

than the sum of the separate activities (antagonism). It has been pointed out, however, that it is not possible generally to predict which of these results will ensue. For this reason, sulfonamide-penicillin mixtures should usually not be chosen because of the ever-present possibility of drug antagonism.

*Treatment of infections before etiology is known or where it is impossible to determine etiology*

It is necessary at times to treat patients with severe infections before the etiology has been determined. There are indeed valid indications for the use of drug combinations in such instances, particularly in infections of the newborn. In all such circumstances, the drugs used should be given by the parenteral route which in itself precludes the use of oral sulfonamide-penicillin mixtures. In addition, the use of other drug mixtures has been shown to be much more effective than sulfonamide-penicillin combinations.

Many of the same points can be made regarding the use of sulfonamide-penicillin combinations in patients in whom it is difficult or impossible to determine an etiologic agent. A possible exception to this is the use of penicillin-sulfonamide combinations in the treatment of acute otitis media. The common causes of acute otitis media are group A streptococci, pneumococci, and *Hemophilus influenzae*. However, *Hemophilus influenzae* causes otitis media very rarely after the age of 3-4 years, so multiple antibacterial agents are not indicated for the treatment of this entity in older children or in adults. Because *Hemophilus influenzae*, group A streptococci and pneumococci cause otitis media during the first few years of life, it has been the common practice to use sulfonamide-penicillin combinations in this age group. Data to support this regimen are lacking. Indeed, recent evidence indicates that sulfonamides have limited action against *Hemophilus influenzae* and that results with penicillin alone are as good as results with penicillin in combination with the sulfonamides. Furthermore, other drugs, such as the tetracyclines and ampicillin, have been shown to be effective in *Hemophilus influenzae* infections when given alone.

*Exposure of patients to multiple drugs*

The sulfonamides and penicillin are potentially dangerous drugs; reactions are common and can be severe and even fatal. The use of both drugs simultaneously therefore increases the risk to the patient and is to be avoided for this reason. Another troublesome aspect of this problem is the difficulty in detecting the drug causing a reaction when multiple drugs are used.

*Use of "fixed" drug mixtures*

The question of control of drug dosage should always be considered when using "fixed" drug combinations. In this situation, it is never possible for the physician to raise or lower the dose of either component without affecting the dose of the other. The tendency, then, is to raise the dose of one drug to a desired level and inadvertently give an overdose of the other, or to lower the dose of one to a desired level and consequently give an insufficient amount of the other. This subject is well covered by Weinstein as follows:

"The most important problem in the field of combined chemotherapy is the use of 'fixed-dose' mixtures. On the basis of the presently available knowledge, it appears patently clear that these mixtures have no place in the treatment of infection. The attitude that physicians should adopt toward such preparations has been outlined in an editorial by Finland (1957), written as a joint expression of the views of investigators and teachers in the field of infectious diseases, as follows:

"Considerable caution is warranted in accepting the trend to fixed antibiotic combinations as inevitable or in lending support to a trend that may not be desirable. We would be remiss in our duties as physicians, teachers, and investigators were we to encourage, adopt, and recommend the use of new agents that we cannot consider to be as good as, or no better than, those previously shown to be good, even if they are legally certified. It is particularly incumbent on us to be very circumspect about the use of drugs of any sort in fixed combinations that do not offer the physician discretion as to the choice of components, or of the ratios in which they are used. The presence in any combination of a new or unproved component, or of a substance that may be inferior to others that might well be used instead, should make us even more cautious. They should be recommended and adopted, if at all, only after adequate, carefully controlled, and critically evaluated, study shows them definitely to be useful and superior."