Treatment of Bacterial Endocarditis
Dosage of Penicillin, Use of Other Antibiotics and Treatment of Patients with Negative Blood Cultures

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The status of the therapy of subacute bacterial endocarditis, as of June 1950, was thoroughly and authoritatively reviewed by Bloomfield in his Lewis A. Conner Lecture of the American Heart Association which was published in this journal. The same author has recently presented and discussed the problems of diagnosis and briefly touched on the prophylaxis of bacterial endocarditis in a recent issue. The present discussion will, therefore, be limited chiefly to a consideration of certain topics of current interest. These will include: (1) the optimum method of administration of penicillin, (2) the use of antibiotics other than penicillin, and (3) the treatment of patients with negative blood cultures.

Dosage of Penicillin

It is now generally agreed that penicillin, when properly used, is the antibiotic which by itself, or when used in proper combinations with other antibiotics, is responsible for all but a small proportion of the cures of cases of bacterial endocarditis. For an appreciation of the optimum method of administering penicillin in cases of bacterial endocarditis, one must consider the various factors entering into its curative action. These include: (a) the manner in which penicillin is absorbed and excreted, (b) the manner in which penicillin gets at the infecting organisms and eliminates them, and (c) the nature of the specific infectious lesion in this disease. Each of these features will be considered briefly.

Absorption and Excretion of Penicillin. Almost all of the penicillin that is given parenterally is accounted for by excretion through the kidney. The renal clearance of penicillin G in man approximates the total renal plasma flow and is independent both of the concentration of penicillin in the plasma and of the rate of urine flow. Thus, the more rapidly penicillin gets into the blood, the higher and briefer is the peak level attained and the more rapidly will that level fall. That being the case, it is obvious that when repository preparations are used, the greater the delay in the absorption of the penicillin, the lower must be the peak level from any given dose and the more slowly will the blood level drop so that the lower levels will be sustained for longer periods.

Action of Penicillin. The experiments of Eagle and his associates on the manner in which bacteria are cleared from a focus of infection should be studied in detail in order to be appreciated. For present purposes, however, it will suffice to note that from their experimental model, which was a streptococcal infection of the muscle of a mouse, they calculated that concentrations of up to 5 to 20 times those of the minimum inhibiting concentration for the organisms in vitro were required in order to achieve the maximum effective concentration at the site of infection. They also found that the aggregate time over which such concentr-
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The concentration of penicillin at the site of infection must be maintained at the focus of infection. This concentration must be sufficient to eliminate all or almost all of the organisms. Moreover, the greater the number of organisms at the site of infection, the higher must be the concentration that is reached at that point and the longer must that concentration be sustained. Host mechanisms, which bring into play the circulating antibodies and leukocytes, may be effective in eliminating residuals of small numbers of certain organisms after the concentration of penicillin at the site of the infection has reached ineffective levels.

The Lesion in Bacterial Endocarditis. The important characteristics of the lesion as they relate to antibiotic therapy have now been well described. The characteristics are: the absence of a blood supply in the tissue upon which the vegetation is implanted and the thick layers of dense fibrin, with some fibrous tissue and even calcium deposit which enclose the heavy concentrations of bacteria within the vegetations. Access to these organisms by elements within the blood, including penicillin, antibodies and leukocytes, is greatly impeded so that, on the one hand, it is difficult to attain the high concentrations of antibiotic needed at the site where the large numbers of organisms are congegated, and, on the other hand, there is little or no opportunity for the mediation of host mechanisms through the action of antibodies and leukocytes.

Weinstein, Daikos and Perrin studied the diffusion of penicillin into subcutaneously implanted fibrin clots in rabbits. They found that after a large intramuscular dose, an equilibrium between the concentration of penicillin in the blood and within the clot may be reached after about two hours; by that time the blood level has already dropped to a fraction of its peak concentration. After that time, however, the concentration within the clot may be sustained at higher levels and for longer periods than in the plasma. These experiments, together with others of Eagle's which indicate that the action of penicillin on bacteria, both in vitro and in vivo, may persist for a limited period of time after the concentrations to which the organisms have been exposed has dropped to subinhibitory levels, serve to validate the effectiveness of "discontinuous" treatment, that is, the use of intermittent injections. They also suggest that perhaps the very high peaks of concentrations which are obtained by intermittent intramuscular injections of soluble preparations of penicillin are more desirable than the lower and more sustained concentrations achieved with equal or smaller total amounts of repository preparations, including the aqueous suspensions of procaine penicillin.

From these considerations it is the writer's present conviction that aqueous solutions of sodium or potassium penicillin are the dosage forms of choice for the treatment of bacterial endocarditis. The choice between these salts depends only on considerations of the status of the cardiac and renal function of the patient. Intermittent intramuscular injections at intervals of two to four hours are also considered to be the optimum method of administration.

The total dose of penicillin has been determined only empirically, and is one which will produce favorable effects in the great majority of cases. It is related only in a general way to the in vitro sensitivity of the organism, for that is only one of the factors entering into its effectiveness; the nature of the lesion, as already suggested, is probably of equal and sometimes of greater importance, and may be crucial. In general, daily doses of 1.2 to 3.0 million units per day (individual doses of 100,000 to 500,000 units) are adequate and probably offer a good margin of safety for the majority of cases which are due to Streptococcus viridans; most strains of these organisms are sensitive in vitro to concentrations ranging between 0.01 and 0.1 units per cubic milliliter. The need for larger doses is indicated when the organism is more resistant (the minimum inhibitory concentration for most strains of enterococci is usually in the range from 0.1 to 5.0 units per milliliter, but may be even higher), when bacteremia is not controlled, or when there is other evidence of persistence of active infection. Under such conditions, the dose should be increased rapidly to about 10 million units per day or more, and serious consideration should be given to the added use of other antibiotics, particularly streptomycin.

When the dose of penicillin required becomes
of such magnitude that the size of the individual intramuscular injection is difficult to tolerate,* it is best to resort to probenecid (Benemid), which, at present, is the best available agent to inhibit the renal excretion of penicillin. Doses of 2.0 Gm. per day (0.5 Gm. every six hours) given continuously, may permit reduction of the dose by one half or lengthening of the interval between doses; this interval, however, should never be more than six hours. An increase in the individual doses of probenecid from 0.5 to 0.75 or 1.0 Gm. will increase the retention and hence the blood levels of penicillin still further. When probenecid is used, it may also be possible to substitute some rapid intravenous injections for at least some of the intramuscular doses; this may have the advantage of producing still higher peaks of concentrations than are attainable by the intramuscular route, and at the same time reducing the local distress of the large injections.

In using probenecid during the treatment of cases of bacterial endocarditis it is important to bear in mind that in spite of the fact that this agent enhances the blood levels of paraaminosalicylic acid, its action may be neutralized by other salicylates; when probenecid is used, therefore, salicylates should not be given at the same time. Also, while probenecid serves to enhance the blood levels of penicillin and phenolsulfonphthalein, it does not have any effect on the excretion of streptomycin or of any of the broad-spectrum antibiotics. In patients with impaired renal function, probenecid is not usually needed, since relatively higher levels of penicillin are sustained from any given dose, as compared with those observed in patients with normal renal function.

Use of Antibiotics Other Than Penicillin

There are reports of cases in which almost every one of the antibiotics that have become commercially available has been used, either alone or in various combinations, for the treatment of cases of bacterial endocarditis. In some of the cases these antibiotics were used during clinical investigations of the activity of the new agents, but in most instances they were given either because of apparent failure to achieve a good response from penicillin or because the sensitivity of the organism in vitro was such as to suggest that a more favorable effect might be expected. The results of the use of these agents in cases of bacterial endocarditis are reviewed elsewhere; they will be mentioned here only briefly, and the discussion of the different agents will be concerned primarily with those features of their use which pertain to their application in the treatment of cases of bacterial endocarditis.

Streptomycin. Next to penicillin, streptomycin has probably been used more than any other antibiotic for the treatment of cases of bacterial endocarditis. Its first and logical use was for the treatment of cases in which the causative organism was highly sensitive to streptomycin and relatively or markedly resistant to penicillin. However, the demonstration of an additive or synergistic effect in vitro on strains of streptococci from cases of subacute bacterial endocarditis when penicillin and streptomycin are used together, and the early favorable clinical reports on its use in patients with this disease led to the more frequent application of streptomycin, usually with penicillin, to all types of cases of bacterial endocarditis.

A brief survey of the results achieved in successive groups of cases in which streptomycin was used alone or with penicillin appears to indicate a steady improvement in the proportion of recoveries. Thus, cures were reported in only one-third of 39 cases with bacterial endocarditis collected by Keefer and Hewitt during the early clinical trials of streptomycin conducted under the auspices of the National Research Council. By May 1949, Wallach and Pomerantz were able to collect reports of 50 patients of whom 56 per cent recovered.

In 76 cases collected from other reports of patients who were treated subsequent to the appearance of these publications, the cure rate

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* Some of the pain from large intramuscular doses may be minimized by introducing 1 cc. of 2 per cent procaine hydrochloride into the syringe containing the penicillin solution immediately before each intramuscular injection.
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was 75 per cent. This increase in the cure rate, however, was associated with the more frequent use of the streptomycin in combination with large doses of penicillin; there was also a decrease in the proportion of cases due to gram-negative bacilli or to organisms highly resistant to penicillin, and an increase in the proportion of cases due to nonhemolytic streptococci and other gram-positive organisms, in a large proportion of which penicillin alone might have proved effective if used in adequate doses.

In the last two series of cases there appeared to be a striking correlation between the sensitivity of the infecting organisms to streptomycin and the percentage of cures from treatment with that antibiotic; almost all of the patients whose organism was sensitive to less than 10 micrograms per milliliter recovered, whereas cures were infrequent among patients with more resistant strains. Moreover, contrary to what might have been expected, the development of resistance to streptomycin during treatment was only rarely encountered in the cases in which its use failed to bring about a cure. In most, though not all of these cases, the failure to develop resistance to streptomycin may have been due to the fact that this antibiotic was used in combination with penicillin. In vitro experiments in this laboratory have indicated that the development of resistance to various antibiotics, including penicillin and streptomycin, by staphylococci and some enterococci and nonhemolytic streptococci may be depressed or delayed, and sometimes prevented when the organisms are exposed to the combination of two antibiotics. Personal observations have also indicated that streptomycin resistance may develop quite rapidly during even brief periods when this antibiotic is used alone for the treatment of cases of bacterial endocarditis.

These results would appear to warrant the conclusion that streptomycin is a highly useful agent in bacterial endocarditis when used alone for the treatment of infections with organisms that are highly sensitive to that antibiotic; it appears to be particularly useful in combination with penicillin for the treatment of infections due to organisms that are only slightly or moderately sensitive to the latter and to penicillin alone.

The dose of streptomycin most commonly used has been 2 Gm. a day, given either in two or four equally spaced intramuscular injections. It is usually possible to reduce this to 1 Gm. a day after two or three weeks when large doses of penicillin are also being employed. Larger doses of streptomycin have been used, but it is important to bear in mind that very high and toxic levels may be obtained in patients who have impaired renal function; in such patients, therefore, it should be possible to reduce the dose and thus avoid the early appearance of severe neurotoxicity from the streptomycin.

There is no sound basis for the prevailing trend toward use of dihydrostreptomycin instead of streptomycin. Both forms produce damage to the eighth nerve when they are used in moderate or large doses continuously over long periods; however, with dihydrostreptomycin, loss of hearing predominates and occurs in about the same frequency as do the vestibular symptoms from the use of streptomycin, which only rarely produces deafness. Sensitization reactions are somewhat less frequent with dihydrostreptomycin, but when sensitization occurs with the use of streptomycin, a change to dihydrostreptomycin can generally be made without further reaction.

There is some recent evidence that the toxicity of these agents on the eighth nerve may be markedly reduced and possibly eliminated by using the two forms in a 1 to 1 ratio. However, until this is confirmed in a large number of cases, it would appear safer to use the one, and then changed to the other at the first evidence of the appearance of toxicity. Because deafness from dihydrostreptomycin is often insidious in appearance, may not be made out until after the treatment is stopped and is usually irreversible, whereas the evidence of vestibular damage can be detected early, at a stage when it is still reversible, it would appear preferable to start treatment with streptomycin and then to change to dihydrostreptomycin if toxicity develops.

Bactracin. This agent is active only against gram-positive organisms and its possible use-
fulness in bacterial endocarditis is suggested by the fact that in vitro an additive or synergistic effect with penicillin has been demonstrated against some strains of streptococci obtained from cases of this disease. The major drawback to the use of bacitracin has been its nephrotoxicity which is apparently intimately related to its antibacterial action. However, when used in intramuscular doses of 100,000 units per day or less, only minor and transient effects on renal function and on the urinary findings are noted. The daily dose is usually given in three or four equally spaced intramuscular injections. Local irritation at the site of the intramuscular injections is frequently encountered; this may be reduced by diluting the bacitracin in 1 or 2 per cent procaine.

The results in the reported cases that are available for evaluation have been almost uniformly favorable with the doses mentioned, given in combination with large doses of penicillin. There was one favorable result from the use of bacitracin alone, and the only failure was recorded in a patient who was treated with increasing doses of bacitracin for pneumococcal pneumonia complicated by meningitis and endocarditis. In the latter case evidence of renal damage attributable to bacitracin was found at autopsy, but doses up to 400,000 units per day had been given.

From the meager data that are available, it may be stated that bacitracin can be recommended as an agent which merits further trials under controlled conditions and in conjunction with penicillin in cases of bacterial endocarditis due to gram-positive organisms, particularly those which are not highly sensitive to the latter antibiotic alone.

Broad-Spectrum Antibiotics. The three antibiotics commonly included in this category are chlorotetracycline (Aureomycin), oxytetracycline (Terramycin), and chloramphenicol (Chloromycetin). Each of these antibiotics has been used for the treatment of cases of bacterial endocarditis; they were used only rarely alone, but more often in various combinations involving one or more of them with penicillin, or streptomycin, or both, and in an occasional patient a sulfonamide was thrown in for good measure. An analysis of reports collected from the literature in more than 67 cases of bacterial endocarditis treated with Aureomycin, 27 with Terramycin and 13 with chloramphenicol is given elsewhere.7 Between 32 and 44 per cent of the patients were cured during treatment with one or another of these agents and in most, though not all, of the cured patients other antibiotics were given at the same time. The results with Aureomycin appeared to be slightly, though not significantly superior to those obtained with the other two agents, but comparisons in such small numbers hardly seem warranted.

In most of the patients, these antibiotics were given only by mouth, but the intravenous route was used in some of the patients who received Aureomycin, especially at the beginning of therapy or as a supplement to oral treatment later during times when untoward gastrointestinal symptoms were encountered. The most frequent oral dose of each of these agents was between 2 and 4 Gm. per day, given in four to eight doses. The usual intravenous dose was 500 mg. given as an infusion in saline twice a day, but only one daily injection was generally used to supplement oral therapy.

From the review of these cases it would appear that some patients may be favorably affected and even cured with one or another of these broad-spectrum antibiotics. The results with these agents, however, are far less impressive than those with penicillin alone and particularly with the combination of penicillin and streptomycin. However, some of the cures, particularly as a result of Aureomycin, were obtained in patients in whom penicillin alone or in combination with streptomycin had apparently failed. With each of these agents highly favorable clinical effects and failure to obtain positive blood cultures were noted in some patients during their administration, but clinical and bacteriologic relapses occurred either during the continued therapy or promptly after that antibiotic was stopped. These effects are usually attributed to the mode of action of the broad-spectrum antibiotic which is considered to be bacteriostatic rather than bactericidal. In some of the cases of failures from each of these three antibiotics cures were subsequently obtained by the use
of other antibiotics, singly or in various combinations (some of which included the broad-spectrum antibiotic which alone had failed) but most frequently with large doses of penicillin combined with streptomycin.

Considerable interest has been focused recently on the problem of synergism and antagonism which may of course come into play in the treatment of cases of bacterial endocarditis when multiple antibiotics are employed. Some aspects of this subject have recently been reviewed by Jawetz and Gunnison.12 Judging from experimental data, antagonistic action between antibiotics may be expected in certain cases from the use of the broad-spectrum antibiotics in combination with penicillin or streptomycin. However, there is as yet no proof that such an effect has been responsible for any significant number of failures in bacterial endocarditis, although the findings in some cases may be open to such interpretations.

The only recommendation that seems warranted from the results thus far obtained is the obvious one that the sensitivity of the infecting organisms in cases of bacterial endocarditis should be tested with all of the antibiotics which might possibly prove useful and that tests with pairs of these antibiotics should also be included. The use of the broad-spectrum antibiotics would then be reserved only for patients in whom penicillin alone or in combination with streptomycin or bacitracin has failed, or where such failure might be predicted from the resistance of the organism to these agents in vitro, or when the use of these agents is not possible because of marked hypersensitivity. The broad-spectrum antibiotics are not to be recommended for the initial therapy of doubtful cases, or when treatment is undertaken before the sensitivity of the organism is known, or in patients with negative blood cultures.

Erythromycin (Ilotycin) and Carbomycin (Magnamycin). The use of these new antibiotics, each of which has an antibacterial spectrum similar to that of penicillin, has been reported in only a few patients with bacterial endocarditis. However, in only one of the cases reported at the time of this writing was treatment with erythromycin successful, whereas similar treatment failed in six other patients and four of these failures were associated with the rapid development of resistance to erythromycin in the infecting organism during treatment with that agent. Carbomycin failed to yield a single cure in the six patients with bacterial endocarditis in whom it was used.

Maximum tolerated doses were used orally in all of these patients, and in some of those treated with carbomycin they were supplemented with intravenous injections of the same agent. In the majority of the patients in whom failures were reported from these two antibiotics, cures were subsequently obtained by the use of large doses of penicillin, either alone or together with streptomycin.

In vitro experiments in this laboratory have shown that when certain bacteria are exposed to the combination of erythromycin with either penicillin or streptomycin, the development of resistance to each of these antibiotics may be delayed or depressed. Whether or not the use of such combinations in the treatment of bacterial endocarditis due to susceptible organisms will prove more successful than the use of these new antibiotics alone remains to be determined. At present the use of these antibiotics in the treatment of bacterial endocarditis cannot be recommended, except where carefully controlled studies could be made.

TREATMENT OF PATIENTS WITH NEGATIVE BLOOD CULTURES

Patients with bacterial endocarditis in whom one fails to obtain positive blood cultures present a special and difficult problem. The importance of these cases may be judged from the fact that in some of the reported series, the mortality is twice as high, or even greater, among those patients as in those in whom positive blood cultures are obtained. Among the reasons offered for this difference in mortality are: (1) delay in treatment, (2) erroneous diagnosis, (3) inadequate or improper treatment; all of these are due to the fact that a positive blood culture is not available as a guide.13 It may also be suggested that in such cases a deep focus of infection well protected
by fibrin and fibrous tissue and perhaps by calcium deposits may be responsible for both the failure to obtain a positive blood culture and for the poor therapeutic results. If the latter explanation is valid, one should expect improvement in the results if such patients are treated with massive doses of penicillin, perhaps in combination with streptomycin. The good results reported by Loewe and Eiber\textsuperscript{14} in a group of such cases may be cited in support of this view. On the other hand, the poor results have usually been correlated with the presence of severe complications, particularly congestive heart failure and serious or extensive embolization.

In order to reduce to a minimum the number of failures in these cases, Friedberg\textsuperscript{13} has suggested that insistence on obtaining a positive blood culture be eliminated from the criteria for the diagnosis of bacterial endocarditis for the purpose of initiating antibiotic therapy. This is a reasonable suggestion, but, if adopted, one should also insist on certain other steps: (a) some definitive clinical criteria for the diagnosis of bacterial endocarditis; (b) exclusion of other important diseases which could account for the clinical findings; (c) a delay of at least two days before treatment is initiated, during which period blood cultures should be made on several occasions; (d) the media used for the cultures should include those which permit the growth of anaerobic bacteria, fungi and certain fastidious organisms like Brucella, Hemophilus and Neisseria, and the cultures should not be discarded until they have been incubated and examined over a period of three weeks; (e) cultures of aspirated bone marrow may also be useful particularly in patients who have recently been treated with antibiotics.\textsuperscript{15} A delay of more than 48 hours under the above conditions is probably of very little if any advantage.\textsuperscript{16}

For the initial treatment of these cases before the results of a blood culture are obtained a regimen comparable to that which is used in the treatment of subacute bacterial endocarditis due to a relatively resistant organism is adopted. This includes massive doses of penicillin plus streptomycin. One may begin with a dose of 1.2 to 3.0 million units per day of penicillin alone, but this should be increased within a week to at least 10 million units a day and 2 Gm. of streptomycin daily should also be given if clinical improvement does not result. Should any of the cultures obtained before treatment subsequently turn positive, the organism should be tested for sensitivity, and any treatment that has been undertaken could then be changed to accord with the results of these tests if the response of the patient by that time appears to be inadequate or poor.

The use of corticotropin (ACTH) or cortisone in such cases has been suggested, but is not to be recommended, except as an investigative procedure carried out with the greatest of care and under strictly controlled conditions. The depression of resistance to infection during administration of these hormones has now been demonstrated in a wide variety of experimental and clinical infections. Even in cases with active acute rheumatic fever, the use of corticotropin and cortisone involves a definite risk of bacterial infection developing on valves not previously infected, or of aggravating a bacterial endocarditis that is already present, and possibly also of reducing the efficacy of antibacterial therapy.\textsuperscript{17}

**Summary and Conclusions**

The dosage of penicillin has been discussed on the basis of the known properties of that antibiotic and the characteristics of the lesion in the patients with bacterial endocarditis. Reasons have been given for the choice of large and frequent intramuscular doses of the aqueous soluble salts of penicillin G, supplemented in certain cases by the oral use of probenecid (Benemid) as the optimum method for using penicillin in this disease.

The status of the use of antibiotics other than penicillin in the treatment of cases of bacterial endocarditis has also been reviewed. Streptomycin appears to be firmly established as a highly valuable agent in this disease, particularly when used in conjunction with large doses of penicillin. Favorable reports of the use of bacitracin in doses of 100,000 units per day in combination with large doses of penicillin indicate that further trials of this
antibiotic are warranted. The broad-spectrum antibiotics particularly chlorotetracycline (Aureomycin) have proved to be life-saving in individual cases; the over-all results from the use of these agents, however, have not been nearly so impressive as from penicillin and streptomycin. Erythromycin and carboxymycin have thus far proved ineffective.

The problem presented by the patient with a clinical diagnosis of bacterial endocarditis but with negative blood cultures is also discussed. Intensive clinical and bacteriologic study during a period of about 48 hours, followed by treatment with large doses of penicillin in combination with streptomycin is suggested for the management of these cases, with less delay only when they are particularly severe and of long standing, or already show evidence of cardiac failure or extensive or significant embolic phenomena.

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