

important that white papers were prepared to present our thoughts in some detail. We also felt that it would be most important for practicing physicians to be aware of our arguments since the judgment recently taken by the FDA to remove them from the market would affect their practice. To this end, a paper was prepared for publication in The New England Journal of Medicine which will appear in the May 22, 1969, issue. A copy of the paper is now submitted to you, but we respectfully request that its contents not be released until published. This is asked as a courtesy to the Journal. I am, however, at complete liberty to discuss our opinions and some of this testimony will contain direct quotes from the paper.

Other Panel Chairmen testifying before you will provide information on their judgments concerning fixed combinations of tetracycline and novobiocin and tetracycline and antifungal agents.

The issue of fixed combinations is not new. It has been commented upon extensively in the literature as long as 10-15 years ago. Excellent reviews of the situation have been prepared by Dr. Ernest Jawetz, professor of Microbiology at the University of California, Dr. Maxwell Finland of Harvard Medical School, Dr. Louis Weinstein of Tufts Medical School, and Dr. Harry Dowling of the University of Illinois. Each of these men have repeatedly condemned the use of fixed dosage forms and given most cogent arguments. The task before our own Panels was to once again review the evidence and bring the matter to a head.

I shall now provide you with the following excerpts from our white paper on penicillin-streptomycin and penicillin-sulfonamide to permit you to see how we developed our arguments.

PENICILLIN-SULFONAMIDES

One of the most common indications given for the use of oral sulfonamide-penicillin combinations is mixed bacterial infection. Bronchiectasis, peritonitis, urinary tract infections, and chronic otitis media are the most common entities that can be caused by simultaneous infection with more than one kind of bacterium. Because many bacteria cause these infections and because the bacteria are commonly very resistant to antibacterial therapy, treatment should not be started until appropriate cultures and sensitivity tests have been initiated. In most instances, therapy need not be started until these data are determined, thus allowing the use of specific and effective agents. It is highly doubtful that oral penicillin-sulfonamide mixtures would ever be the drugs of choice in such cases.

Weinstein has shown that, under some circumstances, a "broad-spectrum" effect is produced when sulfonamide-penicillin mixtures are given. It is pointed out, however, that the degree of antibacterial activity is generally unpredictable, and antimicrobial effectiveness is often decreased by this type of therapy. In another publication, Weinstein refers to this same subject as follows:

"Such therapy is given not to produce an increase in antibacterial effectiveness but for the purpose of a 'broad-spectrum' effect in the hope that any infecting agent may be eradicated. This combination of drugs is used most extensively for the treatment of upper respiratory infections, the bulk of which are known to be due to viruses. There are no data in support of the concept that antibiotic-sulfonamide mixtures are more active in any way than the single constituent compounds. There is therefore no basis on which such combinations can be recommended, and their use must be considered to be entirely empiric."

For the above reasons, recommendations cannot be made from available data for the use of penicillin-sulfonamide combinations for the treatment of most "mixed" bacterial infections.

Enhancement of antibacterial activity

Another reason commonly given for the use of drug combinations is that some types of infections are more effectively treated by two or more drugs given in concert. Tuberculosis, subacute bacterial endocarditis due to group D streptococci, and possibly some strains of *Streptococcus viridans* are cited as examples of such infections. Some data suggest that this may be true also for some forms of brucellosis and some infections due to *Proteus mirabilis*. Penicillin and sulfonamide combinations, however, are never the mixtures of choice in any of these infections.

Careful laboratory studies have shown that the use of the combination of penicillin and a sulfonamide can have three possible results: enhancement of antibacterial activity beyond the additive effects of the two drugs (synergism), activity equal to the additive effects of the two drugs (additive), and activity less