THE TREATMENT OF SOME BACTERIAL INFECTIONS OF THE HEART AND PERICARDIUM*

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PURULENT pericarditis is rapidly becoming a medical curiosity. Infections of the pericardium by pyogenic organisms used to be a fairly common accompaniment of severe uncontrolled infections such as pneumococcus pneumonia, staphylococcus septicemia, meningococcemia and the like. With the modern antibiotic armamentarium at hand patients rarely progress to the stage of sepsis where this complication arises. It is interesting that in reviewing the literature for the past five years I was unable to find a single article in English devoted to the subject, and for this reason as well as because of my own lack of first hand experience in treating patients with purulent pericarditis, I should like to limit my remarks to a few general suggestions.

The therapeutic problem appears to be analogous to that in empyema with the additional hazards of cardiac tamponade and the later development of constrictive pericarditis. The first point of similarity is that the diagnosis can only be made with a needle. Secondly, as in empyema, systemic antibiotics alone cannot be counted on to handle purulent pericarditis. Local instillation of appropriate antibiotics is indicated since diffusion of adequate concentrations from the blood stream into serous cavities is problematical. Actually there are no adequate data that I know of on the levels of antibotics in pericardial fluid after parenteral administration.

Should signs of uncontrolled infection or persistent cardiac compression continue in spite of repeated paracenteses, the presence of loculation with the formation of adhesions between the parietal and visceral layers of the pericardium must be suspected and appropriate measures in-

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stituted. The choice lies between surgical drainage and "medical debridement" with enzymes. Although I would hesitate to recommend it as an established procedure, the use of streptokinase and streptodornase would seem logical as a less drastic measure to be tried before resorting to surgery. These enzymes were instilled in the pericardium of one patient in Barnes Hospital this year without serious untoward effects.

The remaining time will be devoted to a discussion of some aspects of the treatment of bacterial endocarditits, which is still by far the most important bacterial infection involving the cardiac structures both in terms of frequency of occurrence and gravity of prognosis. During the past decade, it is true, the outlook in this disease has been transformed from one of utter hopelessness to one in which cure is to be expected as the general rule. Recently there has been a tendency on the part of some physicians to consider the subject a closed book, and to think that all one has to do in treating the infection is give several million units of penicillin a day for a few weeks. While such an attitude is understandable, it is also somewhat dangerous when one remembers that the mortality in bacterial endocarditis still averages around 30 per cent and has not been reduced appreciably in the past five years in spite of the appearance of several new antibiotics on the market during that time. Furthermore I cannot help being somewhat alarmed by the fact that three of the last four patients I have seen with the disease have had infections caused by an enterococcus. During the past year and a half only five patients harboring penicillin-sensitive streptococci have come under my care. I am sure that my experience does not reflect the true incidence of penicillin-resistant infections, but there is other evidence that resistant non-hemolytic streptococci are probably on the increase and account for somewhere around 20 per cent of cases[1] now rather than the 4 or 5 per cent encountered six years ago. The situation with staphylococcal infections is even worse in that two thirds of the strains isolated from a recently published series of cases[1] were found to be resistant to penicillin.

These facts make it clear that now more than ever before rule-of-thumb therapy with penicillin alone is hazardous and that every reasonable effort should be made to establish an etiologic diagnosis together with a careful evaluation of the infecting organism as to its resistance or sensitivity to the available antibiotics.

This leads us to the next real reason for discussing bacterial endocarditis at this time. How is one to decide which antimicrobial agent, or

what combination of them to use in a given situation?

With this problem in mind I should like to turn to a consideration of some of the fundamental mechanisms which seem to be involved in the cure of this disease, and to review some experimental work designed to have bearing on the therapy of this infection.

Bacterial endocarditis presents, I think, a rather special therapeutic problem which sets it apart from many of the other bacterial infections of man, in that it seems to be necessary with chemotherapeutic agents to eradicate the last viable organisms from the vegetations without expecting much help from the natural and acquired defense mechanisms of the host. Of course the latter are important in the recovery of the patient and in holding the infection in check, but by themselves they almost never succeed in completely eliminating the bacteria.

Furthermore I think it is safe to say that clinical experience to date suggests strongly that administration of a bacteriostatic drug even for many weeks is usually not successful. Specifically the sulfonamides, aureomycin, chloramphenicol and terramycin are all primarily bacteriostatic for the non-hemolytic streptococci and all have been disappointing in the treatment of bacterial endocarditis,[2-10] although the data on the last two are still scanty.

In contrast to the usual sensitivity tests which measure only the concentration of antibiotics necessary to produce inhibition of the growth of a small inoculum of organisms, generally under optimal conditions for the action of antibiotics, the studies reported here are designed to test antibiotics under conditions less favorable to their action.

The typical in vitro responses of the enterococci to various antibiotics are seen in Figures 1-5. In these figures, as in subsequent ones to be shown, are plotted the results of some experiments which were carried out as follows: A large inoculum of an overnight culture of the organism to be studied was added to a series of flasks containing 50 ml of nutrient broth so that a final concentration of between 10 and 100 million viable organisms per ml was obtained. Antibiotics were added at the time of inoculation to all flasks except the control to give the concentrations noted on the charts. At various intervals thereafter counts of the numbers of viable organisms remaining were made by means of poured agar plates which were counted finally after 72 hours incubation. Penicillinase was added whenever 0.01 u/ml or more of penicillin was present. Counts marked zero were usually checked by subculturing in broth and streak-

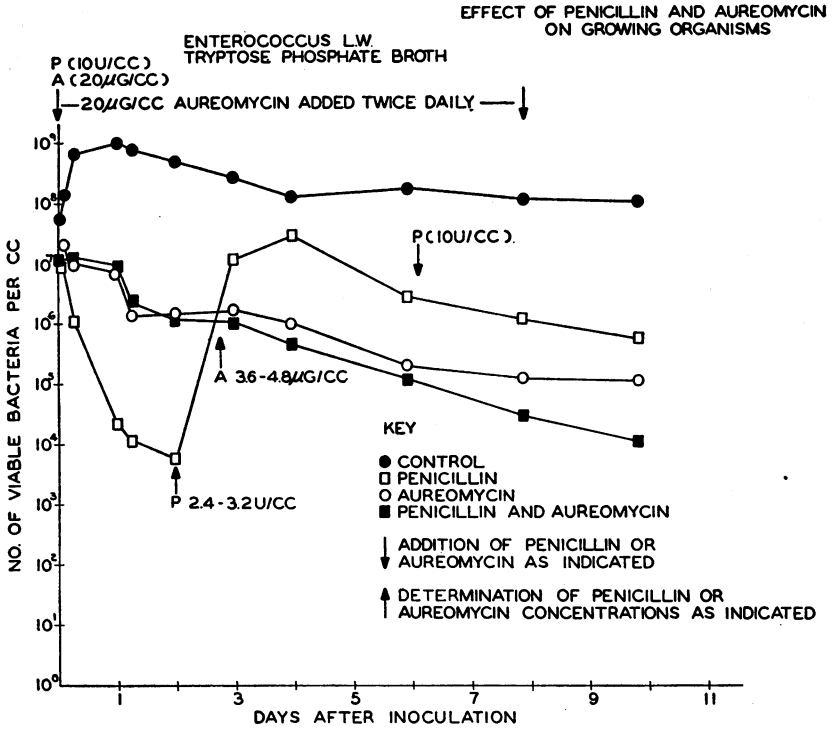

Fig. 1

ing on blood agar plates. Antibiotics were added to the flasks except in the experiments shown in Figures 1 and 2 at intervals as follows: Penicillin 20 per cent of the original concentration per day, aureomycin 100 per cent twice a day, and terramycin 30 per cent per day, so as to restore the antibiotic levels approximately to their original values at intervals.

These quantitative studies of the effects of some antibiotics on enterococci are particularly interesting when correlated with clinical experience and with the results of the usual sensitivity tests, which measure only the bacteriostatic effect of drugs. If one were guided by inhibition tests the drug chosen would usually be aureomycin, terramycin, or chloramphenicol, for as little as one microgram per cc. of one or another of them inhibits the growth of most enterococci. Yet when we follow what happens to a bacterial population exposed to 10 or 20 times the inhibiting concentration of one of these agents (Figures 1, 3, 5) we see that many viable organisms persist for weeks. If a similar effect exists in

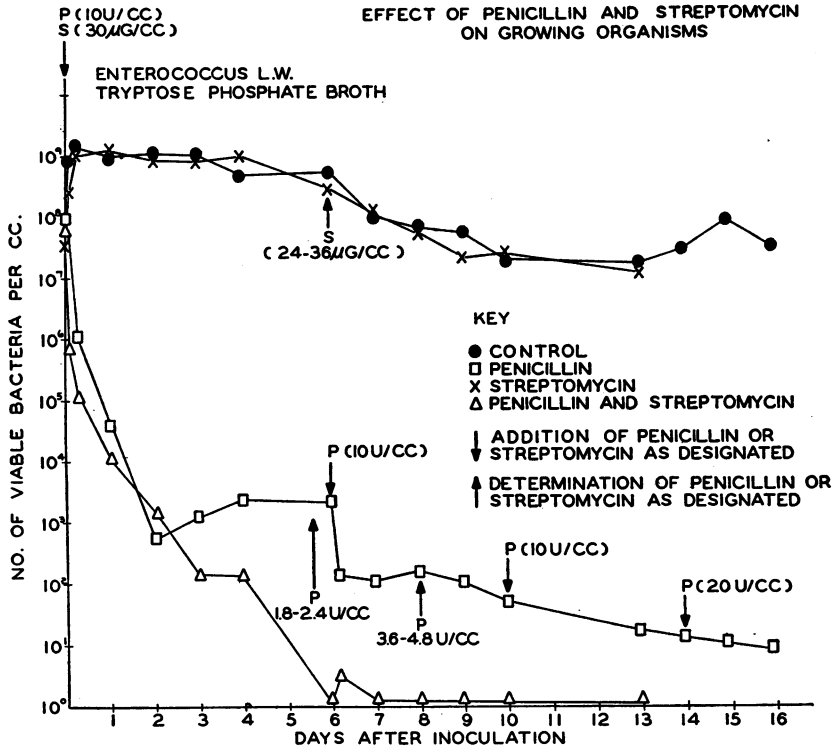

Fig. 2

the vegetation it is then not surprising that a good many patients relapse after treatment with these static drugs.

Penicillin (Figures 1 and 2) in this case does somewhat better at first, but at a concentration of 10 units per cc., which would correspond roughly with the average blood level attained by giving 10 million units a day, one still does not kill all of the bacteria. This finding in turn fits with the clinical experience that massive doses of penicillin alone frequently fail to cure enterococcal endocarditis.[3]

The effect of streptomycin is interesting and mysterious. By itself (Figure 2) no effect whatever on the growth curve of this organism is demonstrated, yet when streptomycin is added to penicillin (Figures 2 and 5) a rapid and complete killing of the whole bacterial population results. Again the clinical results with this combinaion of drugs fit with the in vitro findings. Several reports from this country and from Eng-

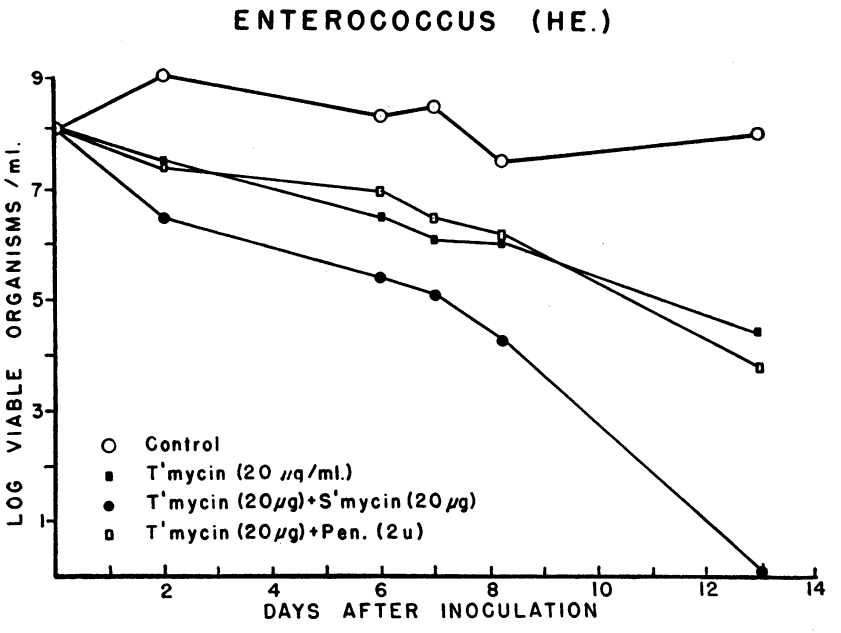
ENTEROCOCCUS (HE.)
LOG VIABLE ORGANISMS /ml.
9
7
5
3
1
2
4
6
8
10
12
14
DAYS AFTER INOCULATION
Control
T'mycin (20 µg/ml.)
T'mycin (20µg)+S'mycin (20µg)
T'mycin (20µg)+Pen. (2u)

Fig. 3

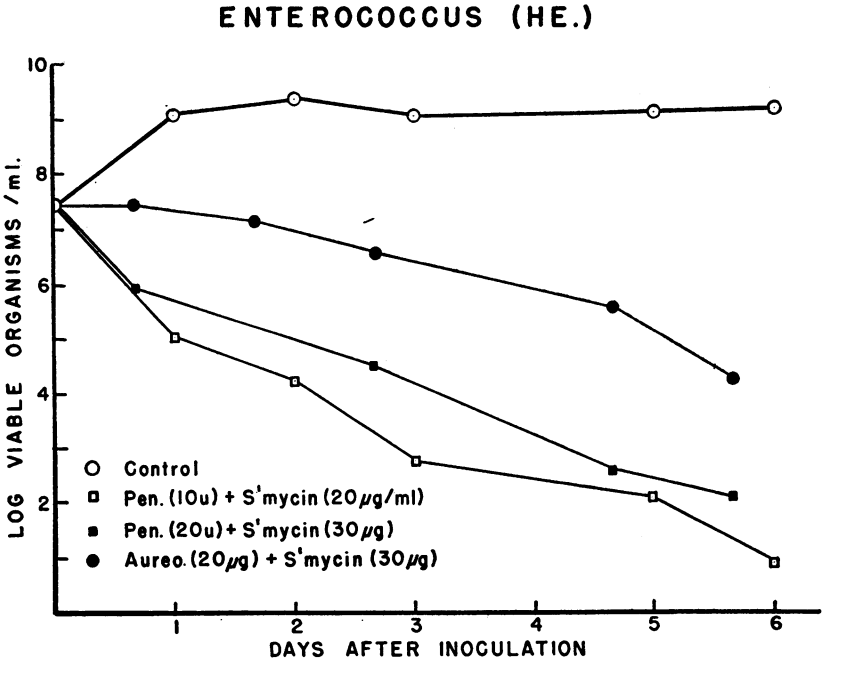
ENTEROCOCCUS (HE.)
LOG VIABLE ORGANISMS /ml.
10
8
6
4
2
1
2
3
4
5
6
DAYS AFTER INOCULATION
Control
Pen. (10u) + S'mycin (20µg/ml)
Pen. (20u)+ S'mycin (30µg)
Aureo. (20µg) + S'mycin (30µg)

Fig. 4

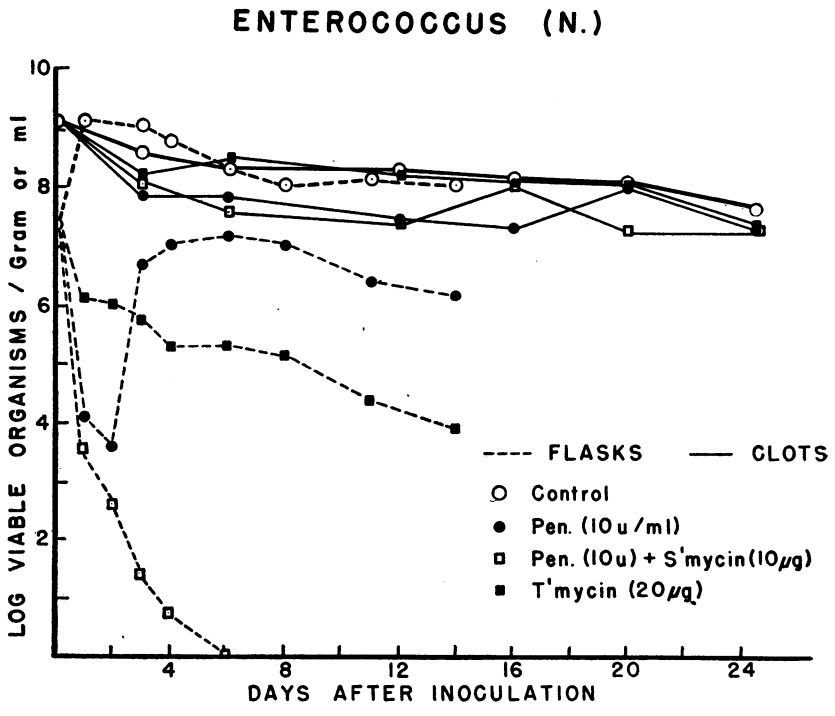

Fig. 5

land,[4-6] are in agreement as to the effectiveness of penicillin and streptomycin in the great majority of cases of enterococcal endocarditis.

The effect of combining penicillin with one of the bacteriostatic agents, aureomycin, chloramphenicol or terramycin, is difficult to evaluate at present because clinical data are largely lacking. In vitro it has been shown[7-10] that these agents all seem to interfere with the early bactericidal effect of penicillin, (Figures 1 and 3), but in some instances the bacterial population may eventually be markedly reduced. Success with this type of combination has been reported,[11] but for the time being at least it seems advisable to use penicillin and streptomycin as the first choice.

From observations on the in vitro effects of adding streptomycin to aureomycin or terramycin (Figures 3 and 4) one would be encouraged to try these combinations clinically. Personally I have not done so, in part because Dr. Geracci at the Mayo Clinic informs me that he has had a number of clinical failures using terramycin and streptomycin. Cates[6]

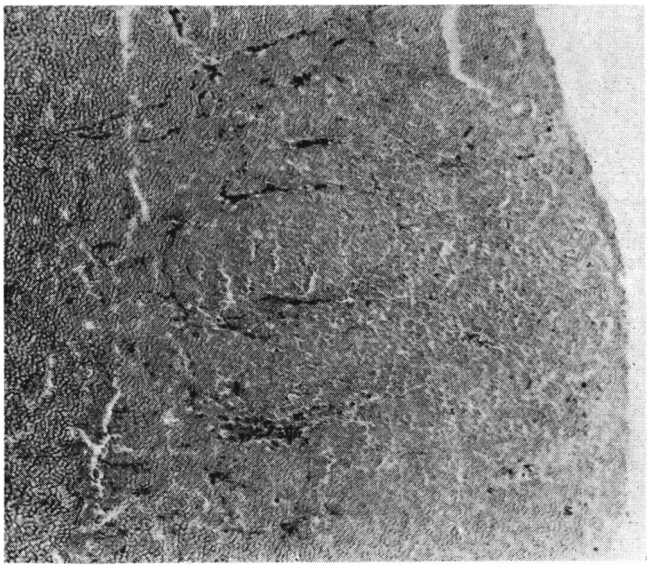

Fig. 6

also reports success with penicillin and streptomycin after failure with aureomycin and streptomycin.

It is notoriously dangerous to attempt to predict the clinical effectiveness of an agent from in vitro observations alone, but so far as we have gone the correlation of in vitro bactericidal action with results in patients is fairly good. Discrepancies exist, however, and in an attempt to elucidate other mechanisms which might have bearing on the problem, we have made some in vitro studies of the effects of antibiotics on infected blood clots.

The method is briefly as follows: 1 cc. of an overnight culture of the organism is added to a series of 25 silicone coated sterile Wassermann tubes to each of which is then added 2 cc. of freshly drawn human blood. The tubes are then mixed and allowed to clot. When the clots have retracted they are removed aseptically and transferred to tubes of nutrient broth. Thus a series of infected clots approximating the size of a large vegetation and weighing about 1 gram is obtained. These are then incubated and antibiotics are added to the surrounding media at intervals as in the previous experiments. The clots maintain their integrity for periods of weeks under these conditions, and individual clots from a

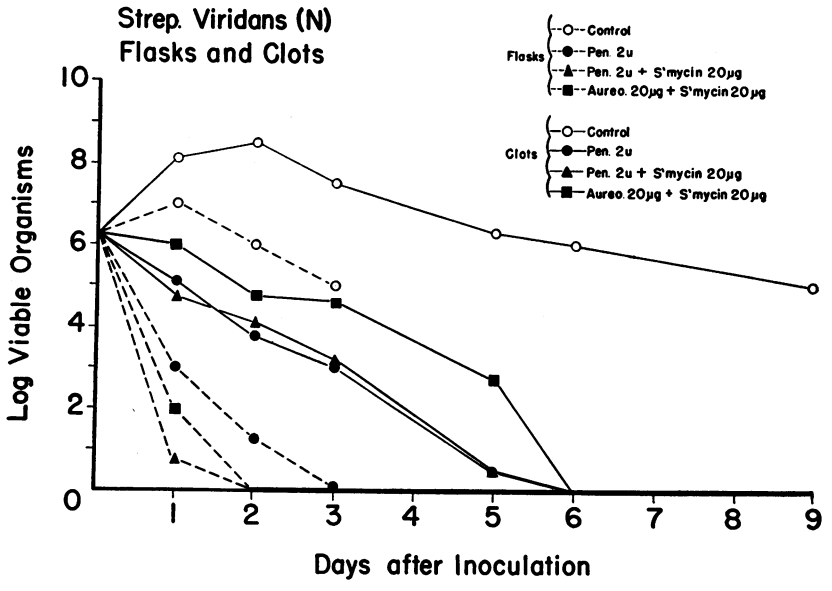

Fig. 7

series all exposed in the same fashion can be removed at intervals, weighed and ground aseptically. The numbers of viable organisms per gram can then be determined and a growth or killing curve constructed which provides a measure of the ability of antibiotics to eliminate organisms from a nidus of fibrin and blood cells. Figure 6 shows a low power photomicrograph of such a clot stained by the Gram-Weigert technique. The clot had been incubated for seven days and aureomycin 20 micrograms per ml had been added twice daily to the surrounding medium. One can see masses of bacteria in the depths as well as a few in the surface layer of fibrin in spite of the fact that the organism is sensitive by inhibition test to about 1.5 micrograms per ml of the drug. The viable count on this particular clot was 7 million organisms per gram.

Figure 5 shows the marked protective effect of the clot which we have found for an enterococcus. One sees that although the organisms can be eliminated from liquid media in six days by penicillin and streptomycin, large numbers of viable organisms remain for as long as four weeks in the clots. The patient from whom this organism was recovered was cured by a six weeks course of penicillin and streptomycin, however, which suggests that enterococci can be more readily eliminated

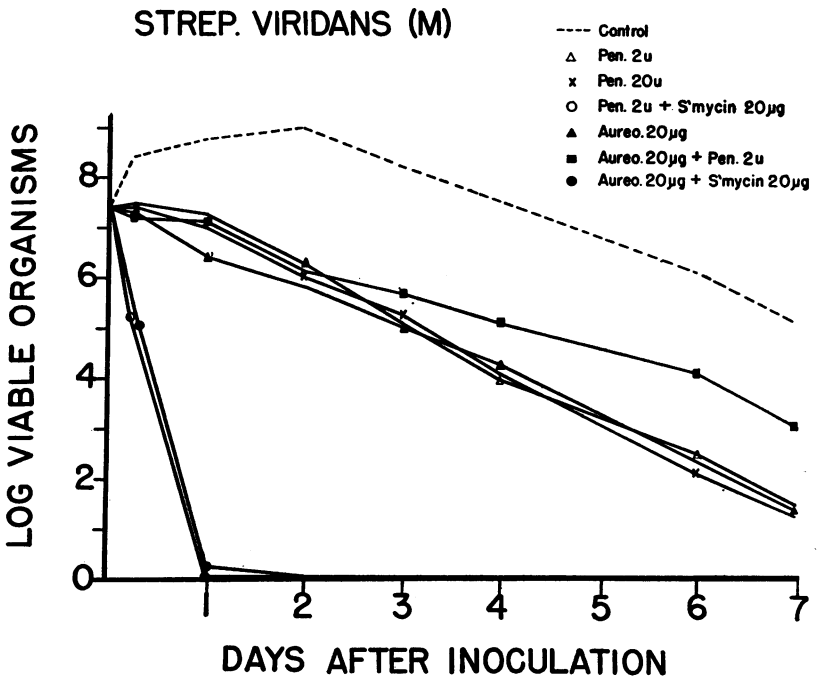

Fig. 8

from patients' vegetations than from clots in vitro at least under the conditions of this experiment.

So far we have considered only the enterococci and I think it is justifiable to stress infections caused by these organisms because of their refractoriness to the usual forms of therapy. Before leaving this subject it should be mentioned that occasional successes have been reported using truly heroic doses of penicillin alone (as high as 120 million units a day[12]) or in a few instances the combination of penicillin with bacitracin.[13]

Next I should like to present some data on ordinary penicillin-sensitive streptococci of the viridans variety with the following problems specifically in mind. What accounts for the occasional failure of penicillin therapy in a patient harboring a "sensitive" organism? Does the addition of streptomycin to penicillin offer any promise in treating this type of infection? What type of action do the antibiotics singly and in various combinations have on Streptococcus viridans?

In Figure 7 we see the response of a typical penicillin-sensitive strain. It is killed in a few days by penicillin alone when grown in liquid media

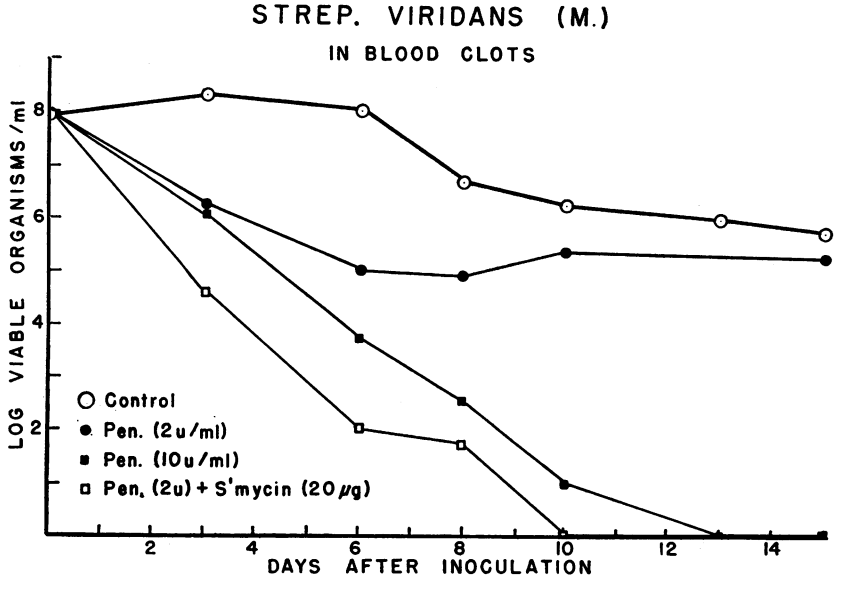

Fig. 9

and survives only for about 1 week in clots. The addition of streptomycin does not speed up the death of the organisms appreciably. On the other hand Figure 8 demonstrates that penicillin is not rapidly lethal for all strains even at a concentration of 20 u/ml. By inhibition tests this organism is as sensitive to penicillin as the first but it is killed much more slowly. Furthermore the addition of streptomycin in this case greatly enhances the bactericidal activity of penicillin in a fashion similar to that observed for the enterococci. Data on blood clots using these two organisms (Figures 7 and 9) demonstrate several points. In the first place penicillin, and penicillin with streptomycin are actively bactericidal in clots, but the latter afford some protection to the organisms and extend the time necessary for total killing of the bacteria two or more fold. Secondly, the strain variation noted in liquid media is still apparent but not so striking in the clot experiments. Nevertheless in every case penicillin and streptomycin together are at least as effective as penicillin alone and often more rapidly and completely so (Figure 10). Thirdly, in Figure 9 it can be seen that a high concentration of penicillin is definitely more effective than a moderate one in sterilizing the clot, whereas in liquid media (Figure 8) the same organism is killed just as quickly by 2 units as by 20 units of penicillin. Incidentally these strains of Streptococ-

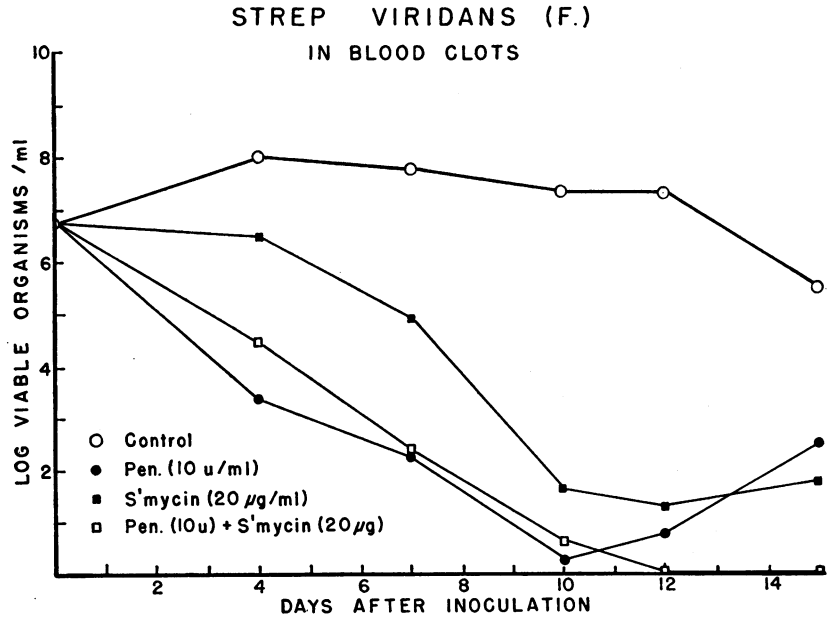
STREP VIRIDANS (F.)
IN BLOOD CLOTS
LOG VIABLE ORGANISMS /ml
10
8
6
4
2
Control
Pen. (10 u/ml)
S'mycin (20 µg/ml)
Pen. (10u) + S'mycin (20µg)
2
4
6
8
10
12
14
DAYS AFTER INOCULATION

Fig. 10

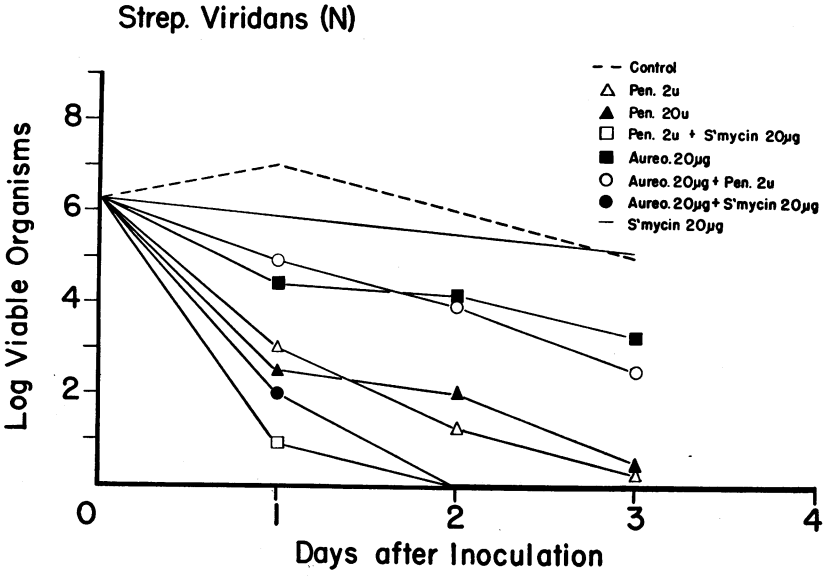
Strep. Viridans (N)
Log Viable Organisms
8
6
4
2
0
1
2
3
4
Days after Inoculation
Control
Pen. 2u
Pen. 20u
Pen. 2u + S'mycin 20µg
Aureo. 20µg
Aureo. 20µg + Pen. 2u
Aureo. 20µg + S'mycin 20µg
S'mycin 20µg

Fig. 11

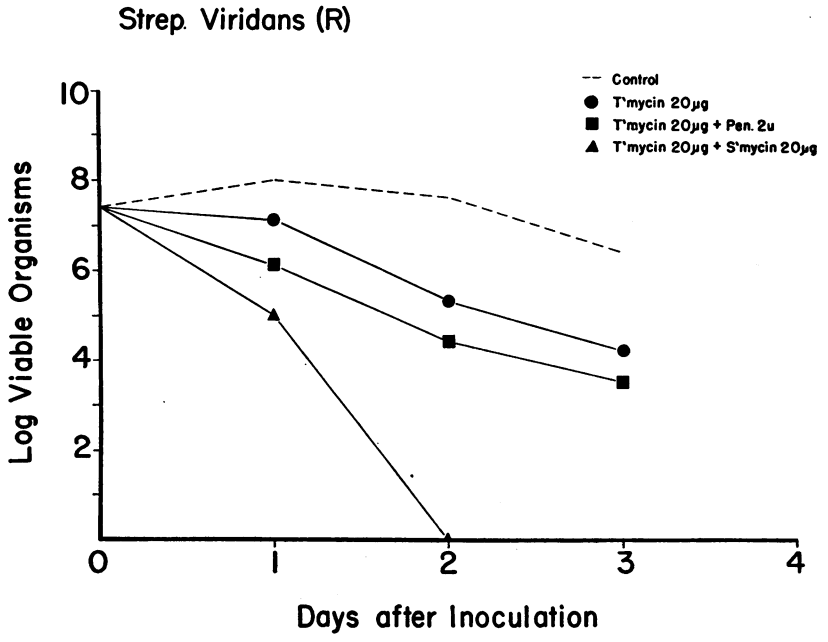

Fig. 12

cus viridans were recovered from a group of 5 patients, all of whom have been cured by a course of 2.5 million units of penicillin together with 2.0 grams of streptomycin daily for ten days. These organisms are all inhibited in vitro by 0.1 unit of penicillin or less.

The in vitro effects of aureomycin and terramycin on penicillin-sensitive strains are shown in Figures 11, 12, 13. In liquid media a bactericidal action is sometimes apparent (Figure 13) but bacteriostasis is the rule. The addition of streptomycin under these conditions usually results in rapid killing, again in spite of the fact that streptomycin by itself is usually ineffective. However, when the combinations of terramycin or aureomycin with streptomycin are tried on infected clots, the results are disappointing. Although aureomycin and streptomycin occasionally sterilize (Figure 7), the effects are usually those shown in Figure 14 where a marked protection of the organisms is apparent. Clinical data concerning the effectiveness of these combinations in patients are so scanty as to be of no great help at present, although a few failures with terramycin and streptomycin have already been alluded to.

The mechanisms whereby organisms are protected in clots against various antibiotics in varying degrees have not yet been elucidated, but

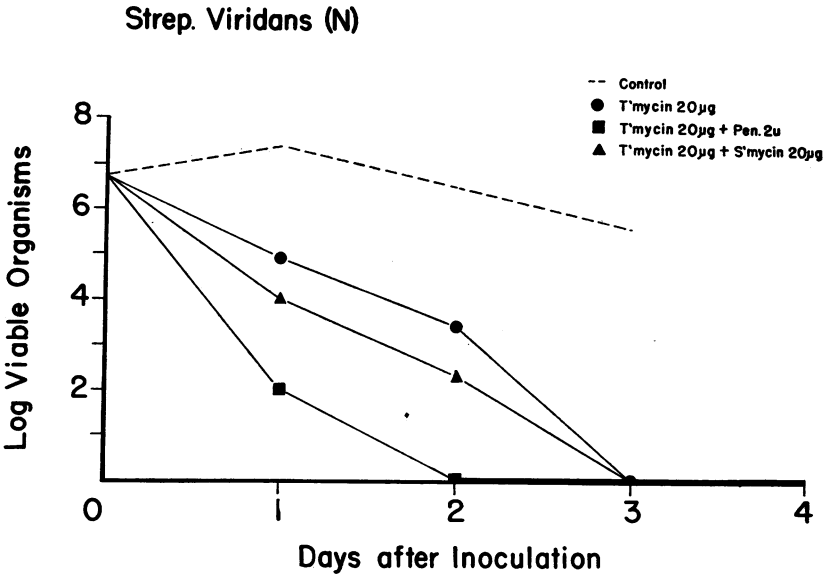
Strep. Viridans (N)
Control
T'mycin 20µg
T'mycin 20µg + Pen. 2u
T'mycin 20µg + S'mycin 20µg
Log Viable Organisms
8
6
4
2
0
1
2
3
4
Days after Inoculation

Fig. 13

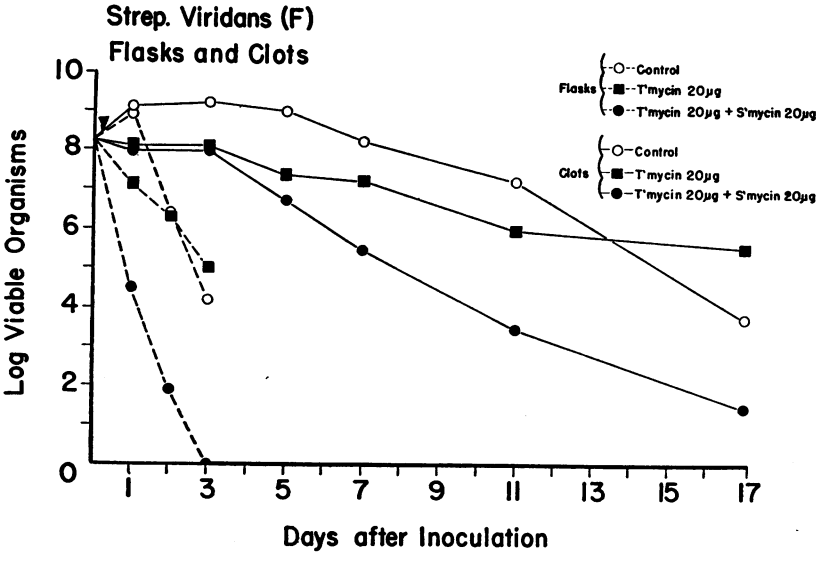
Strep. Viridans (F)
Flasks and Clots
Flasks
Control
T'mycin 20µg
T'mycin 20µg + S'mycin 20µg
Clots
Control
T'mycin 20µg
T'mycin 20µg + S'mycin 20µg
Log Viable Organisms
10
8
6
4
2
0
1
3
5
7
9
11
13
15
17
Days after Inoculation

Fig. 14

several possibilities come to mind. Variable diffusion into fibrin or chemical interactions with fibrin may play a role. A number of organisms are seen to be located intracellularly both in human vegetations and in infected clots, and it is possible that these intracellular bacteria may be protected against some antibiotics and not others. Lastly it is known that the metabolic and reproductive activity of bacteria influences very strikingly their susceptibility to antibacterial agents, rapidly multiplying organisms being, in general, more susceptible and resting organisms resistant. This is notoriously true of penicillin and in our hands is also true of other antibiotics. We have been unable to demonstrate total killing of resting populations of non-hemolytic streptococci by any antibiotic or combination of them which we have tried. It is not unreasonable to suppose that in some areas of a vegetation or clot, organisms may be in a state of maximum population density and hence in a temporary refractory state.

The practical implications of these observations and speculations are difficult to summarize. Perhaps the most important point to emphasize is that as new antibiotics come along, and many more undoubtedly will, their proper role in the treatment of bacterial endocarditis cannot be predicted by simply considering their inhibitory activity for non-hemolytic streptococci. The final court of appeal is of course clinical trial, but already the numbers of antibiotics and combinations thereof are so large as to force us to be selective in deciding what to try in patients. The studies reported herein are designed to give some leads as to possible means of selecting antibiotics which have a reasonable chance of proving effective in this infection.

Present evidence strongly favors the use of penicillin and streptomycin combined in enterococcal endocarditis. Optimal dosage and duration of treatment are not clearly defined, however; 10 million units of penicillin together with 2 grams of streptomycin daily for six weeks is probably the best current estimate. Although this regimen carries a high risk of damage to the vestibular apparatus, we feel that in such a serious infection taking this risk is justifiable.

In endocarditis caused by penicillin-sensitive organisms the evidence is not so clear-cut, but if it turns out that cure can be effected regularly in from ten days to two weeks using combined penicillin and streptomycin, the risk of encountering streptomycin toxicity will be small and the advantages over long courses of penicillin considerable.

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