PRINCIPLES OF COMBINATION THERAPY*

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SYSTEMIC antibacterial combinations have been studied as early as the 1930s, when the results of combined antisyphilitic therapy with arsenic and bismuth and the combinations of sulfonamides and antisera against streptococci and pneumococci were published. In 1945 Hunter[1] became a pioneer in this field when he successfully treated alpha streptococcal endocarditis by means of penicillin and streptomycin.

In the ensuing years many *in vitro* studies were performed in the effort to elucidate the action of antibiotic combinations. The laboratory results were used as a basis for therapeutic recommendations.

In the past 25 years many articles[2-22] have been written about combination therapy. Eight presently acceptable indications for combination therapy are summarized in Table I. The first, decreasing toxicity without loss of therapeutic efficacy, is always a primary goal. This is easily demonstrable when only one of the drugs used in a combination has antibacterial activity or when there is no question that the total antibacterial effect could be obtained by a larger dose of either drug alone. Triple sulfonamide is an excellent but outmoded example; toxicity related to the solubilities of individual drugs is clearly reduced, while antibacterial activity is additive. In a different manner, the combined use of penicillin and probenecid will yield serum levels not reached with orally tolerated doses of penicillin alone. Methods of this kind may

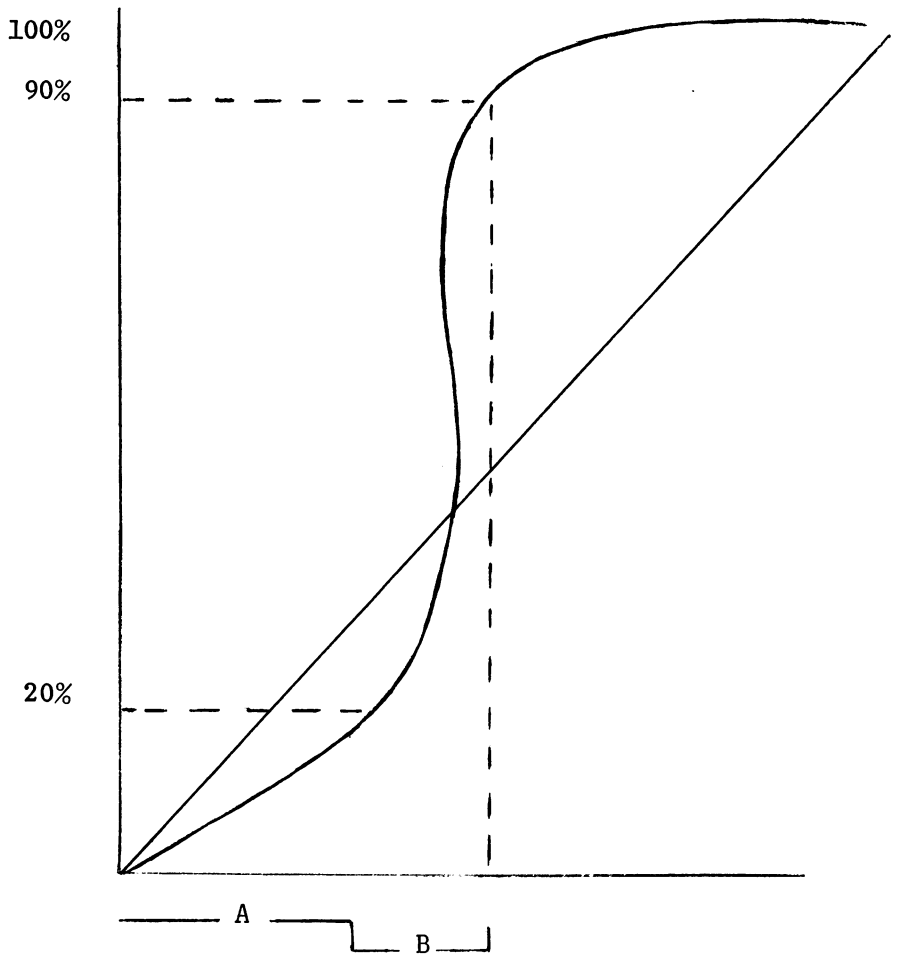
*Presented as part of a *Symposium on Antibiotics: Mode of Action, Pharmacology, and New Clinical Uses* held by the Section on Medicine of the New York Academy of Medicine November 11, 1974.

TABLE I. INDICATIONS FOR THE USE OF MULTIPLE ANTIBIOTICS

Indication	*Examples*
1. Decreased toxicity without decreased efficacy	Triple sulfa—yes; streptomycin + dihydrostreptomycin—no
2. Synergy: 1 + 1 = 4 or more	Endocarditis caused by *Pseudomonas cepacia*
3. Initial emergency treatment of seriously ill patients with no time to be wrong: "shotgun therapy"	Data not available
4. To prevent and attack mutants bacteria—second antibiotic delays emergence of resistant bacteria, prolonging the effect of the active agents	Cavitary tuberculosis; other uses are controversial
5. Mixed infection with each microorganism requiring a different drug	Appear self-evident except in certain anaerobic infections in which organisms are interdependent
6. To prevent superinfection by new bacteria	Topical or local nonabsorbable therapy is possible but controversial, since broad-spectrum drugs here lead to superinfection in most studies
7. To attack nonsusceptible population	L-forms which are resistant to penicillin would be attacked by a second drug such as tetracycline. Example: Recurrent staphylococcal disease, unproved
8. To reach otherwise unaccessible organisms; an uncommon but important consideration	Brucellosis — intracellular, tetracycline trypanosomiasis—central nervous system—pentavalent arsenicals. Staphylococcus (dysphagocytosis syndrome) —rifampin

obviate the need for parental therapy and hospitalization, each of which has its own risk. Of the eight indications mentioned, decreasing toxicity is the only one which is host-directed and in which the results are measured in the patient only. In the remaining seven indications, toxicity is theoretically held constant (i.e., a low "acceptable" level is present), while increased action is sought.

True synergy is often defined, poorly understood, extremely controversial, and rarely proved *in vivo*. The formula 1 + 1 = 4 has been a common method of showing synergistic rather than additive interaction. This is based on the assumption of a linear dose-effect relation (see accompanying figure). However, dose-effect relations in biological systems are more often logarithmic than linear.[23] For example, if the addition of small amounts of drug B to drug A produces a three to five-fold increase in effect with only a 25% increase in drug dosage,



Dose of antibiotic. In true synergy, dose-effect relations are more often logarithmic (S-shaped curve) than linear (straight line). Thus, the addition of small amounts of drug B to drug A produces a 90% increase in effect in the synergistic relation, whereas the some additional amount of drug A would produce a much smaller increase in effect.

this would be labelled synergy. However, when we identify drugs A and B as the same agent it becomes apparent that true synergy is not simple to determine. Since an apparently true synergistic effect may be accomplished by increasing the dose of a single agent, *in vitro* proof of synergy should require multiple dose-response curves. These are

lacking in many published studies. Synergy is the only one of the eight indications for combination therapy that is demonstrated in a homogeneous population. This makes its measurement easily adapted to *in vitro* laboratory settings independent of the host. We believe that this leads to a common phenomenon: the study of what can be determined easily rather than what is necessary.

The last six indications for antibiotic combination therapy are dependent upon a heterogeneous population of microbes or a heterogeneous environment for a single mixed population of microbes. Of these six indications, the two most commonly followed in clinical practice are "shotgun therapy" and attempts to prevent the development of resistant mutant organisms. The use of multiple drugs to prevent superinfection is controversial. One of the few controlled studies has demonstrated an increased incidence of superinfection with increased drug dosage or a broadened drug spectrum.[24] Most of the indications have been studied poorly; they will be discussed in terms of the individual organisms or disease states.

Lacey[25] has presented an outline of cytotoxic and noncytotoxic addition or synergy with one, both, or neither member of each therapeutic pair active against a microorganism. Cytotoxic synergy[26-32] involves antimicrobial drugs and nonantimicrobial drugs in combinations of similar or dissimilar drugs combating a homogeneous population. Two active antimicrobial drugs acting *in vitro* at the same site, sequence, or route are used together against a homogeneous population in order to obtain a given effect without increase in toxicity. An example of this is triple sulfonamide therapy, where solubilities are independent but activities are additive. Two drugs acting at different sites but forming a similar sequence are sulfonamide and pyrimethamine[33] or sulfonamide and trimethoprim.[26, 27] The expected synergy of this sequential blockage is dependent upon a situation in which only a small amount of drug may be necessary to cause partial blockade, but a large increase in dosage may be necessary to complete the blockade. For instance, the activity of an enzyme may be inhibited to the extent of 75% by a relatively small dose of either drug A or drug B. Drug A and B together, each at the same small dose, will cause 95% inhibition of the end product. A much larger dose of either drug alone would be required to obtain 95% inhibition of the same end product, and these doses may be clinically unfeasible. A drug possessing the activity of

trimethoprim was sought prospectively for this very reason. Sequential synergy is shown well *in vitro*, but information obtained *in vivo* is lacking. Most combinations of antibiotics in clinical use contain drugs acting at different sites, sequences, and routes. In this group, as defined by Lacey, there is implied absence of cross resistance and the inability to inhibit the two drugs with a single substance.

Cytotoxic synergy in which one antimicrobial and one nonantimicrobial agent are combined is evidenced by the increased activity of penicillin when temperature, the second factor, is raised from 4° C. to 37° C. This results in increased bacterial growth and a paradoxical increased destruction of the bacteria. In infections of the urinary tract an inactive nonhydrolyzable methicillin protects a hydrolyzable but potentially active ampicillin from the beta lactamase of *Pseudomonas aeruginsoa* and other Gram-negative bacilli.[32] Used alone, either drug is ineffective. This phenomenon has been demonstrated with both *in vivo* and *in vitro* urinary tract infections, where, unfortunately, it rarely benefits the patient to a significant extent. Another example with clinical applicability is the use of alkalizing agents to increase the activity of the aminoglycosides[34] in urine.

Coalitive synergy is the term applied to the cytotoxic activity produced by two nontoxic agents. Examples of clinical applicability are not available. The effect may be mimicked by an interaction of two so-called inert chemicals to produce one active agent.

Noncytotoxic synergy[35-39] involves the use of two agents against a heterogeneous population. This is usually demonstrable *in vivo* only. Indeed, the term noncytotoxic denotes inability to demonstrate the phenomenon *in vitro* and not an absence of cytotoxity. A second drug (for example, para-aminosalicylic acid, PAS) may prolong the effect of the first more active drugs (e.g., isoniazid) by killing resistant mutants. Different stages of the same organism may require different drugs. In the treatment of infections caused by *Onchocerca volvulus* suramin is active against the mature worm and diethylcarbamazine destroys the microfilaria.[35] A different physiological state of the same bacteria may require a different antimicrobial drug, as demonstrated by the ability of lysostaphin to kill the majority of dormant staphylococci in an abscess. However, lysostaphin must be discontinued immediately because of allergenicity. Methicillin, which alone would be inactive against the dormant bacteria in the undrained abscess, becomes active against the

small numbers of bacteria that remain after a single dose of lysostaphin.[40] Trypanosomiasis of the central nervous system is of interest because two drugs are required, both of them active against the same stage of the organism. The diffusion characteristics of the blood-brain barrier exclude the more active drug—suramin—from the major area of infection in the central nervous system. A less active arsenical is given in order to penetrate into this system.[36]

The examples of noncytotoxic synergy that have been discussed involve the use of two antimicrobials. However, an antimicrobial combined with a nonantimicrobial may provide similar synergy through different mechanisms. The use of probenecid to delay the excretion of penicillin or rifampin is well known. Pyridoxine or folinic acid can prevent some of the predictable toxicity of isoniazid or trimethoprim[37] without impairment of efficacy. Theoretically, polymyxin might reduce the intensity of septicemia caused by a polymyxin-resistant strain of proteus by forming a complex with endotoxin,[41] while a second drug such as gentamicin is used for its antibacterial action.

Jawetz,[42] a pioneer in the development of combination antibiotic therapy, has made predictions for drug interactions which he classifies as inattention, addition, antagonism, or synergism based upon the mechanism of action of antibiotics. These predictions are concerned basically with the cytotoxic synergy of two drugs acting at different sites, sequences, and routes, i.e., the type most frequently used and studied. Manton and Wisse[43] present a modification based only upon expectations of antagonism. The present data are insufficient to prove either classification superior. The problems of physical and chemical reactions at the site of infection and the combined effect upon antimicrobial and nonantimicrobial interactions make prediction risky. In addition, it is possible that inattention, addition, antagonism, or synergism are all present in a single clinical setting at different times. Jawetz himself has decried the overinterpretation of his bacteriostatic/bactericidal classification of drug interactions.

Combination Therapy in Specific Diseases

Endocarditis[44-59] is one of the few diseases that lends itself to study with combination therapy. Despite some variance of opinion, intravascular infection remains one of the few clinical settings in which bacteriostatic drugs are consistently less effective than bactericidal drugs

in the actual disease. The clinical course correlates with *in vitro* results when the dosages used produce serum levels four to eight times the minimal bactericidal concentrations determined in the laboratory. With the possible exception of leukopenic states, the efficacy of bactericidal agents has not been proved superior to that of bacteriostatic agents if the microorganism is sensitive to both.

The infectious agents that cause endocarditis can be divided into two groups by these laboratory studies. The first group consists of those in which a single drug is bactericidal at clinically tolerated levels; in the second group are those that are not sensitive to available bactericidal agents.

Alpha streptococcal and enterococcal endocarditis have usually been treated with combinations of penicillin and aminoglycosides. Moellering[50, 53] has studied the effect of penicillin and aminoglycosides upon enterococci *in vitro*. Radioactive C-14 aminoglycosides were utilized to demonstrate that penicillin enhances the penetration of aminoglycosides into the bacteria. This is the apparent reason for synergy *in vitro*. There are many tests which demonstrate the synergy, including the relative superiority of gentamicin over tobramycin, of this in turn over kanamycin, and of this over streptomycin. There are no studies which demonstrate that higher doses of penicillin or ampicillin alone are inadequate to produce eventual cure in streptococcal endocarditis. The major benefit of the added aminoglycoside appears to be in reducing the duration of treatment. While this is important, it must be weighed against the added toxicity of the aminoglycosides, which is not insignificant in the elderly persons who are the usual sufferers from enterococcal endocarditis. In addition, the necessary duration of aminoglycoside administration is unknown. The necessity for the use of a second drug in pneumococcal and staphylococcal endocarditis has never been demonstrated.

Endocarditis in patients who are allergic to all available bactericidal drugs or endocarditis caused by *Pseudomonas cepacia*, penicillinase-producing diphtheroids, or fungi appears highly suitable for studies of combination therapy.

Pseudomonas cepacia endocarditis has been studied because of its relatively high incidence in narcotic addicts and in the endocarditis which follows replacement of valves.[57-59] The organism is usually sensitive only to *in vitro* bacteriostatic agents—sulfonamide and trimetho-

prim or chloramphenicol. For clinical cure, valve replacement is required in addition to chemotherapy. Sulfonamide, trimethoprim, and polymyxin[59] has been the only clinically active combination. This triple therapy is the most promising, but true nonsurgical antibiotic cures remain to be demonstrated consistently. Clinical cures of endocarditis achieved with multiple drugs in situations in which single agents were ineffective might be said not to need controls, since untreated the mortality of endocarditis approaches 100%.

Combinations of Antibiotics for Specific Bacteria

Triple therapy has been advocated for nonendocarditic infections caused by highly antibiotic-resistant Gram-negative bacteria. In these cases sulfonamide, trimethoprim, and polymyxin have been used to treat infections caused by *Serratia marcescens*,[60] indole-positive Proteus,[61, 62] providencia,[63] and some pseudomonads.[64, 65] Polymyxin may add to the sequential block of the sulfonamide and trimethoprim combination, leading to a bacterial absence of thymine. Alternatively, the combination may change the cell-wall barrier allowing the polymyxin to reach the site of activity in the membrane.

Combinations of antibiotics have been most often used against *Pseudomonas aeruginosa* or coagulase-positive staphylococci in *in vitro* studies. Antistaphylococcal combinations[40, 66-73] have included: oxacillin and rifampin when intracellular polymorphonuclear function is defective[74] (rifampin penetrates intracellularly); fusidic acid and lincomycin in cystic fibrosis[72] (other agents penetrate the thick mucus poorly and combination therapy supposedly prevents the development of resistant mutants); and methicillin or cefalothin plus kanamycin or vancomycin for their supposed synergy against methicillin-resistant staphylococci,[75] although the latter combinations have not been proved to be superior to kanamycin, gentamicin, or vancomycin alone. Multiple antibiotics have been used to treat staphylococcal infections in an attempt to prevent resistant bacteria from arising. Demonstration of this phenomenon has required elegant laboratory techniques. Erythromycin or fusidic acid have been added to penicillin or methicillin in order to prevent penicillin resistance.[68] Fusidic acid requires a large bacterial inoculum to demonstrate this effect, while erythromycin appears to be independent of the size of the inoculum. Intermediate production of penicillinase by the staphylococcus is necessary in these special environ-

mental situations. Erythromycin or fusidic acid kills most of the bacteria and the penicillin kills the remaining small number of penicillinase-producing staphylococci, since penicillin is active against small inocula of beta lactamase producing staphylococci.[76] The requirements for this synergy are not likely to be found and surely will not be recognized in a clinical context.

In the treatment of infections caused by *Pseudomonas aeruginosa*[77-90] the purported reasons for adding a second drug (gentamicin) to carbenicillin include: 1) the prevention of superinfection with *Klebsiella*,[78] 2) the prevention of mutations which were *in vivo* resistant, 3) the fear of a mixed infection including a primarily resistant organism,[79] and 4) the fear that the *Pseudomonas aeruginosa* possesses primary carbenicillin resistance.[77] No controlled clinical studies support any of these claims. Infections of the urinary tract caused by *Pseudomonas* have been treated with hydrolyzable and nonhydrolyzable penicillin combinations,[85, 86] but mediocre results are obtained and seem most related to the depressed condition of the patient who develops an infection of the urinary tract caused by *Pseudomonas*.

Gram-negative infections, including sepsis,[90-100] have been treated with combination therapy. *In vitro* synergy to a penicillin-aminoglycoside combination is limited by either relative or complete bacterial resistance to the aminoglycoside.[101]

In animals with Gram-negative sepsis, Andriole[82] has shown the greater clinical efficacy of two-drug combinations compared with either drug alone, Klastersky[84] has been the only observer to show positive correlation of *in vitro* synergy or lack of synergy with clinical outcome in Gram-negative sepsis. However, he has presented no control data and he did not make comparisons using the single best agent. A similar criticism can be made of a study[99] showing ampicillin and chloramphenicol to be superior to chloramphenicol alone in the treatment of typhoid fever. The question of whether ampicillin alone is as effective as the combination is left unanswered. Keflin and carbenicillin was the best combination in one study,[102] but synergism of these agents is expected only *in vivo* at the high concentrations that are obtainable only in the urine. The studies of Bodey[103] purport to demonstrate the superior clinical efficacy of carbenicillin alone or in combination with gentamicin over gentamicin alone in leukopenic states. This has not been verified or refuted by other investigators. Clinical

studies, while admittedly difficult to perform, remain the only method whereby practical conclusions can be reached with any confidence.

Synergy Studies—Miscellaneous Organisms

Combinations of antibiotics have been used in the treatment of a miscellaneous group of microorganisms.[78-104-116] They have been used in treating infections of *Nocardia asteroides*, especially when the disease involves the central nervous system, because poor results have been obtained with any single agent.[107] However, the rarity of the disease has made it impossible to draw definite conclusions as to the best therapy. Nocardiasis of the central nervous system, like endocarditis, would be an excellent disease in which to determine whether *in vitro* synergistic measurements can be used as predictors of clinical response, but cooperative studies will be required. Minocycline is less active than rifampin against nasopharyngeal meningococci but is added because of the high rate of resistant mutation that occurs when rifampin is used in a closed community.[111] However, the high rate of vestibular reaction to minocycline may limit the usefulness of even this combination. Relapses of brucellosis were decreased by adding streptomycin to the usual tetracycline therapy;[110] however, continuing the oral tetracycline for 20 days (an increase of seven to 10 days) obviates the need for the more toxic, parenterally administered streptomycin.[109] *In vitro* synergism (particularly against various fungi) has been demonstrated by using low levels of amphotericin B with fluorocytosine[107] and also with the antibacterials tetracycline[104] and rifampin.[105, 106] This may be caused by increased penetration by the usually less active drug (antibiotic) after amphotericin B has modified the fungal cell membrane. Clinical studies are lacking.

Specific Drug Combinations—Fixed Dose

The combination of sulfamethoxazole and trimethoprim has been released recently. This is one of the few such drugs approved by the Food and Drug Administration since the late 1950s. There are a remarkable number of excellent *in vitro* studies which demonstrate synergy,[26, 27, 58] but only one clinical study indicating synergy has been done. The combination was given in the treatment of gonorrhea,[117] a condition not considered to be treated well by the sulfonamide and trimethoprim combination, when compared with many single antibi-

TABLE II. DISADVANTAGES OF MULTIPLE DRUGS

1. Increased superinfection (in either the same organ, e.g., pneumonia, or a new organ, e.g., enteritis and vaginitis).
2. Increased drug reactions, interactions, and toxicity and lessened ability to determine the source.
3. Increased environmental spread of antibiotic-resistant bacteria.
4. Academic approval encourages the rapid proliferation of completely illogical combinations in a never-ending search for the perfect drug, Godamycin.
5. False security and lessened enthusiasm for correct diagnosis.
6. The seduction of convenience leads to fixed—and therefore rarely appropriate—drug dosages.
7. Unnecessary increased expense.
8. Antagonism against the activity of the superior agent or, at best, no improvement.

otics. The reasons for using this combination have been summarized by outstanding specialists in infectious disease in the United States, England, and Australia.[118, 119] These reports bring out most of the points seen in Table I. Trimethoprim has been used alone in long-term infections of the urinary tract without evidence of increased resistance.[119] Since 1) trimethoprim alone is an excellent drug, 2) a bactericidal combination is not obviously superior to a bacteriostatic drug in conditions other than endocarditis, 3) trimethoprim at a higher dosage might be more effective and less toxic than the fixed combination, 4) allergy to sulfonamides prevents the physician from using the combination in patients who might otherwise receive trimethoprim, and 5) 100 editorials will not be a substitute for clinical data, it is impressive that this combination of drugs has been released in the United States 17 years after the revolt of "the academician against the drug houses."[120]

DISADVANTAGES OF COMBINATIONS

The disadvantages of multiple drugs are described in Table II. Prescott[121] has recently reviewed drug interactions. The first two items listed as disadvantages of using multiple antibiotics in Table II also are listed in Table I as advantages for the use of multiple antibiotics. This makes obvious the need for more data and further discrimination in this area. The disadvantages of drug interactions have been reviewed.[122-124] Some 20 different antibiotics are incompatible in the intravenous bottle, and each antibiotic has about 10 incompatibilities. It is

also important to note that additive or synergistic toxicity may compromise the additive or synergistic efficacy of some combinations.

Considering the many effective regimens available for treating bacterial infections, antagonism should be easier to demonstrate *in vivo* than synergism. However, studies[97, 125-135] showing antagonism are as rare as those showing synergism. The inhibition by ampicillin of the activity of carbenicillin against Enterobacter[129] is of note, since Eagles[148] showed some 25 years ago that increasing concentrations of penicillin G., i.e., penicillin G plus penicillin G, could lead *in vitro* to a lessened activity against certain species of enterococci. The alleged antagonism of fusidic acid and penicillin[133] is contradicted by other *in vitro* studies which show synergy.[68] The different results are related to size of inoculum and to concentration of drug; this again illustrates the difficulty of extrapolating *in vitro* data to *in vivo* situations.

Occasional investigations in animals have shown either indifference or antagonism.[136-139] Very few studies in man[24, 140-145] have demonstrated true antagonism in a controlled situation. One important study[24] showed a marked increase in superinfection when drug combinations with broadening spectrums were used in the treatment of bacterial pneumonia. Studies[140-143] which have indicated antagonism of antibiotic combinations in clinically dangerous situations such as bacterial meningitis present a warning against the future use of such combinations. In similar settings, ampicillin and chloramphenicol[146] or penicillin and chloramphenicol are being considered as primary therapy for meningitis in children since ampicillin-resistant cases of infection with *Haemophilus influenzae* have been reported. What is required is a demonstration that the excess danger of the drug combination is overcome by the excess risk of not covering a percentage of a specific antibiotic-resistant microorganism.

Some 30 years after Hunter[1] used combination treatment in a case of subacute bacterial endocarditis caused by streptococci and 17 years after fixed-dose combination antimicrobials were being rejected by the academic community, we remain barely able to understand the problems associated with the use of combinations of antibiotics. We need only look at recent developments to appreciate the attack that is being mounted against the single-drug approach. Sulfamethoxazole and trimethoprim are available in fixed-dose combination but the efficacy of this combination is supported only by *in vitro* studies. Com-

binations containing up to five or six drugs are being used when sepsis is suspected in a leukopenic immunocompromised host.[147] This practice, once condemned on theoretical grounds by specialists in infectious disease,[119] is now supported only by our inability to predict the pathogenic infectious agent. We continue to study what is easy to measure, namely, laboratory synergy. Test-tube results must be demonstrated to predict a therapeutic effect or failure in the patient. Controlled clinical studies comparing combinations with the best single agents, while toxicity is carefully monitored, are greatly needed.

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