patient has fully recovered from the initial reaction. The initial dose should be in the microgram range if it is given orally or in the nanogram range if it is given parenterally. It should be recognized that this sort of procedure may cross the vague boundary between medical care and clinical experimentation.

Avoidance of Adverse Drug Reactions

There are some obvious points. Dangerous drugs should be avoided. A careful history, including a history for the specific drug which one plans to use, should be obtained from the patient, and one should believe the patient's state-

ments. One should be aware of drugs to which a genetic predisposition to intolerance occurs and look for evidences of that predisposition. An estimate of renal and hepatic function is desirable. If a reaction develops, the offending agent should be removed. Sometimes manifestations of the reaction can be suppressed with antihistaminics or corticosteroids. Desensitization should be attempted only if there is a life-threatening need for the particular drug in question. The procedures and schedules to follow in performing desensitization are really not as important as the careful follow-up of the patient and observation of reactions as the drug is administered. If the patient has had an anaphylactic reaction in the past, he will probably again have an anaphylactic reaction during the "desensitization." This, however, can be controlled and the effects minimized by the use of antihistamines, epinephrine, steroids, and continued administration of the antigen. In any case, this procedure is very seldom necessary if alternate drugs or forms of treatment are carefully considered.

Renal Complications

RICHARD J. GLASSOCK, M.D.*

RENAL DISEASE, with or without functional impairment, may be complicated by infections, and, of course, diseases of an infectious nature are also frequently accompanied by abnormalities in renal function. Clinicians are frequently confronted with a therapeutic dilemma in the treatment of serious infections with potentially nephrotoxic agents. There are several approaches to this dilemma. First, one may avoid a potentially nephrotoxic agent, even though alternative drugs may be less effective. Second, a potentially nephrotoxic agent may be used with appropriate reduction of dosage. Third, a beneficial agent may be continued in spite of impaired renal function. If the latter course is adopted, the toxic effects at sites other than the kidney must be considered.

No formula can be devised which can answer each individual clinical problem. The choice among these and other approaches depends upon a number of factors, most notably the nature and severity of the infection, the extent of renal disease underlying the infection, the character of non-renal toxicity of the agent employed, and the availability of effective alternative drugs. One extremely important and often very difficult question to answer is whether or not renal abnormalities observed during treatment with potentially nephrotoxic agents are the consequence of the infection or the result of the nephrotoxic drug itself. Examples of situations where this question arises include glomerulonephritis associated with subacute bacterial endocarditis, consumption coagulopathy associated with renal cortical necrosis in the presence of Gram-negative sepsis, and necrotizing papillitis in diabetic subjects with catheter-induced septicemia.

As a general rule, nephrotoxic antibiotics can be used safely and effectively if an appropriate alteration in dosage is observed when renal function is decreased or diminishing.[14] Unless the renal abnormalities observed during therapy can be clearly related to the effects of the agent itself, it is often best to continue the drug if no effective alternative therapy is available.

Table 4 lists some of the antibiotic agents which have been associated with renal complications. The sulfonamides were the first antimicrobial agents in which significant renal problems were encountered.[15] The use of sulfapyridine, sulfathiazole and sulfadiazine in the early 1940's was associated with the finding of crystalluria. The crystallization of sulfonamides in the renal tubule is dependent upon their concentration, and therefore upon the state of hydration of the individual, the urine flow and the urine pH. Extremely acid urine favors the precipitation of most of these agents. High concentrations of the older, less soluble sulfonamides could cause direct toxic tubular injury, and acute renal failure. With the use of modern sulfonamides, hypersensitivity reactions involving the kidney are more common. These reactions include diffuse interstitial nephritis, diffuse glomerulonephritis, and necrotizing arteritis.[15] There does not appear to be any difference among the individual sulfonamides in their propensity to cause this type of abnormality.

The penicillins, including the semisynthetic penicillins, may cause hypersensitivity reactions, particularly of the diffuse interstitial nephritis va-

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TABLE 4.—*Antimicrobial Agents Associated With Renal Complications*

Major Direct Nephrotoxicity	*Minor Direct Nephrotoxicity*
Kanamycin	Gentamicin
Neomycin	Streptomycin
Colistimethate	Sulfonamides
Polymixin B	*Cephalothin
Bacitracin	*Rifampin
Vancomycin	*Capreomycin
Amphotericin	
Cephaloridine	
Viomycin	
Hypersensitivity	*Anti-Anabolic*
Penicillin	*Tetracycline (except doxycycline)
Semisynthetic Penicillins	
Sulfonamides	
Nitrofurantoin	
Para-aminosalicylic acid	

*May cause rise in BUN without other evidence of nephrotoxicity.

riety. The penicillin derivative most frequently incriminated in production of interstitial nephritis is methicillin, and there have been reports of acute renal failure following large doses and prolonged therapy with methicillin.[16] Occasionally, hyperkalemia may develop in patients with oliguric renal failure following treatment with potassium penicillin G in large doses, as this preparation contains 1.6 milliequivalents of potassium per million units.

The cephalosporins have also been associated with reactions of the diffuse interstitial nephritis variety. Cephaloridine has caused acute renal failure when employed in doses of over 6 grams a day.[17]

The aminoglycoside antibiotics, including streptomycin, kanamycin, gentamicin and neomycin, are potentially nephrotoxic agents. The parenteral use of streptomycin, in the early days of anti-tuberculous therapy, was commonly associated with albuminuria, azotemia and diminished glomerular filtration rate in patients receiving more than 4 grams per day.[15] Nephrotoxicity may have been caused partially by the impurities in the early lots of streptomycin. Recent experience has indicated that this agent has probably a very minimal degree of nephrotoxicity when employed in conventional dosage.[15] However, streptomycin may act synergistically with other aminoglycoside antibiotics in inducing nephrotoxicity, particularly when renal function is already impaired. Kanamycin in doses of 25 mg per Kg of body weight or larger, frequently, if not universally, produces urinary abnormalities, with proteinuria, hematuria, casts and the pathologic changes of proximal tubular necrosis. Acute renal failure has been an uncommon event in instances of kanamycin therapy. However, it may occur at high doses and may also be aggravated by concomitant use of other aminoglycoside antibiotics. Kanamycin has been demonstrated to cause decreases in glomerular filtration rate, renal blood flow and maximum urinary osmolality.[18] These abnormalities are entirely reversible and their development is not necessarily an indication to discontinue therapy, particularly if the infection is severe and kanamycin is the preferred agent of treatment. Neomycin, given orally in doses of 4 grams or greater to patients with hepatic and renal disease, may result in the accumulation of significant blood levels which are potentially ototoxic as well as nephrotoxic.[19] This toxicity has occurred in as many as 25 percent of such patients receiving a dose of 8 grams or more a day. Gentamicin has a degree of nephrotoxicity comparable to streptomycin and not as severe as that of kanamycin or neomycin.[20]

The polypeptide antibiotics, polymyxin B and polymyxin E (colistimethate), are nephrotoxic, particularly at higher dosage. Polymyxin B may induce tubular alterations and decrease creatinine or inulin clearance. Again, this effect is potentiated by other nephrotoxic agents. Minimal urinary abnormalities are not necessarily a contraindication to continued therapy. Adverse renal reactions, including acute renal failure, occur in about 20 percent of patients.[8] Most of the reactions are readily reversible upon discontinuance of the agent. Renal complications usually occur in the first three or four days of therapy. A dosage calculated on a weight basis may result in overdosage for patients with above average weight. Dosage based on square root of weight appears to be better.[8] A seldom used antibiotic, vancomycin, has been associated with nephrotoxicity. This was particularly true with the early preparations. Many centers use this agent as their treatment of choice for staphylococcal septicemia in patients on hemodialysis programs, a situation where one need not fear the nephrotoxicity but only the neurotoxicity.

Tetracyclines given in therapeutic dosage interfere with protein anabolism in man as well as within the bacterial cell. The use of these agents in azotemic patients may result in a dramatic worsening in azotemia and clinical condition.[21]

Since most of the agents, with the exception of chlortetracycline, have a prolonged half-life in the serum of uremic patients they should not be used when patients are significantly azotemic.[14] It has recently been shown that the long-acting tetracycline, doxycycline, can be given safely in the presence of azotemia; this is the only tetracycline now recommended for treatment of susceptible infections in patients with renal impairment.

Outdated tetracycline which has been exposed to a warm, moist temperature at a low pH may develop high concentrations of the breakdown products anhydrotetracycline and epianhydrotetracycline. The Fanconi syndrome, sometimes accompanied by azotemia, has been reported with the use of tetracycline preparations containing these breakdown products.[22] Since citric acid has been omitted from most of the formulations of tetracycline, this phenomenon is a disappearing entity in clinical medicine.

A major hazard of therapy with amphotericin B is the development of nephrotoxicity, manifested by the formation of casts, decreased concentrating ability, defective acid excretion, diminished glomerular filtration rates and hypokalemia. In rare instances, continued use of amphotericin B in the face of progressive azotemia has caused chronic irreversible interstitial nephritis.[23] Although amphotericin B therapy may be associated with a depression of glomerular filtration rate by as much as 80 percent, normal renal function will usually be regained upon discontinuance of therapy. Full recovery is less likely when the total course of amphotericin therapy exceeds 5 grams.

Nitrofurantoin has been associated with interstitial nephritis which appears to be reversible on discontinuance of therapy, and paraminosalicylic acid has also, on occasion, been associated with hypersensitivity reactions.

Obviously, those agents which depend upon glomerular filtration rate for their excretion will be retained in the blood of patients with reduced renal function and therefore the dosage must be diminished to avoid potentially toxic serum levels. Recommendations for the use of antibiotics in renal insufficiency have been reviewed recently.[14,24] In general, antimicrobial agents can be divided into three groups with respect to dosage modifications for patients with abnormal renal function. The penicillins, cephalothin, erythromycin, lincomycins and chloramphenicol require little or no reduction in dosage. Since some agents in this group have prolonged half-life in renal failure, high dosage should be avoided. The aminoglycoside and the polypeptide antibiotics, kanamycin, neomycin, gentamicin, streptomycin, vancomycin, polymyxin and colistimethate, are largely excreted by the kidney and require major modifications in their dosage in renal insufficiency. A useful formula for kanamycin therapy is based on precise correlations of antibiotic half-life and serum creatinine levels. A loading dose of 7 mg per kg of body weight followed by a repeat of the same dose every third half-life will achieve therapeutic blood levels without risk of serious toxicity.[25] The kanamycin half-life in hours can be calculated by multiplying the serum creatinine by 3. Thus, a patient with serum creatinine of 10 mg per 100 ml would receive a dose of 7 mg per kg of body weight every 90 hours to maintain therapeutic blood levels. Similar relationships for gentamicin, polymyxin B and colistimethate may be obtained by studying the half-life of these agents in uremic subjects.

Finally, certain antibiotics should not be used if renal impairment is moderate or severe. These agents have significant toxicity and alternate drugs of equal efficacy are available. Included in this group are tetracyclines (with the exception of doxycycline) for the reasons cited, nitrofurantoin because it does not achieve effective tissue levels and it is effective as a urinary antiseptic only when renal function is relatively normal, and cephaloridine because of its decided potential for nephrotoxicity.

Gastrointestinal Complications

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ALTHOUGH THE gastrointestinal tract bears much of the brunt of the complications of antibiotic treatment, most reactions are not of a serious

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nature.[26] Stomatitis and glossitis occur with a high frequency, especially with the use of broad-spectrum antibiotics, and one often finds that superinfection with Candida albicans is responsible. Candida esophagitis it not an uncommon problem, and this may be a more elusive diagnostic problem than oral Candidiasis. Cessation of antibiotic treatment is often all that is required in a mild infection, but treatment with oral nystatin is very effective in the management of an established infection.

There are very few antibiotics and antibacterial agents which cannot be included in the list of those that may, on occasion, produce anorexia, nausea, or vomiting. These symptoms are not only distressing to the patient, but in addition they may produce diagnostic confusion for the physician who, for example, may be treating a patient with pyelonephritis and vomiting. Some of the more notorious offenders include the tetracyclines, nitrofurantoin, erythromycin and the anti-tuberculosis drugs such as para-aminosalicylic acid, pyrazinamide and ethionamide. In some series the latter drug is blamed for upper gastrointestinal symptoms of a significant nature in as much as a third of the patients. In most instances it is possible to administer these drugs successfully by advancing the doses in a step-wise fashion and by directing that they be taken with meals. Antacids are sometimes used concomitantly with an antibiotic to quiet a complaining stomach, but it should be kept in mind that aluminum-containing antacids bind tetracycline drugs, thus preventing both the symptoms and the therapeutic effectiveness of the drug. These gastric symptoms are often attributed to "gastritis," but not very much is known about the mechanisms involved. Because of the high frequency of occurrence and the early onset with therapy, changes in the bacterial flora and hypersensitivity are not satisfactory explanations. A direct toxic effect of the drugs is likely, but its precise nature is unknown. On rare occasions, nausea, vomiting and epigastric distress accompanying the administration of a sulfonamide may actually be the result of pancreatitis.[27]

Diarrhea is another frequent complication of antibiotic treatment, presumably due to the proliferation of antibiotic-resistant bacteria and fungi. As an example of this, the frequency of isolation of Candida from rectal swabs was studied in a control group and in patients after at least four days of chlortetracycline. Whereas approximately 6 percent of the control group was found to have Candida in the rectal swabs, after four days of broad-spectrum therapy the incidence was approximately 70 percent. A similar study was also performed after penicillin administration: here the incidence after four days was only 14 percent.[28] It is clear that Candida itself may be a cause of an enteritis, but this is uncommon. The majority of the cases in which diarrhea occurs with antibiotics are probably associated with a shift in the bacterial flora, but again its mechanism is not well understood. Occasionally, severe diarrhea occurs in association with an overgrowth of resistant species of Proteus and Pseudomonas in the bowel; similarly, resistant Staphylococcus aureus strains may become predominant and produce a serious problem. Lincomycin is of particular interest since it has caused diarrhea in 5 to 50 percent of patients; this at times may be very severe, and can persist for several weeks after discontinuance of the antibiotic. Clindamycin appears to be less toxic in this respect.

In post-surgical patients the problem of staphylococcal entercolitis is not rare, although in my experience it seems less frequent now than in the past. In early series a mortality rate as high as 50 percent in patients with staphylococcal entercolitis was reported. The broad-spectrum antibiotics such as the tetracyclines are the most frequently associated predisposing factors, but combination therapy of any type that is used in so-called "gut sterilization" can produce the problem, and even penicillin alone has been associated with this entity. The lesion itself is a superficial necrosis of large areas of the intestinal mucosa, probably produced by a staphylococcal exotoxin. The patients usually manifest this illness with a diffuse watery diarrhea, but in about 10 percent bloody stools, shock and abdominal pain are prominent features.[29] The diagnosis must be made promptly on the basis of the clinical picture and a gram-stain of the stool, and therapy instituted immediately. The gram-stain of the stool usually will show sheets of staphylococci. The use of methicillin or vancomycin by mouth is quite effective and has greatly reduced the mortality rate of this disease.

Another interesting complication of antibiotic

therapy related to the intestine is malabsorption brought about by neomycin, kanamycin or para-aminosalicylic acid. Most of the work has been directed toward elucidating the mechanisms associated with neomycin malabsorption, and several factors have been implicated. Alterations in bacterial flora constitute a major factor, but the mechanism by which the change in flora induces malabsorption is uncertain. Changes have been noted in the small intestinal mucosa which resemble those of non-tropical sprue, but are much less severe, and are readily reversible with cessation of treatment. A defect in the hydrolysis of fats has also been demonstrated, apparently due to inhibition of pancreatic lipase.[30] Although this complication of antibiotic therapy is an intriguing one, it really does not represent a common clinical problem.

Hepatic Complications

Many types of drugs, including antibiotics, may produce hepatic dysfunction. These reactions are generally thought to be a result of sensitization, although it is recognized that certain features are difficult to explain on the basis of classic anaphylactic or delayed hypersensitivity. The various types of hepatic dysfunction which result from drugs have been classified into the hepatocellular, hepatocanalicular and canalicular varieties.[31] With the hepatocellular variety, liver function tests performed on the serum mimic those seen in viral hepatitis with transaminase values in excess of 300 units, and commonly over 1000 units. The alkaline phosphatase in these cases is usually less than 15 Bodansky units, a level which is usually associated with non-surgical types of liver disease. The histologic findings are those of diffuse hepatocellular necrosis and inflammation, features that cannot be distinguished from those seen in viral hepatitis. The mortality rate is significantly higher in this group than in the remaining groups, and it varies with the particular agent involved. Among the antibiotics that may be placed in this group are isoniazid, pyrazinamide, ethionamide, and tetracycline. Some of the sulfonamides may also produce this picture.

One of the most thoroughly studied drugs which may cause the hepatocanalicular variety of hepatic dysfunction is chlorpromazine. The mortality rate from hepatic dysfunction resulting from drugs in this category is much lower than in the hepatitis-like group, and biochemical changes mimic those found in obstructive jaundice. Histologically, one expects to find bile stasis and inflammation of the portal triads without a great deal of hepatocyte necrosis. In most instances it is not possible by liver biopsy to distinguish between this type of drug-induced jaundice and extra-hepatic obstruction. Antibiotics which may produce this type of reaction would include the estolate ester of erythromycin, as well as some of the sulfonamides.

The last category, the canalicular variety of hepatic dysfunction, is produced by methyl testosterone and the anabolic steroids. Liver function tests performed on the serum reveal only mild abnormalities of the transaminase and alkaline phosphatase values, and liver biopsy reveals only cholestasis.

Two of the antibiotics mentioned above deserve further comment. In contrast to many of the other antibiotics where sensitization appears to be the major factor, a dose relationship also has been demonstrated with tetracycline. The administration of large doses of tetracycline to women in the third trimester of pregnancy, particularly those with pyelonephritis, or to patients with renal insufficiency can cause hepatic failure. The histopathologic features of this drug reaction are very characteristic, with fine fat droplet deposition in the liver cells. In contrast to the situation a decade ago, a great variety of potent antibiotics is now available, and because of the complications which can occur with high dose levels of tetracycline, there is no longer any indication for treating patients with more than two grams of this antibiotic a day. Erythromycin estolate may produce abnormal transaminase values in 10 to 25 percent of patients treated with this drug, and in an additional 4 percent a condition resembling obstructive jaundice may develop. However, the effect appears to be specific for this ester, and hepatic complications associated with the erythromycin base have not been reported.[32]

Pulmonary Complications

MATTHEW O. LOCKS, M.D.*

THE LUNGS ARE particularly susceptible to superinfection following the administration of antibiotics, although the presence of abnormal bacteria in the sputum must be critically evaluated to distinguish simple colonization from infection. The lungs are relatively immune to the direct toxic effects of excessive accumulations of antimicrobial agents, but 12 antimicrobial agents have been clearly implicated as inducing some form of lung disease.[33] The pathogenic mechanisms responsible for antimicrobial-induced lung reactions originally had been considered as one or more forms of hypersensitivity reactions. However, hypersensitivity alone cannot fully account for the spectrum of drug-induced lung diseases. It is possible that the idiosyncratic reaction, as well as one or more of the allergic reactions, is operative in some, if not all, of the clinical syndromes of antimicrobial-induced lung diseases.

These clinical syndromes include, in rank of increasing frequency of occurrence, systemic lupus erythematosus, polyarteritis, pulmonary eosinophilia, and asthma. In a recent review of patients seen at certain hospitals in New York City, up to 12 percent of the cases of systemic lupus erythematosus were found to be drug-induced.[34] Since patients with systemic lupus erythematosus have a higher propensity for drug reactions, it is possible that in some of them the disease process may have preceded the administration of the drug. However, in others, the systemic manifestations of lupus erythematosus and the presence of antinuclear antibodies were clearly related to the drug. The pulmonary manifestations of the patients with antimicrobial-induced systemic lupus erythematosus appeared in three basic patterns, with some degree of merging of these patterns in individual patients. In one group, the dominant gross pathologic presentation was the involvement of the serous membranes within the thorax. Accordingly, pleuritis, frequently with effusion involving both lungs, and pericarditis with or without significant effusion were the major findings on physical and radiologic examinations. Although the patients were severely ill and had high fever, withdrawal of the suspected agent and the administration of corticosteroids were accompanied in large part by a rapid recovery.

A second group showed changes primarily within the pulmonary parenchyma, with recurrent bouts of cough, dyspnea and chest pain. Physical examination and radiologic findings were consistent with changes suggesting pneumonia, pulmonary infarction, or pulmonary edema. Despite the presence of severe illness, these patients also showed an excellent response, with recovery after corticosteroid therapy. The third group of patients did not fair so well. The pulmonary involvement included a diffuse interstitial infiltration of both lungs with resultant restrictive dysfunction without obstructive airway disease. This was manifested clinically by dyspnea, hyperventilation, poor respiratory excursions of the chest wall and diaphragm, and hypoxemia. Although symptoms were improved by corticosteroid therapy, restrictive dysfunction of the lungs persisted.

A necrotizing vasculitis of the lung, usually as a part of systemic vasculitis, has been associated with the administration of antimicrobial agents.[35] There are sufficient clinical and experimental examples of exacerbations and remissions of the process related to administration and withdrawal of the drug to strongly suggest a causal relationship. The respiratory manifestations of vasculitis frequently include destructive lesions in the upper respiratory tract before the finding of pulmonary lesions. Subsequent changes in the lower respiratory tract resemble pneumonia, pulmonary infarction, pulmonary abscess, and nodular densities of varying size. The constellation of findings included in the description of Wegener's granuloma, with lesions in the upper and lower respiratory tract, as well as the kidneys, is frequently associated with a history of antimicrobial hypersensitivity and the repeated administration of various antimicrobial agents.

Of increasing interest in recent years has been the pulmonary disorder described as pulmonary eosinophilia. Although the clinical syndrome may be causally related to various etiologic agents including parasitic infection, it has also been clearly demonstrated to be drug-induced. Characteristically, the illness is abrupt in onset, with

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shaking chills, high fever, dyspnea and a cough productive of mucoid sputum. The patient is visibly in respiratory distress with tachypnea, and rales are generally heard in both lungs, but wheezing is notably absent. Occasionally there is a cutaneous eruption. Peripheral eosinophilia is present to variable degree. Chest x-ray films generally show scattered broncho-pneumonic infiltrations with an occasional pleural effusion. Generally, rapid recovery is achieved when the offending drug is discontinued. Infrequently, the illness can persist for several weeks, but fortunately it is responsive to corticosteroid therapy. The most common drug causing pulmonary eosinophilia at present is probably nitrofurantoin.[36] Penicillin, sulfonamides and para-aminosalicylic acid have also been implicated.[37-39]

Perhaps the most common drug-induced disorder is asthma. This can present as an immediate hypersensitivity reaction purely in an isolated form or as part of a generalized anaphylactic response. Delayed types of asthmatic reactions to antibiotics have also been seen, occurring after repeated administration of the drug. Penicillin, tetracycline, erythromycin, neomycin, streptomycin, griseofulvin, cephaloridine and ethionamide have been associated with one or both types of asthmatic reactions.[40]

Drug-induced disorders of the respiratory tract can occur in circumstances that challenge one's diagnostic acumen. This is especially true when the route of administration of the offending agent may be deceptive. For example, a woman had recurrent episodes of pulmonary eosinophilia which were eventually found to be caused by a vaginal cream containing sulfanilamide.[41]

When evaluating a patient with a respiratory disorder who is receiving or has received a drug, either for treatment or for a diagnostic study, one's index of suspicion should be sufficiently aroused to answer the question "Could a drug (or drugs) be the causative agent?" The history of possible exposure to a drug coupled with the finding of non-specific associated findings such as rash, eosinophilia, or thrombocytopenia suggests the likelihood of a drug-induced disorder. Withholding all drug therapy may also yield the correct diagnosis. By the use of specific testing procedures, including (if considered safe) a provocative challenge, the causative agent or agents may be identified.

Neurological Complications

JAMES R. NELSON, M.D.*

THE NEUROLOGICAL COMPLICATIONS of antibiotic therapy are many and varied. Some are produced by a mechanism similar to that responsible for the antimicrobial action of these agents—that is, effects on cell wall synthesis or integrity, interference with energy production by inhibiting oxidative enzymes, or interference with pyridoxine to simulate a vitamin deficiency state.[42,43] Still other effects, such as slowed nerve conduction and a myasthenic-like state, may be due to a reversible interference with acetylcholine release, perhaps through a disturbance of calcium metabolism.

Although the ototoxic effects of antibiotics are by far the most important neurological complications, this review will progress in an orderly fashion from cerebral through peripheral nerve effects.

Penicillin Encephalopathy. A remarkable syndrome of central nervous system hyperexcitability may result from excessively high blood levels of penicillin, usually after administration of more than 60,000,000 units in normal subjects, but occasionally after less than 20,000,000 units a day in the presence of renal failure or preexisting cerebral disease.[44]

Penicillin is one of the most irritating substances when applied directly to cerebral cortex and often is the drug of choice for producing restricted experimental seizure foci. Injection of less than 2000 units into the cortex of monkeys may produce listlessness and intense myoclonic seizures within 3 minutes.[45] Study of single crayfish stretch receptors showed that penicillin decidedly reduced membrane potential differences and thus increased excitability.[46] This effect was dose-dependent and similar to that of ouabain or lithium and possibly resulted from sodium pump deactivation.

Clinically, penicillin encephalopathy is char-

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acterized by delirium or coma with intense myoclonic and generalized seizures. Forty million to eighty million units given intravenously to 17 patients induced seizures in only one patient.[47] However, numerous cases of encephalopathy with less than 20,000,000 units have been reported in the presence of renal failure. In one case a close correlation was demonstrated between the neurological symptoms and the cerebrospinal fluid levels of penicillin.[48]

In the presence of renal failure it has been recommended that 10,000,000 units be given once and then blood levels determined as a gauge for subsequent doses.[14,50] Because passage of penicillin from the blood into the cerebrospinal fluids is slow, single intravenous doses probably are less neurotoxic than continuous infusions.

Of the other antibiotics, cycloserine in doses of greater than one gram a day is particularly likely to cause myoclonic jerking and other seizures.[42,43] These effects are rapidly reversible. Convulsions are also reported after amphotericin B.[42] Cycloserine may also produce dyskinesias, paresis, tremors and dysarthria, which possibly may be due to interference with pyridoxine metabolism. Transient speech disturbances and other untoward neurological reactions have also been reported with polymyxin B and colistimethate.

Aside from the above acute effects, a potential impairment of memory in humans should be anticipated with development of future antibiotics such as puromycin. This agent is a powerful inhibitor of protein synthesis. Evidence to date indicates that long-term storage of memory traces ("engrams") is dependent upon RNA synthesis, and recently Flexner has reported impaired memory in mice with bilateral puromycin injections into the hippocampal complex, the structure most concerned with memory in man and several lower animals.[49]

Ototoxicity of Antibiotics. These effects are among the most common and serious side effects of antibiotic usage, with potential for severe deafness and severe vestibular loss. Fortunately, many of these effects can be avoided with careful selection of antibiotic dosage and attention to early symptoms of inner ear dysfunction. This topic has recently been reviewed in great detail, and a list of ototoxic antibiotics is shown in Table 5.[50] Although previous reports have suggested that the site of toxicity may be the end-organ, cochlear nerve or central nuclei, recent

TABLE 5.—*Action of Ototoxic Drugs on Hearing and Equilibrium*

Drug	Effect on		
	Vestibule	*Cochlea*	*Kidney*
Streptomycin	+++	+	+
Dihydrostreptomycin	+	++++	+
Neomycin	+	++++	+++
Kanamycin	+	+++	+++
Vancomycin		+++	+
Viomycin	+++	++	++
Framycetin		++++	
Gentamicin	++		++
Colistin	++	+	++

Meuwissen and Robinson[50]

evidence suggests that the loss is overwhelmingly concentrated at the hair cell level of the cochlea or vestibular apparatus, with the infrequently observed central lesions being secondary to transynaptic degeneration.[51]

The predilection of the inner ear hair cells for such damage is unexplained although factors related to the peculiar supply of oxygen to the hair cells or the slow removal of antibiotics from the endolymphatic space may be most important. The hair cells of the cochlea show an abundance of mitochondria and oxidative enzymes which degrade glucose.[50] Because of the peculiar anatomical fact that oxygen must be delivered to the hair cells from the stria vascularis through diffusion across the endolymph, perhaps a relatively greater deprivation of oxygen than seen in other tissues may occur when antibiotics contact the hair cells. Streptomycin combines with a surface component of bacterial walls to increase their permeability, leading to cellular swelling and disruption. Such findings in mitochondrial membranes of the cochlea are prevalent early.[52] Inhibition of protein synthesis may also lead to disruption of the cell.

Clinically, the toxicity may appear gradually with minor tinnitus and high tone hearing loss but if these symptoms are neglected, rapid and severe deafness may result. Since streptomycin, kanamycin and neomycin may be cleared from the endolymph very slowly, cellular damage may progress even though administration of the drug has ceased. Simultaneous renal damage may also prolong the toxic effects. Careful evaluation of renal function before administration of these drugs is obviously essential. Fortunately, many of the drugs that produce greater cochlear than

vestibular loss have limited usefulness. Dihydrostreptomycin has been removed from use and neomycin has essentially been restricted to only topical or oral use; an inflamed gastrointestinal tract or denuded skin surface may allow excessive absorption and toxicity may follow oral neomycin therapy.[52]

Kanamycin should be restricted to less than 1 to 2 grams a day, and in the presence of renal failure a total course of less than 5 grams has been associated with complete deafness. Vancomycin is used infrequently and has been largely replaced by the newer penicillins. The vestibular symptoms from the aminoglycosides, and particularly streptomycin, may be acute, with severe vertigo and dysequilibrium. An early symptom, before these severe side effects emerge, may be slight postural vertigo with rapid head movements. If administration of the antibiotic is stopped at this time, additional severe loss may be prevented. The usual dose of streptomycin of 1 gram a day may be given for over a month without difficulty but doses of 2 to 3 grams a day will invariably be associated with symptoms within three or four weeks. The ototoxicity of gentamicin is almost exclusively vestibular.[53]

Ocular Toxicity. Fortunately, effects of antibiotics on the visual system are minimal but toxic retinopathy and optic neuritis have both been reported in association with chloramphenicol and streptomycin therapy.[42,43] The cause and effect relationships are not clear, with underlying malnutrition possibly playing a role. Isoniazid and ethambutol have also been implicated in optic neuritis.

Peripheral Neuropathy. This complication may occur with many of the previously discussed antibiotics including dihydrostreptomycin, streptomycin, neomycin, kanamycin, chloramphenicol, polymyxin B, colistimethate, nitrofurantoin, sulfonamides, amphotericin B and griseofulvin.[42] The syndrome is that of typical metabolic polyneuropathy with symmetrical stocking-and-glove impairment of both motor and sensory nerves. Onset usually will be gradual, with early paresthesias. These are particularly common about the mouth with streptomycin, neomycin, kanamycin, polymyxin and colistimethate. These paresthesias may not necessarily indicate development of peripheral neuropathy, although with nitrofurans and griseofulvin peripheral neuropathy usually follows.

Isoniazid also produces peripheral neuropathy. This effect has been more extensively studied than with other agents and a clear-cut relationship to pyridoxine metabolism has been established. It is hypothesized that INH combines with pyridoxine to form a hydrazine compound that replaces pyridoxal phosphate in several enzyme systems of oxidative metabolism, including amino-acid decarboxylase and several transaminases. A cerebral syndrome with acute delirium has also been noted with isoniazid and perhaps the metabolic cause is similar to that for neuropathy.

Myasthenic Syndrome. One of the most interesting and fortunately rapidly reversible complications of antibiotic therapy is a syndrome of severe weakness of the respiratory muscles and limbs resembling myasthenia gravis but with additional features of pupillary unreactivity and visual changes. Almost 90 percent of the 123 reported cases have appeared in the postoperative period where drugs implicated as synergists to neuromuscular blocking agents such as ether, tubocurarine or other agents have been used.[54] The myasthenic syndrome occurs after administration of neomycin, streptomycin, kanamycin, polymyxin, bacitracin, dihydrostreptomycin, colistimethate and gentamicin. There appears to be little relationship to the route of administration, and the syndrome has been reproduced by a single dose of colistimethate in one patient.

Antibiotics are thought to produce a deficient release of readily releasable acetylcholine, thus accounting for the enhanced muscular response to higher frequency stimulation. Also, this syndrome is quickly reversible by calcium administration, which has been shown to enhance the liberation of acetylcholine. The presynaptic origin of the syndrome is further substantiated by the response of the pupils and gastrointestinal tract to calcium administration. Neomycin has been shown to decrease the concentration of ionized calcium, thus possibly accounting for its effect, although this mechanism may not apply to other agents.

In summary, this review has mentioned several types of neurotoxicity associated with antibiotic usage. The neurotoxic effects do not coincide entirely with the results predicted from the effects of antibiotics on bacterial cell membranes, mitochondrial metabolism or protein synthesis. Further study of these matters is in order, with

emphasis on ways to prevent toxicity as has been done with the use of pyridoxine in isoniazid toxicity.

Dermatologic Complications

RONALD M. REISNER, M.D.*

THIS PRESENTATION IS concerned with a few specific entities which because of their hazard to the patient or because of their peculiar interest should be recognized and associated with the causative agent. An old, but highly accurate, dermatologic aphorism states that "any drug can cause any cutaneous reaction in any patient at any time," another way of saying that drug reactions should always be considered in the differential diagnosis of skin eruptions. Thus drug reactions, along with syphilis, remain the two "great imitators" in dermatology today.

Black Hairy Tongue. This peculiar reaction pattern has been associated with a number of drugs.[55] Among the antibiotics it has been particularly associated with the penicillins, chloramphenicol and the tetracyclines, whether given systemically or applied topically in the mouth, as with penicillin troches. Other causative factors associated with the development of black hairy tongue have been poor dental hygiene and excessive smoking. In some patients there is no evident cause.

This is essentially a disease of adults. It is usually asymptomatic, although occasionally when the hairy projections are rather long, they may tickle the roof of the palate or induce retching if the patient has a sensitive gag reflex.

The "hairs" are actually tremendously enlarged projections of the filiform papillae of the tongue due to a defect in epithelial desquamation which results in the development of hyperplastic keratin caps. The pigmentation appears to be due predominantly to proliferation of pigment-producing bacteria trapped in the interstices of the enlarged papillae. The keratin itself also lends some of the yellowish or yellow-tan color to the mass, and trapped food particles undergoing degradation may contribute to the pigmentation.

The initial area of involvement is usually the posterior dorsum of the tongue, and extension is usually forward and laterally. The color of the "hair" may vary from yellow to tan to brown or black. Untreated, the condition may last for months or years.

Therapy consists of removing the causative agent or condition if discoverable, followed by mechanical or chemical removal of the hyperplastic keratin caps of the filiform papillae. This may be most readily accomplished by gentle brushing of the tongue with a toothbrush once or twice a day. This is sufficient in most patients to produce pronounced improvement or complete clearing. At times, more vigorous methods have been used to induce desquamation, including the application of 20 percent podophyllin in alcohol, or of 10 percent (or even higher concentrations) trichloracetic acid. These are obviously much more hazardous modes of therapy and must be undertaken with great care.

Toxic Epidermal Necrolysis. Toxic epidermal necrolysis, also known as the scalded skin syndrome or Lyell's disease, is a serious, at times fatal, cutaneous reaction pattern more common in children, but occurring at all ages. It has been associated with bacterial infection of the skin, measles and a variety of drugs.[56] The two antibiotics that have been most notoriously associated with this particular syndrome are penicillin and the various sulfonamides. Among published cases, about one-fourth of the patients died, but this figure is biased by the tendency to report the more severely affected patients.

The typical sequence of events is initial development of mild erythema of the eyelids with or without associated mild conjunctivitis or stomatitis or mild erythema of the genitalia. This may persist for one or two weeks before the more severe acute stage develops, often ushered in by mild malaise and rise in temperature. Tenderness and then erythema develops in the skin of the body folds, the neck, the axillae, the groin and often around the eyelids. Within 24 hours bullae with clear contents develop at the site of erythema. These rupture promptly, creating moist strips of necrotic epidermis that slide off leaving oozing, weeping areas. Nikolsky's sign can be demonstrated in the areas of ery-

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thematous skin by firmly sliding the fingertips across the skin surface to produce a shearing force which results in the removal of a sheet of epidermis, leaving an oozing, weeping, open area. The erythema and blistering rapidly spread to cover most of the body's surface except for the hair-bearing areas, which tend to be spared.

If this severe cutaneous reaction does not prove fatal at the time of its acute phase, it gradually disappears spontaneously over a one or two week period without leaving residual scarring unless there has been sufficient superimposed local infection to produce dermal damage. As was previously noted, the prognosis may be grave, particularly in infants with extensive involvement of the skin surface.

The most important aspect of management is supportive with nursing care, maintenance of nutrition, fluid and electrolyte balance, and isolation to protect against infection. In cases associated with pyoderma, identification of the causative organism and the initiation of suitable antibiotic therapy are also indicated. There is controversy over the value of systemic steroid therapy, but in some patients systemic steroids given early in the course of the disease have had a favorable effect, especially if they are started before the onset of necrotic and bullous changes.

Fixed Drug Eruption. This intriguing and peculiar cutaneous reaction pattern is characterized by the recurrence in a small limited site, often the size of a nickel or a quarter, of eruption with each systemic administration of the offending drug. It commonly presents as a well demarcated area of erythema and edema which may or may not have a bullous component. This eruption recurs at the same site every time the patient takes the drug, and is limited to that site. The lesions gradually heal by crusting and scaling and very commonly leave an area of marked post-inflammatory hyperpigmentation. The two groups of antibiotics most commonly associated with this reaction pattern are the sulfonamides and the tetracyclines.[57]

General Exfoliative Dermatitis. This very serious complication of antibiotic therapy is associated with serious systemic manifestations and at times, particularly in elderly patients, a fatal outcome. The antimicrobials most commonly associated with the development of generalized exfoliative dermatitis are the sulfonamides and para-aminosalicylic acid, and less commonly penicillin and streptomycin. In one large series, drugs accounted for about 10 percent of all patients with generalized exfoliative dermatitis.[58]

Patients with generalized exfoliative dermatitis undergo profound metabolic and physiologic changes which require careful medical and nursing management. These patients have widespread vasodilatation and cannot vasoconstrict, and hence constantly radiate heat. The patient feels cold, shivers, and the core temperature may fall. A sufficient degree of hypothermia may develop, particularly in elderly debilitated patients, to cause death. This tendency toward heat loss is further aggravated by fluid loss through the skin as evaporative heat loss adds to the radiant heat loss from the dilated vacular bed. Conversely, because of plugging of the sweat glands by the exfoliation, these patients cannot increase their heat loss sufficiently to compensate for warm environments and hence fever or even heat prostration may develop in response to elevated environmental temperatures.

It is important to remember that there are many other causes of exfoliative dermatitis including antecedent dermatoses such as atopic dermatitis and psoriasis. In several large series about 10 percent of patients with generalized exfoliative dermatitis proved to have an underlying lymphoma. Because of the associated reactive lymphadenopathy that may occur with generalized exfoliative dermatitis, careful interpretation of lymphadenopathy and of biopsy of lymph nodes is necessary in evaluation of possible lymphoma. Among physical signs, splenomegaly is probably the most useful indicator of underlying lymphoma in the presence of generalized exfoliative dermatitis.

Photosensitive Drug Eruptions. Another fascinating group of eruptions associated with antibiotic use are the photosensitive drug eruptions.[59] Usually the eruption is confined to light-exposed areas, but the patterns may not always be absolutely clear.

The light reaching the surface of the earth contains wave lengths from about 2,800 Angstroms (Å) to about 18,500 Å—that is, the near ultra-violet through the visible and on into the infrared spectrum. Wave lengths of about 2800 to 3200 Å are the so-called sunburn spectrum, with a peak at around 2950 Å. Ordinary window glass will block out almost everything below the 3200 Å range, the common range for causing

photosensitivity eruptions, but the action spectrum for some drugs is higher than 3200 Å. Thus some photosensitive drug reactions may be activated through window glass.

Reactions are of two types: phototoxic and photoallergic. Phototoxic eruptions occur in everybody if the right amount of a drug or its metabolite reaches the skin and is exposed to a sufficient quantity of the right wave length of light. Photoallergic reactions occur only in a very small proportion of people. They have an antigen-antibody basis, with light being simply one factor participating in the development of the reaction. Clinically, photoallergic reactions are of all types – urticarial, exanthematous, plaque-like, nodular, eczematous, and others. Phototoxic eruptions, however, are simply exaggerated sunburn eruptions; phototoxic substances lower the threshold for the development of erythema.

Among the antibiotics, demethylchlortetracycline can cause phototoxic reactions in about 10 to 15 percent of patients. This reaction can deliberately be produced in about 80 percent or more of patients by administering an ordinary dose of 600 mg a day coupled with exposure to the noon-day sun in mid-latitudes in the summer. Even then, about 20 percent of patients do not have a reaction; an undefined factor of individual susceptibility plays an important role. The reaction may be avoided by simply avoiding light exposure; but since the action spectrum for demethylchlortetracycline is between 3500 and 4200 Å with a peak at around 4000 Å, patients must avoid even window-transmitted sunlight. In demethylchlortetracycline photosensitivity the interesting phenomenon of photo-onycholysis, manifested by discoloration and separation of the nail-plate from the nail-bed, may also be seen.

Other antibiotics that produce phototoxic reactions, although much less frequently, are other tetracyclines, sulfonamides, penicillin and occasionally isoniazid. Very commonly, the submental area and philtrum area are spared because of the shadowing effects of the chin and the nose.

Treatment consists essentially in the recognition of the reaction as a photosensitive one and the removal of the offending agent and avoidance of sunlight, or in the case of those antibiotics whose action spectrum is above 3200 Å avoidance of either direct or window transmitted light exposure. Symptomatic therapy with compresses or topical steroids is usually effective. In extensive severe reactions, systemic steroid therapy may be indicated. Protective chemical sunscreens may be helpful, but are often ineffective. Protective clothing, while helpful, may often be unacceptable to the patient for regular wear. The intensity of sunlight is greatest in mid-latitudes from about 10 in the morning to about 3 in the afternoon, and exposure under these conditions should be particularly avoided.

Eruptions Due to Ampicillin. Eruptions due to ampicillin deserve special mention because of their very high incidence and some unusual characteristics of their course.[60] It was noted early that the incidence of eruptions associated with ampicillin seemed to be unusually high. Subsequent experience has demonstrated that the incidence of eruptions due to ampicillin is in part a function of dose. Patients receiving 4 to 8 grams a day for typhoid fever and salmonella infections exhibited an incidence of about 20 percent. In large series of patients receiving smaller doses the incidence of eruptions has varied from about 3 percent to 8 percent. The one intriguing exception to this pattern has been the almost 100 percent incidence of ampicillin eruption in patients with infectious mononucleosis receiving ampicillin regardless of dosage.[9-11] These eruptions are usually rather florid, maculopapular, morbilliform eruptions involving most of the cutaneous surface. In contrast, patients with infectious mononucleosis receiving benzylpenicillin or phenoxymethylpenicillin have shown no increased incidence of skin eruptions. The explanation for this peculiar response in infectious mononucleosis is not known.

It now appears clear that eruptions associated with ampicillin may be divided into two broad classes. The first consists of urticarial eruptions which tend to occur within the first week of ampicillin therapy, and persist or become worse with continued therapy. The second consists of macular, papular, morbilliform rashes which tend to occur after the first week, even up to three weeks after the initiation of therapy. These eruptions may have onset after ampicillin therapy has been discontinued. They follow a variable course and may become worse, remain the same, or clear completely during continued ampicillin therapy. It appears likely that the early urticarial reactions to ampicillin are analogous

to those from penicillin and are due to the drug itself, whereas the anomalous late erythematous eruptions which account for the excess incidence of ampicillin eruptions over penicillin eruptions are due to impurities contaminating ampicillin during the course of its manufacture. It has been proposed that these impurities may be protein in nature or may result from polymerization of ampicillin into dimers, trimers and polymers of higher molecular weight—a process which proceeds rapidly in aqueous environments, thus requiring prompt use of ampicillin after it has been reconstituted. A recent study using a highly purified ampicillin preparation from which the majority of the protein impurities had been removed, demonstrated a pronounced reduction (about 50 percent) in the incidence of eruptions observed in patients receiving the drug.[60] It seems likely that the highly purified preparation will become standard preparation and we may look forward to a reduced incidence of cutaneous reactions to ampicillin.

Hematologic Complications

KOUICHI R. TANAKA, M.D.*

THE SIGNIFICANT HEMATOLOGIC complications of antimicrobial drugs constitute a diverse group (Table 6). They develop in only a very small proportion of the population exposed to a drug, and occur, in most instances, unpredictably.

Aplastic anemia is the most frequently fatal of these reactions, and, next to agranulocytosis, the most commonly reported. Chloramphenicol is clearly the leading drug implicated in cases of aplastic anemia.[61-65] In the American Medical Association Registry on Adverse Reactions, there were 163 reports of aplastic anemia in which chloramphenicol was the only drug administered; the next most frequent antimicrobial agents implicated were three instances each of sulfamethoxypyridazine and sulfisoxazole.[64] Of 138 persons in California whose death was attributed to aplastic anemia between January 1957 and June 1961, 30 (22 percent) had had therapy with chloramphenicol.[66] From a subsequent study in California, the risk of fatal aplastic anemia from chloramphenicol within one year of exposure was estimated to be between one in 24,500 and one in 40,800.[67] The exact incidence of bone marrow aplasia among recipients of chloramphenicol is not known, but is rare.

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TABLE 6.—*Hematologic Complications of Antimicrobial Therapy*

1. Anemia
   a) Aplastic anemia
   b) Hemolytic anemia
   c) Sideroblastic anemia
2. Granulocytopenia
3. Thrombocytopenia
4. Eosinophilia (allergic response)
5. Positive Coombs test
6. Disorders of hemostasis
   a) interaction with coumarins
      (i) increasing prothrombin time
      (ii) decreasing prothrombin time
   b) other (e.g. bleeding)

Chloramphenicol produces two types of toxicity (Table 7). As yet, there is no evidence that reversible bone marrow suppression and aplastic anemia from chloramphenicol are related. Reversible toxicity is a pharmacologic effect of the drug, but the pathogenesis of aplastic anemia remains unknown. However, the occurrence of chloramphenicol-induced bone marrow aplasia in identical twins[68] as well as *in vitro* metabolic studies on bone marrow from patients who had recovered from chloramphenicol-induced aplastic anemia[62] supports the hypothesis that this complication occurs on the basis of a genetically determined biochemical predisposition. At present there is no reliable way to predict in which patients aplastic anemia may develop after chloramphenicol therapy. Therefore, the wise judgment of the physician concerning the need for the drug constitutes the only effective preventive measure.

Depression of bone marrow has been reported with the use of other antimicrobial agents—for example, various penicillins, sulfonamides, streptomycin, nitrofurantoin and amphotericin. Significant marrow damage as a result of these drugs must be extremely rare, and the true toxicity of various antimicrobials is difficult to evaluate.[69]

Hemolytic anemia is being recognized with in-

TABLE 7.—*Two Types of Chloramphenicol Toxicity*

Reversible Bone Marrow Suppression	*Aplastic Anemia*
Common	Rare (? genetic basis)
Dose-related	Not dose-related
Reversible	Usually fatal
Occurs concurrently with therapy	Late clinical onset
Cellular marrow usually	Aplastic or hypoplastic marrow
Vacuolization of early erythroid cells	
Reticulocytopenia	
Elevation of serum iron	

creasing frequency and is of particular interest because certain pathogenetic mechanisms have been elucidated (Table 8). The most frequent cause of drug-induced hemolysis is glucose-6-phosphate dehydrogenase (G6PD) deficiency;[70] its occurrence is particularly high among Negroes and among Caucasians of the Mediterranean area and of the Middle East. G6PD deficiency is an X-linked trait; thus, males are primarily affected clinically. There is wide variability of expression among heterozygous females. Erythrocytes with deficiencies of 6-phosphogluconic dehydrogenase, glutathione reductase, or glutathione synthetase are also susceptible to hemolysis upon exposure to certain drugs, but these deficiencies are rare. Recently acute hemolytic anemia has been reported following the administration of sulfisoxazole and nitrofurantoin in an adult patient with partial glutathione peroxidase deficiency.[71] Subjects with unstable hemoglobins such as hemoglobin Zürich may also develop hemolysis upon exposure to certain compounds, such as sulfisoxazole.

On rare occasions certain antimicrobial agents cause hemolysis on an immune basis (Table 8). Of these, penicillin has been most frequently implicated.[72] All cases of penicillin-induced hemolytic anemia have been associated with administration of high doses of the drug; all of the patients had received 20 million units a day at some time during their treatment with the exception of one patient who had received 10 million units daily for 26 days. A strongly positive reaction to direct antiglobulin test was noted in all patients at the time hemolytic anemia was diagnosed. The penicillin antibody has been characterized to be IgG and reacts specifically with penicillin-treated red cells. The usual manifestations of penicillin allergy are not necessarily present. Evidence of hemolysis may be present for several weeks after cessation of penicillin administration.

TABLE 8.—*Antimicrobial Drugs and Hemolytic Anemia*

Mechanism	*Drugs*
1. Enzyme deficiency	
(A) G6PD deficiency	Chloramphenicol (Caucasians only) Sulfisoxazole (large doses) Sulfamethoxypyridazine N-acetylsulfanilamide Nitrofurantoin Nalidixic acid Para-aminosalicylic acid
(B) Glutathione peroxidase deficiency	Sulfisoxazole Nitrofurantoin
2. Hemoglobinopathy	Sulfonamides
(A) Hemoglobin Zurich	
(B) Hemoglobin H	
3. Immune mechanisms	Penicillin Cephalothin (? other cephalosporins) Isoniazid Para-aminosalicylic acid
4. Unknown mechanisms	Streptomycin Amphotericin B

Both cephalothin and cephaloridine not infrequently give rise to a positive reaction to direct Coombs test. The primary mechanism of the positive Coombs reaction has been shown to be the result of nonspecific (nonimmune) binding of a cephalothin (or cephaloridine) protein complex to the red blood cell surface; this is not associated with hemolytic anemia. This phenomenon is of clinical significance only in beclouding crossmatching of blood if the minor match is performed. In rare instances, hemolytic anemia may develop in those patients capable of producing a specific IgG anticephalothin antibody.[73]

Cases of hemolysis have also been described as occurring with streptomycin therapy, but the mechanism is unknown. Similarly, the anemia accompanying amphotericin B treatment has not been fully elucidated, but has been attributed to both hemolysis and marrow depression.

The mechanism of granulocytopenia associated with antibiotics is not known. In the case of chloramphenicol, however, granulocytopenia may be a component of the overall picture of aplastic anemia or it may be a dose-related complication

which is reversible and of no serious consequence if the drug is stopped. Most antimicrobial agents have been reported to cause granulocytopenia; in particular sulfonamides, cephalosporins, penicillins, nitrofurantoin, lincomycin and rifampicin have been implicated. The mechanism of this reaction is not understood. Many antimicrobial drugs may also be associated with thrombocytopenia, although there is less evidence for this reaction in the cases of cephaloridine, clindamycin, capreomycin, griseofulvin and the nitrofurans. An immune mechanism for this complication has not as yet been clearly demonstrated.

A bleeding disorder characterized by abnormalities of clotting time and prothrombin time has been described during the administration of carbenicillin.[74] Aggregation of platelets by adenosine diphosphate was substantially decreased in these patients. Antimicrobial agents affecting prothrombin time are discussed in the following section by Dr. Lubran.

In summary, the hematologic complications are diverse. The cytopenias develop in only a very small proportion of the population exposed to the drug, and occur for the most part unpredictably. The pathogenetic mechanism is understood in some, such as in the enzyme deficiency or immune hemolytic anemias, but is poorly defined in most instances.

Alterations of Laboratory Tests

MICHAEL LUBRAN, M.D., PH.D.*

ANTIBIOTICS AND CHEMOTHERAPEUTIC drugs may occasionally be responsible for altered values of laboratory test results. These effects (drug interferences) may be due to the following mechanisms:

1. Interference in the actual test. Many broad spectrum antibiotics (for example, tetracyclines) are excreted in the urine as fluorescent metabolites, which interfere in some fluorimetric tests such as those for the determination of catecholamines. Nitrofuran derivatives spuriously elevate creatinine levels by reacting with the color reagent; they also give false positive reactions in glucose tests which employ Benedict's reagent (copper-reducing methods), but not with glucose-oxidase methods.

2. Modification of some physiological function, resulting in a change in some factor. Chloramphenicol may cause an elevation of serum iron and an increase in the saturation of the iron-binding capacity, reflecting a decrease in the iron uptake of the erythroid tissue, which is depressed by the drug.

3. A pathological (usually toxic) effect on some cells or organs or their functions. Almost all antibiotics and chemotherapeutic drugs have been reported to have been hepatotoxic in a few patients. Positive liver function tests (transaminase, alkaline phosphatase, BSP clearance) and elevated bilirubin may occur single or in combination. Some antibiotics (for example, kanamycin, colistimethate) are nephrotoxic and cause changes reflected in blood chemistry and urinalysis. Griseofulvin induces microsomal enzymes which destroy coumarin anticoagulants and decrease the prothrombin time.

4. Modification of some metabolic process (for example, enzyme induction or inhibition; protein synthesis; acting as an antimetabolite; altering the rate of utilization of a substrate). Tetracyclines inhibit protein synthesis, thereby increasing urinary nitrogen loss; if renal impairment is significant, azotemia may result. Novobiocin inhibits glucuronyl transferase; hyperbilirubinemia is associated with the use of this drug in infants.

5. By modifying the effect of another drug (for example by potentiation or inhibition). Sulfonamides potentiate the activity of oral anti-diabetic drugs such as tolbutamide, causing a decrease in blood glucose concentration.

6. By affecting the rate of absorption, metabolism or excretion of another drug. Neomycin, given orally, has been shown to damage the mucosa of the small intestine. Malabsorption, particularly of fat, may occur and the d-xylose absorption test may become abnormal.

7. By altering the degree of binding of another drug to protein carriers in the blood. Sulfonamides displace the coumarin anticoagulants from carrier serum protein, thus enhancing their anticoagulant effect; prothrombin time rises.

8. By interfering with the role of the intestinal bacteria. Broad spectrum antibiotics change the

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intestinal flora and suppress microorganisms producing Vitamin K; prothrombin time consequently is increased.

9. By stimulating the production of antibodies. Penicillin, which in high doses acts as a hapten, may stimulate the production of an antibody, thus giving a positive direct anti-gamma Coombs test.

10. Through metabolic changes in sensitive patients. Griseofulvin and some sulfonamides induce hepatic d-ALA synthetase formation, with a resulting increase in the synthesis of pyrrole compounds. An acute attack of porphyria may be precipitated in sensitive patients. Griseofulvin may increase urinary porphyrin excretion in normal persons.

11. In many cases the mechanism of the drug interference is unknown or conjectural.

Artefactually altered results are not always encountered in patients on antibiotics and chemotherapeutic drugs: some patients appear to be more susceptible than others. This difference may be related to genetically-determined abnormalities (such as G6PD deficiency) or hypersensitivity due to previous exposure to the drug, or to previous or concurrent disease (for example, hepatitis). Usually, however, there is not apparent reason for this idiosyncrasy. Many such side-effects are reported, but some are very rare or are poorly documented. Reported drug interferences due to antibiotics, chemotherapeutic and antifungal drugs are listed in Table 9 (only the more important effects are given[75,76,77,78]). Toxic effects on the formed elements of the blood are discussed in the preceding section on Hematologic Complications, and are not included here.

Conclusion

Dr. Ziment:

This review had covered most of the important and a number of the rare complications of antibiotic therapy, and has delved into some of the mechanisms involved. The range is enormous and is ever-increasing.[79,80] The importance of a thorough awareness of the dangers of antibiotic therapy confronts every practicing physician, since these drugs are in constant use by practitioners in every clinical speciality. The overall problem of drug misuse is of considerable economic importance; as Melmon[81] points out (in a conservative estimate), one-seventh of all hospital days is devoted to the care of drug toxicity,

TABLE 9.—*Effect of Antimicrobials on Laboratory Tests*

Key: ↑ = Elevated; ↓ = Depressed; + = False positive; alt. = Altered (either ↑ or ↓); D = Direct organ toxicity or *in vivo* effect; L = Laboratory finding due to *in vitro* interference with tests: f = Frequent; o = Occasional; r = Rare.

Penicillins and Cephalosporins

1. Urinary "glucose": Benedict's test +, dipstick not affected. (L,f)
2. Plasma catecholamines ↑ (especially ampicillin and carbenicillin). (L,f)
3. Urinary 17-ketosteroids ↓ and 17-hydroxysteroids alt. (L,f)
4. Serum K ↑ (high doses of I.V. potassium penicillin). (D,f)
5. Serum Na ↑ (high doses of I.V. disodium carbenicillin). (D,f)
6. Coumarin anticoagulant effect ↑, prothrombin time ↑ (large doses). (D,f)
7. Serum B-12 ↓ (only in microbiological assay). (L,f)
8. Direct Coombs test + (penicillin, methicillin, cephalothin). (L,f)
9. May cause + L.E. test (penicillin). (L,r)
10. May be nephrotoxic: Albumin, casts, red blood cells in the urine; PSP test abnormal, BUN ↑ (cephaloridine, methicillin, oxacillin). (D,o)
11. May be hepatotoxic (especially carbenicillin and oxacillin): BSP ↑, SGOT ↑, SGPT ↑, bilirubin ↑, alkaline phosphatase ↑, singly or jointly. (D,o)
12. Serum Ca ↓ (methicillin). (D,o)
13. Serum K ↓ and metabolic acidosis (high doses of carbenicillin). (D,r)
14. Urinary porphyrins ↑ (high doses of penicillin). (D,r)
15. Bisalbuminemia (high doses of penicillin). (L,r)

Erythromycins and Lincomycins

1. Urinary catecholamines ↑ (erythromycin). (L,f)
2. May be hepatotoxic (erythromycin estolate, lincomycins). (D,o)
3. Urinary 17-ketosteroids ↑. (L,o)

Tetracyclines

1. Urinary "glucose": Benedict's test +, dipstick not affected. (L,f)
2. Urinary catecholamines ↑. (L,f)
3. Urinary urobilinogen ↓. (D,f)
4. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,f)
5. Prolonged use may cause laboratory evidence of intestinal malabsorption and steatorrhea. (D,f)
6. Serum cholesterol ↑. (D,o)
7. May be hepatotoxic: BSP ↑, SGOT ↑, SGPT ↑, alkaline phosphatase ↑. (D,o)
8. May be nephrotoxic (BUN ↑ is most common effect, other effects include serum uric ↑, phosphate ↑ and acidosis.) (D,o)
9. Urinary estrogens alt. (L,o)
10. Urinary porphyrins ↑. (D,r)
11. May cause + L.E. test. (L,r)

Chloramphenicol

1. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,f)
2. Urinary "glucose": Benedict's test +. (L,f)
3. Urinary urobilinogen ↓. (D,f)

4. Tolbutamide potentiated: blood glucose ↓. (D,f)
5. Serum iron ↑, unsaturated I.B.C. ↓. (D,o)
6. Serum bilirubin ↑ in mildly jaundiced patients. (D,o)

Aminoglycosides, Viomycin and Gentamicin

1. Urinary "glucose": Benedict's test +. (L,f)
2. Nephrotoxic. (D,f)
3. Serum cholesterol ↓ (oral neomycin). (D,f)
4. May cause laboratory evidence of intestinal malabsorption syndrome (especially oral neomycin). (D,o)
5. Urine Ca ↑, K ↑, Cl ↑ (viomycin, gentamicin). (D,o)
6. Serum Ca ↓, K ↓, Mg ↓, P ↓, alkalosis (viomycin, gentamicin). (D,o)
7. May cause + L.E. test (streptomycin). (L,r)
8. (?) Coumarin anticoagulant effect ↑.

Polymyxins and Vancomycin

1. Nephrotoxic. (D,f)

Sulfonamides

1. Urinary "glucose": Benedict's test +. (L,f)
2. Serum amino acids ↑. (L,f)
3. Plasma catecholamines ↑ (sulfadimidine). (L,f)
4. Urine discolored brown or yellow. (D,f)
5. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,f)
6. ^{131}I uptake ↓, PBI ↓. (D,f)
7. Urinary urobilinogen ↑. (D,f)
8. May be nephrotoxic, and cause crystalluria. (D,L,f)
9. May be hepatotoxic. (D,o)
10. Oral antidiabetic drugs potentiated, blood glucose ↓. (D,f)
11. Methemoglobinemia. (D,o)
12. Urinary porphyrins ↑. (D,r)
13. May cause + L.E. test. (L,r)

Paraminosalicylic Acid

1. Urinary "glucose": Benedict's test +. (L,f)
2. Urinary urobilinogen ↑. (L,f)
3. Urinary porphobilinogen ↑. (L,f)
4. Test for phenothiazines in urine +. (L,f)
5. Serum cholesterol ↓ (if initially high). (D,f)
6. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,f)
7. ^{131}I uptake ↓, PBI ↓. (D,f)
8. May be hepatotoxic. (D,f)
9. May cause laboratory evidence of intestinal malabsorption. (D,f)
10. May be nephrotoxic. (D,o)
11. Serum K ↓. (D,f)
12. Acidosis. (D,f)
13. Urine discolored. (D,f)
14. May cause + L.E. test. (L,r)

Isoniazid

1. Urinary "glucose": Benedict's test +. (L,f)
2. May be hepatotoxic. (D,f)
3. Serum folate and B_{12} ↓ (biological assay). (D,f)
4. Direct Coomb's test positive. (L,f)
5. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,o)
6. May cause + L.E. test. (L,o)
7. Blood sugar ↑ and true glycosuria (high dose). (D,o)

Pyrazinamide and Ethionamide

1. May be hepatotoxic. (D,f)
2. Urinary 17-ketosteroids ↓ (pyrazinamide). (L,f)
3. Serum uric acid ↑ (pyrazinamide). (D,f)

Cycloserine

1. Serum folale ↓ (biological assay). (D,f)
2. May be hepatotoxic. (D,o)
3. May cause malabsorption syndrome. (D,o)

Rifampin

1. Coumarin anticoagulant effect ↓, prothrombin time ↓. (D,f)
2. Urine discolored red-orange. (D,f)
3. May be hepatotoxic. (D,o)
4. May be nephrotoxic: BUN ↑. (D,o)
5. Serum uric acid ↑. (D,r)

Capreomycin

1. May be nephrotoxic: BUN ↑. (D,o)
2. Serum K ↓, Mg ↓, Ca↓, alkalosis. (D,o)

Nitrofurans

1. Urinary "glucose": Benedict's test +. (L,f)
2. May be hepatotoxic. (D,r)
3. Urine discolored brown or yellow. (D,f)

Methenamine

1. Urinary catecholamines ↑; VMA ↑. (L,f)
2. 17-ketosteroids ↑, 17-hydroxysteroids ↑. (L,f)
3. Urinary urobilinogen alt. (L,f)
4. Urinary estrogens ↑. (L,f)
5. Pregnanediol ↑. (L,f)
6. 5-HIAA ↓. (L,f)
7. May be nephrotoxic (high doses). (D,o)

Nalidixic acid

1. Urinary "glucose": Benedict's test +. (L,f)
2. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,f)
3. Urinary 17-hydroxysteroids ↑. (L,f)
4. May be hepatotoxic. (D,o)

Amphotericin

1. Nephrotoxic. (D,f)
2. Serum K ↓, Mg ↓. (D,f)

Griseofulvin

1. Coumarin anticoagulant ↓, prothrombin time ↓. (D,f)
2. May be nephrotoxic. (D,o)
3. May cause + L.E. test. (L,r)
4. Urinary porphyrins ↑. (D,r)

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at an estimated yearly cost of $3,000,000,000. Antibiotic complications account for a substantial proportion of this amount, and although there is some inevitability which we must accept, it is hoped that increased awareness of the various complications will help reduce the incidence of the problem.

GLOSSARY OF ABBREVIATIONS

d-ALA ..... *delta-aminolevulinic acid*
DNA ..... *deoxyribonucleic acid*
IgE ..... *gamma* E *immunoglobulin*
IgG ..... *gamma* G *immunoglobulin*
IgM ..... *gamma* M *immunoglobulin*
INH ..... *isonicotinic acid hydrazide*
RNA ..... *ribonucleic acid*
SLE ..... *systemic lupus erythematosus*

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