LETTERS TO THE EDITOR

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Combinations of Antibiotics

To the Editor:

I read with interest the paper by Haggerty and Ziai (PEDIATRICS, 25:742, 1960). I fully agree with the authors' recommendation that acute bacterial meningitis of infants be treated with multiple drugs directed at the most likely etiologic agents until a specific single organism has been identified. However, the authors' repeated references to some of my past publications force me to call attention to some possibly misleading statements in their paper.

After the initial demonstration of "antibiotic antagonism" in vitro and in experimental animals, we pointed out repeatedly (Arch. Int. Med., 90:301, 1952; Pharmacol. Reviews, 5:175, 1953; Proc. Fourth Int. Congress of Biochemistry V, 91, 1958) and emphatically:

A. Just as no combination of antimicrobial can be called uniformly synergistic, so no combination can be called antagonistic. The effect of any drug combination depends strictly on the behavior of a specific microbial strain toward each of the members of a given drug combination. The commonest result of combined antibiotic action is "indifference."

B. Antibiotic antagonism is sharply limited by time-dose relationships. The interfering agent must act either before, or simultaneously with, the effective drug. Consequently multiple dose treatment schedules in experimental infections make the demonstration of antagonism difficult. Antagonism is most marked with concentrations of the interfering agents that are barely biologically active. The phenomenon is either obscured or suppressed by a large excess of either member of the drug pair. In clinical practice an excess of drug beyond the minimal biologically effective dose is the rule. Consequently the likelihood of the observation of antagonism in clinical antibiotic therapy is very small indeed.

I must disagree with the authors' statement: "It is not clear why these results are at variance with the experimental data of Jawetz or the clinical data of Lepper and Dowling." In view of the conclusions from experimental findings quoted above, the "antimicrobial agents used in maximal doses" by Haggerty and Ziai could not have permitted any observation of antagonism (even if such a phenomenon had been shown to occur in vitro with the particular microorganisms and drugs). With regard to the clinical observation of antagonism in pneumococcal meningitis by Lepper and Dowling (Arch. Int. Med., 88:489, 1951) the circumstances were peculiarly well suited to its occurrence: A combination of one very effective bactericidal drug (penicillin) with a bacteriostatic agent (chlordetracycline), both present in critical concentration but without any excess at the site of bacterial proliferation (meninges, cerebrospinal fluid), in a disease where rapid killing of microorganisms may be essential for cure. In the majority of human infections, however, the regimen of antimicrobial therapy is such that it virtually precludes antibiotic antagonism. This cer-
ertainly applied to the study of Haggerty and Ziai. The strict time-dose relationships essential for the experimental demonstration of antagonism make its occurrence as the outcome of clinical antibiotic treatment most unlikely.

This letter is written with the hope that it may clarify, once again, our views on antibiotic antagonism and rectify possibly misleading impressions gained from the paper by Haggerty and Ziai.

ERNEST JAWETZ, M.D.
San Francisco, Calif.

To THE EDITOR:

I am delighted to have Dr. Jawetz again bring to the attention of your readers his definitive work on the subject of antimicrobial combinations. We certainly have no quarrel with the points he reiterates. Our choice of words, “It is not clear why these results are at variance with the experimental data of Jawetz or the clinical data of Lepper and Dowling,” was probably unfortunate, for Dr. Jawetz points out why the results did differ from his experimental work. However, our next sentence was designed to provide the same answer he gives: “… that we are dealing … with three organisms quite sensitive to small doses of antimicrobial agents and the agents were used in maximal doses.” It is still not too clear to me why Lepper and Dowling’s clinical results with penicillin and chlortetracycline in pneumococcal meningitis (Arch. Int. Med., 88:489, 1951) were so different from ours (penicillin and chloramphenicol, also a bacteriocidal and bacteriostatic combination) in the same disease, with approximately the same time-dose relations. Chloramphenicol instead of chlortetracycline and age were the most obvious differences in the two groups, but the question of why still remains.

The important point, it seems to me, is that Dr. Jawetz has again made his work clear, for he has been often quoted out of context to us, as advocating never giving so-called “antagonistic” antimicrobial combinations in clinical practice. This misinterpretation of his work by others we believed needed clarification in a disease like bacterial meningitis where early institution of therapy is essential to good results.

ROBERT J. HAGGERTY, M.D.
Boston, Mass.

Management of Otitis Media

To THE EDITOR:

In the past few years I have read several review articles by ear, nose and throat specialists similar to one by Dr. Charles F. Ferguson in PEDIATRICS, 25:1043, 1960.

In all of these articles, myringotomy is strongly advocated as the proper treatment for bulging ear drums. They frequently cite various intracranial complications as evidence that myringotomies should have been done. However, in examination of these histories it is apparent that most of these people received inadequate antibiotic treatment and were not properly followed in the period before these complications developed.

In none of these articles are there any references to any type of controlled study where the short-term and long-term results obtained with antibiotics and myringotomy are compared with antibiotic therapy alone.

In talking with many competent pediatricians, who treat many hundreds of children with otitis media during every year, I find very few do myringotomies for bulging ear drums. None of these physicians has had any of the intracranial complications so frequently cited. Again, these people have no controlled studies to back up their approach to therapy.

Since otitis media is an extremely common disease in children, and since there would appear to be a difference of opinion among competent physicians, I would think the time is ripe to supply some much needed facts. Certainly a controlled study would not be difficult to set up at a large institution and the answers would be of great benefit to all concerned.

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## Combinations of Antibiotics

Ernest Jawetz

*Pediatrics* 1960;26;498

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