The Lewis A. Conner Lecture of the American Heart Association

The Present Status of Treatment of Subacute Bacterial Endocarditis

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Some considerations concerning the fundamental pathology of bacterial endocarditis which have a bearing on treatment are discussed. In using antibiotics the importance of time-dose relationships is emphasized. It is pointed out that tests for strain sensitivity give a useful clue to the total daily dosage but that regardless of this, treatment must be carried out over a period of at least a month in order to achieve permanent bacteriologic cures. The difficulties and complications of treatment are discussed. Special methods for the treatment of highly resistant strains and the results with some of the newer antibiotics are outlined.

I WANT to say first of all how very much I appreciate the honor of being invited to give the Lewis A. Conner Lecture before the members of the American Heart Association. As an internist whose practice is in no sense confined to cardiology I hesitated to accept, but then I took courage from the realization that Dr. Conner himself was, after all, primarily a general doctor who, only after years of practice, claimed a special interest in problems of the circulation. Furthermore, the title suggested by your Chairman was too tempting to resist when one realizes that the new treatment of bacterial endocarditis is, barring insulin, probably the greatest therapeutic triumph of the century in internal medicine.

We were fortunate, as long ago as 1943, in being asked to participate in the bacterial endocarditis program of the Committee on Medical Research. Six years of experience have modified some of our original views, but more or less definite policies as to procedure have now become crystallized, and these we wish to bring before you today. We shall touch especially on the use of newer preparations, singly and in combination, on routes of administration of antibiotics, and on the importance of sensitivity tests in determining time-dose relationships. It is perhaps only natural that emphasis be placed on the work of our own group.

It would be superfluous to review to this audience the background, clinical features, and bacteriologic findings of infectious endocarditis; they are familiar to all. It may be recalled, however, that prior to the introduction of penicillin most clinicians, even those of wide experience, could not recall instances of actual recovery from proved bacterial endocarditis. At best, the measures then in vogue, such as sulfonamides and anticoagulants, were a feeble crutch to lean on and the hazards of therapy almost outweighed the occasional cure which was claimed. One felt that another such vic-
tory and like Pyrrhus we would be undone. Now, although all concede the brilliant results of penicillin therapy there are somewhat divergent views as to just how recovery is effected, and this makes it necessary to outline a few fundamental concepts of *Streptococcus viridans* endocarditis.

**The Nature of Subacute Bacterial Endocarditis**

Lenhartz in Germany, Horder in England, and Osler, Libman, and others in this country early noted the slow and relentless character of the disease. Schottmuller's designation of "endocarditis lenta" pictures well the insidious onset and vague course so often observed. We recall a patient who enjoyed his horseback ride each morning but went to bed with fever every afternoon for months before he was forced to discontinue his activities. A medical student, informed of the diagnosis in her freshman year, went on with her studies for two years with great assiduity. The stormy course occasionally pursued by the disease only emphasizes the usual insidious progress.

Now, when one turns to the character of the lesions some light seems to be thrown on the clinical events. Harbitz years ago, and Libman and others noted that in the verrucose excrescences on valves or endocardium there is often a distinct tendency to fibrosis, scarring and calcification which takes place especially in the older portions of the lesion. In other words the thrombotic vegetative process may spread slowly, fresh and active at the periphery, while healing of a sort takes place in the older or central part. Modern pathologists and clinicians also accept this interpretation. One has, therefore, the paradox of a disease which in the clinicians' hands, if untreated, is always fatal but which to the pathologist shows definite signs of arrest. No less important is the distribution of the cocci in the usual form of *S. viridans* endocarditis. While they are readily stained in the superficial parts of the vegetations, masses of organisms may also be seen trapped and encased in the deeper fibrotic and perhaps even calcified reaches of the lesion, or buried beneath a mass of platelets and fibrin.

These considerations have, we believe, an important bearing on the rationale of treatment with antibiotics. One needs first of all an agent which will prevent the relentless peripheral spread of the lesion. If this can be arrested, then there is time for a long attack on the cocci buried in the older vegetations so that the natural tendency to organization and healing may take effect. In actual practice it is indeed very hard to say to what extent healing is due to direct antibiotic action and how much nature contributes. At any rate it must be quite clear that the essence of the treatment is time. No agent, no matter how great its bactericidal effect, can be expected to dislodge cocci from the depths of vegetations in just a few days, the agent must be present over a long period to aid and abet the natural healing process and to nip off any organisms which stray to accessible surfaces. Otherwise, viable bacteria dormant in the vegetations may again light up an active and progressive process. That this position is sound was shown early by the observations of Christie on time-dose relationships. He demonstrated that a large amount of penicillin per day for a short time was followed by prompt relapse when the same total dose spread over a longer time effected cure. The common experience during the early days of penicillin of recrudescence in too briefly treated cases confirms these purposeful observations.

**Time-Dose Relationships**

Assuming that an appropriate daily dose of an antibiotic has been selected, over how many weeks should uninterrupted treatment be continued? In our early cases we arbitrarily treated for 60 days and as it happened, this turned out to be a fully adequate period. It is not likely that anything would often be gained by more prolonged therapy. Even so, in a patient who died of cardiac failure four months after "cure" of her bacterial endocarditis by penicillin, masses of cocci could still be seen in the depths of the scarred mitral valve. These lesions are beautifully pictured in the paper by Carnes and Tinsley. Recently we have wondered whether 60 days may not be too long and Rantz and his associates in our clinic have convinced
themselves that 30 days of continuous treatment, provided the daily dose is adequate, yields equally good results. Periods of therapy short of this must, however, be definitely classed as bad practice.

What, then, is the adequate daily dose and how should it be administered? To answer this question intelligently it is essential to isolate and identify the causal organism and to test its sensitivity to the available antibiotics. Many strains of *S. viridans* can be grown only with considerable difficulty. Repeated blood cultures at intervals of a few days, a dozen if necessary, should be made using solid and liquid media kept under both anaerobic and aerobic conditions. In one of our patients a single colony on the fourteenth culture confirmed the clinical diagnosis. We have summarized elsewhere the reasons why failure to recover bacteria in ordinary cultures does not exclude the presence of living organisms in the vegetations or in the blood stream. Even arterial blood gives only slightly higher counts than blood from antecubital veins according to the thorough studies of Beeson and his colleagues. So that occasionally a patient with adequate clinical evidence must be treated even though there is no bacteriologic confirmation. In such cases, or if strain sensitivity has not been tested,* it seems advisable to err on the side of heavy penicillin dosage—4 to 12 million units daily.

In the early days of penicillin therapy the question was often raised as to whether it was necessary to keep up a high blood level of the antibiotic around the clock. Continuous intravenous drip was used at first in the hope of maintaining such a level. Subsequently it appeared that an injection every three hours might be equally effective and that continuous infusions of penicillin were not necessary. If the time between injections is lengthened, however, blood levels fall to an insignificant point and actual practice shows that results may be less secure regardless of theoretic considerations. This is well illustrated in the case reported below under reinfection. One hundred thousand units given every six hours failed to extirpate the infection, but 50,000 units every three hours sterilized the blood stream. Today, of course, the question of the number of daily doses is to some extent a dead letter since the slowly absorbed penicillin now in general use maintains desired blood levels even if the total 24 hour dose is given in only one or two injections.

**Importance of Sensitivity Tests**

Not all have agreed that sensitivity tested in vitro gives the correct answer to clinical dosage but an actual exploration of the subject has convinced us as well as others that such testing is of the greatest practical value. In the early work patients whose strains of *S. viridans* were inhibited by 0.05 unit or less of penicillin per cc. of culture medium were uniformly cured (and never yielded another positive blood culture) by daily doses of only 200,000 to 320,000 units of penicillin, but today we would usually give a larger amount. Patients with strains requiring 0.1 unit for test-tube inhibition were invariably and securely cured by doses of 400,000 units daily. When test tube inhibition required larger amounts (0.2 to 0.4 unit per cc. or more) such standard therapy failed in every case and much larger doses of penicillin were necessary. If the strain was even more resistant, we learned that very large doses (5 million to 20 million units daily) might be required, and in such cases the virtues of other antibiotics or combinations of several, should be explored.

An important question is whether subcutaneous doses of penicillin may lead to increased resistance on the part of *S. viridans*. We have seen 2 cases in which such increased resistance occurred. In one the inhibiting dose rose from 0.2 to 1 unit per cc., in the other from 0.4 to 3.2 units per cc. In both, sensitivity increased when penicillin was temporarily stopped and both were later cured by much larger doses of antibiotics. This shows the importance of giving fully adequate doses from the start.

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* In our clinic sensitivity tests have been carried out under the supervision of Dr. L. A. Rantz by a method in which the organism is planted on blood agar plates containing various concentrations of the antibiotic.
THE PRACTICAL PROCEDURE OF TREATMENT WITH PENICILLIN

There can be no discussion of treatment without first emphasizing the importance of early diagnosis. When vegetations are small and the gross destruction and deformity of the late lesions is not yet present, thorough treatment may leave the patient as well as he was before the infection. Every person with signs of a valve lesion or of a congenital defect should be scrupulously watched by his physician for early evidence of bacterial endocarditis. In the aged especially, symptoms may be mild and indefinite and fever very slight, so that the diagnosis of endocarditis is easily overlooked. During the course of respiratory or certain other infections and in connection with dental extraction or oral surgery special care should be taken, and prophylactic injections of penicillin should be generously used. With tooth extraction penicillin should be given not only before the operation but for several (four to six) days thereafter in full doses. The frequency of onset of bacterial endocarditis following dental procedures fully justifies such an effort.

When the diagnosis has been confirmed and the sensitivity tests have been completed, treatment should be systematically planned. The type and extent of the lesions, the general cardiac condition, the degree of fever, the presence of embolic or other complications, must all be considered in deciding whether bed rest is obligatory or whether activity should be allowed. We consider it safer, if possible, to start therapy in the hospital and at bed rest. After a week or two, if all is going well and the basic heart condition allows, mild activity may be permitted. We have never regretted being conservative on this point.

The intravenous and subcutaneous routes for administration of penicillin have long been discarded and intramuscular injections are always used. So, too, we have abandoned all oily preparations and employ either crystalline penicillin or slowly absorbed aqueous procaine penicillin. Even in patients with a highly sensitive strain of S. viridans we use at least 600,000 units daily; the total can conveniently be given in two injections at 12 hour intervals and such treatment has invariably been adequate. In cases with resistant strains where much larger amounts of penicillin (6,000,000 units or more) are required, it seems advisable to break the total into six or eight injections, in which case plain penicillin G is perhaps simpler to administer. However, my associates in a resistant case gave single intramuscular injections of aqueous procaine penicillin G of 1,200,000 units (4 cc.) at three to six hour intervals so that in 27 days the total quantity administered was 165,000,000 units in 550 cc.

The question of anticoagulants has led to rather strong partisan feelings. It has not been our practice to use them and thorough analysis of the problem by Priest, Smith and McGee led them to feel that anticoagulants probably did not prevent major embolism but merely added some difficulty and risk to an already complicated situation.

RESULTS WITH PENICILLIN

During the past few years there have appeared numerous excellent papers on the results of treatment of bacterial endocarditis with penicillin. It would serve no useful purpose, however, to attempt to analyze statistically the figures given in these reports since the clinical material and treatment programs varied widely and the total number of cases is still not large. The nature and extent of the antecedent lesion, the amount of cardiac reserve, the sensitivity of the infecting bacteria to penicillin, the age of the patient, the length of time between infection and start of treatment, for example, all play a part in determining the outcome as well as the actual scheme of therapy. It will be more useful, therefore, to discuss the results achieved in various types of cases.

All agree that the most favorable patient is the fairly young individual with a slight valve lesion or a mild congenital defect such as a patent interventricular septum in whom early diagnosis of bacterial endocarditis is made and whose strain is highly sensitive to penicillin. In patients of this sort one may predict practically 100 per cent permanent cures without noteworthy deterioration of cardiac function when 300,000 to 600,000 units of penicillin per day are given for 30 days. The usual course of
events in such cases is quite constant. Within 24 hours the patient usually declares that he feels better. Malaise and other toxic symptoms abate often with amazing speed. At the same time fever usually subsides so that an essentially normal level is reached within a day or two. At times unexplained rises of temperature may be noted for some time; their exact nature is not clear. Release and absorption of tissue products in connection with resolution of vegetations must be considered. The blood culture usually promptly becomes negative and thereafter no more bacteria can be recovered from the blood stream. As a rule, within a week the patient who has no great impairment of cardiac function feels perfectly well and begins to chafe at restraint of his activity. It must be emphasized, however, that hazard of embolic phenomena, of perforation or rupture of valves persists for some time, in our experience at least as long as 50 days after therapy is started. Some of the greatest disappointments have occurred in patients doing well when a late hemiplegia or other accident takes place. We have had no chance to fully appraise the effect of penicillin therapy on the renal lesion, a problem which deserved very careful exploration, but the possibility of progressive renal damage is another strong argument for early diagnosis and thorough treatment. The following case illustrates how easily the infection may at times be extinguished with small doses of penicillin; it also shows the subsequent excellent prognosis:

An 18 year old girl had had rheumatic fever at the age of 10. She was left with a heart murmur but was essentially well. About four months before entry, in April 1944, she developed fever, malaise, joint pains and palpitation. Seven blood cultures were reported positive for *S. viridans*. She did not appear very ill. There was moderate fever. There were signs of a mitral lesion and blood culture again yielded *S. viridans*, which was inhibited by 0.05 unit per cc. of penicillin. There were a few petechiae, but the spleen was not felt. There was no evidence of a renal lesion. She received 300,000 units of penicillin daily by intravenous drip for eight days and slightly smaller amounts for the next three days. Thereafter, intramuscular injections were given every three hours totalling only 120,000 to 200,000 units daily. Total penicillin was only 10,000,000 units over 60 days. There was a prompt drop of temperature to normal and she felt very well. The blood cultures immediately became negative and remained so. She left the hospital clinically well, but with the cardiac signs unchanged. This patient has been carefully followed and was last seen in May, 1949, five years after the conclusion of therapy. She was perfectly well and had had two successful pregnancies. There was no evidence of deterioration of cardiac reserve and the physical signs were exactly as described on the first entry.

This case illustrates beautifully the very small amounts of penicillin which may be adequate to cure bacterial endocarditis and the preservation of cardiac function if the infection is treated early. Today, however, we would probably give a case like this 600,000 units daily of procaine penicillin in two doses over a period of a month.

Patients with badly damaged valves and with limited cardiac reserve have a much worse prognosis. Here again bacterial sterilization is usually readily achieved if the strain is sensitive but victory gives way to defeat when cardiac failure supervenes. This whole question has been thoroughly analyzed from our clinic by Fiese. He found in the 30 per cent of our treated patients who subsequently developed failure that the following factors were of importance: age, the type of cardiac lesion, previous cardiac reserve, x-ray appearance of heart, length of time until treatment, the height of the fever, degree of bacteremia and care of heart after treatment. The situation is therefore very complex. In several of our cases there has been some suggestion that the type of healing which goes on under penicillin may in itself lead to distortion of valves so as to promote later cardiac failure. In the case reported by Carnes and Tinsley for example, the mitral valves post mortem were mere fibrotic nubbins. Similar experiences have been noted by Rosenblatt and Loewe and others who also have been disappointed when cardiac failure developed in cases bacteriologically cured. Here, then, is another strong argument in favor of early diagnosis and prompt therapy before great damage has occurred.

The following case illustrates cardiac failure following otherwise successful therapy.

A 34 year old man, an accountant, had had polyarthritis at the age of 15. A heart murmur was known to have been present since then. Five months
before entry in 1944 he developed an indefinite febrile illness. There were typical signs of mitral stenosis, a palpable spleen, clubbing, and petechiae. There was evidence in the urinary sediment of a mild glomerulitis. Blood culture yielded nonhemolytic streptococci. Treatment consisted of a total of 9,500,000 units of penicillin, intravenously for 18 days, intramuscularly for 32. He gained 20 pounds and changed from what appeared to be a dying man to one who seemed perfectly well, and the blood cultures remained sterile. The heart murmurs persisted and the pulse was slightly rapid. The signs of the renal lesion disappeared. He had no symptoms of failure at all before treatment but as soon as he became active after treatment there were tachycardia and slight shortness of breath on effort. Cardiac incompetence progressed, the heart enlarged, he developed frank failure and took his life nine months after discharge.

It was the impression that a man only 34 years old with an asymptomatic lesion would not have progressed to failure as rapidly as this man did had it not been for the infection. Although there was no recurrence of bacterial endocarditis one wonders whether, in the process of healing, shrinking and damage did not take place which contributed to his rapid failure.

THE MANAGEMENT OF CASES ASSOCIATED WITH RESISTANT STRAINS OF S. VIRIDANS

A great deal of work has been done on classification of strains of S. viridans isolated from cases of subacute bacterial endocarditis. An excellent discussion is also to be found in Swift's recent article. It seems that, whereas most cases of bacterial endocarditis are caused by streptococci of the viridans group, about 10 per cent have infections with streptococci of group D, especially the so-called enterococci or S. fecalis. These organisms are usually extremely resistant to penicillin in the test-tube. Ten to 50 or more units per cc. of medium may be necessary to inhibit their growth and a corresponding refractoriness to therapy is usually noted. Especially discouraging in patients falling into this group is the fact that intensive treatment often produces an apparent cure, temperature falls, the patient feels well and the blood cultures are sterile; but no sooner is penicillin discontinued than bacteremia returns together with fever and symptoms. Such suppressive therapy must always be looked for in the enterococcal cases. To cope with this situation adequately, therefore, the physician must recruit all his resourcefulness and ingenuity. Stratagems which may be successful are (1) the use of huge doses—up to 20 million units daily of penicillin, (2) measures to raise blood level of penicillin by delaying urinary excretion, (3) combinations of several antibiotics such as penicillin and streptomycin. Clark, Bryner and Rantz in our clinic have made an intensive study of the problem and were able to cure eight out of nine patients with endocarditis caused by unusually resistant streptococci of various groups. One case, for example, whose organism, an enterococcus, required 10 units penicillin per cc. of medium for inhibition, received first six million units and then twelve million units daily, a total of 600 million units being administered in 50 days. This patient had a renal lesion which delayed excretion of penicillin so that blood levels of 100 units per cc. were achieved, which no doubt helped in promptly extinguishing the infection. In another patient alternate courses of penicillin and streptomycin failed to reverse the blood culture and the organisms became more and more resistant so that finally 3.2 units per cc. were required for inhibition. After several months of failure the infection was at last readily eliminated by raising the dose of penicillin to 8 million units daily. This patient is well four years later.

We have made no purposeful attempts to raise penicillin blood levels by blocking urinary excretion with earonamide or paraaminohippuric acid but have depended more on large doses of antibiotics. However such blocking is quite rational and may well turn out to have a useful place in therapy if a really satisfactory agent can be found.

THE COMBINED USE OF PENICILLIN AND STREPTOMYCIN

Robbins and Tompsett recently made the interesting observation that patients with enterococcal infection resistant both to penicillin and to streptomycin were easily cured by a combination of the two in relatively small doses. Several patients who received six million
units of penicillin and 2 Gm. of streptomycin daily promptly had their bacteremia reversed and did not relapse over a 12 month period. One of our own patients in whom a brilliant result was achieved by this useful stratagem is briefly reported.

A 23 year old woman, previously well, induced an abortion in February, 1949, and entered the hospital on April 10. Two weeks previously she noticed fever in the evening. There were no other symptoms, but blood culture was said to show *S. viridans*. On examination the heart was rapid and first sound at apex was replaced by a short, rough systolic murmur. Numerous blood cultures yielded nonhemolytic enterococci which required 5 units of penicillin for test tube inhibition and were not inhibited by 50 µg. of streptomycin. In view of the high resistance of the organisms it was decided to try aureomycin. Four Gm. were given daily by mouth supplemented by two intravenous injections of 100 mg. each for seven days. Although temperature fell to normal and she felt well, enterococci continued to be present in numerous blood cultures. It was therefore decided to try a combination of 5 million units of penicillin and 2 Gm. of streptomycin daily. On the day after this treatment was started blood culture was negative and continued so on many occasions. After two weeks treatment was stopped, blood cultures remained sterile and the patient was clinically well. She was last seen in December, 1949, nearly six months later, and was perfectly well with negative blood culture, but the systolic murmur persisted.

**The Use of Streptomycin Alone**

It must not be forgotten that occasional cases of subacute bacterial endocarditis are caused by a variety of bacteria other than *S. viridans*. Some of these organisms are highly refractory to penicillin but may be sensitive to streptomycin. It has become a routine procedure in our laboratory to test all bacteria isolated from endocarditis cases for sensitivity to both penicillin and streptomycin; the clinician may then select the antibiotic or combination which he considers most suitable. The use of streptomycin is reviewed by Hunter who found it useful when penicillin failed in bacterial endocarditis caused by gram-negative bacilli, enterococci, staphylococci and other organisms. Others report instances of endocarditis caused by bacterioides in which streptomycin was of value.

**Aureomycin and Chloromycetin**

Curiously enough neither aureomycin nor chloromycetin seems to have been widely explored in the therapy of bacterial endocarditis in spite of the obvious advantage or oral administration. We have found few actual reports, and no doubt the great effectiveness of penicillin has discouraged use of other drugs. There seems little doubt, however, that endocarditis caused by strains highly sensitive to aureomycin would be readily cured. Our own experience is confined to 2 patients resistant to penicillin in whom aureomycin was tried without success. The first was the patient with postabortion enterococcal infection already mentioned. The second, also with an enterococcal infection, had a strain which was completely inhibited in vitro by 0.1 µg. of aureomycin per cc. In spite of this, blood culture remained positive during five days on which he received successively 2, 4, 4, 6, and 8 Gm. of aureomycin by mouth. He was eventually cured by huge doses of penicillin.

No doubt still other antibiotics will be developed in the future which will be valuable in bacterial endocarditis. My colleague, Dr. L. A. Rantz, has, for example, treated a case of bacterioides endocarditis not cured by penicillin, aureomycin and streptomycin with a new antibiotic, terramycin. The organism was

* Brainerd and co-workers (J. Clin. Investigation 28: 992, 1949, Part 1) report, without details, that in 2 cases of subacute bacterial endocarditis caused by *S. feccalis*, fever and bacteremia disappeared during treatment with aureomycin but recurred after the drug was stopped. Long and associates (California Med. 70: 157, 1949) also allude briefly to the cure of a child with *S. fecalis* bacterial endocarditis by aureomycin. Harvey, Mirick and Schaub (J. Clin. Investigation 28: 987, 1949, Part 1) report the cure of an *S. fecalis* infection at the site of suture after a Blalock operation on a child. In 3 other cases evidence of infection persisted during or after treatment even when 6 or more Gm. of aureomycin were given for several weeks. From these reports and from various personal communications it is suggested that aureomycin is on the whole less effective than penicillin but many more long-time observations are necessary to draw final conclusions. In some cases patients are unable to take adequate doses by mouth for a long enough period and suppressive effects are followed by relapse.
highly sensitive to this material and was inhibited by 1.0 µg. per cc. Terramycin, in doses of 0.5 Gm. by mouth every four hours reversed the blood cultures, and the patient seems to be cured.

Reinfections

As large numbers of cured cases of bacterial endocarditis have accumulated in the past few years it is evident that reinfection must sooner or later be observed. Herring and Davis reported a patient who recovered from two separate episodes of infection separated by 20 months of apparent good health. Rosenberg also describes a man who reappeared nearly two years after cure of S. viridans bacterial endocarditis with another infection which was again extirpated by penicillin. Whether the organism in the second attack represented an entirely new infection, or whether even after such a long interval of “cure” some bacteria which remained dormant deep in a scarred valve renewed their activity, is an interesting point. We have seen 2 patients who had second attacks of this sort; in one of them it was suggested that the same strain was operative on both occasions.

An 18 year old girl had had a long bout of active rheumatic fever six to seven years ago. Subsequently a loud, rough, systolic murmur was noted and she was followed in this clinic. The heart became considerably enlarged and her pulse tended to be fast but there was no gross failure. About six weeks before entry on Feb. 1, 1946 she had fever, malaise, and aches and pains. Culture for S. viridans was said to be positive. She was pale and thin, the heart was rapid and there was a loud, harsh, systolic murmur maximal at the apex. Blood culture yielded 15 colonies of nonhemolytic streptococcus which grew well in the presence of 0.05 unit of penicillin per cc. but was inhibited by 0.1 unit per cc. One hundred thousand units of penicillin was given every six hours—400,000 per day. Temperature, previously elevated to 38 to 39 C., promptly fell and blood cultures became negative. On the nineteenth day of penicillin, however, a positive blood culture was again obtained. The dosage schedule was then changed to 50,000 units every three hours. This was continued until the sixtieth day. Five blood cultures were subsequently negative, and she was discharged as cured of her infection in May, 1946.

She was carefully followed and remained essentially well with no signs of recurrence for nearly two years. On March 29, 1948, she returned with complaint of fever, malaise, and joint pains for two months. Physical examination was about as before but the spleen was now palpable and the temperature ranged from 37.5 to 38.5 C. Blood culture yielded 20 colonies per cc. of a nonhemolytic streptococcus. The strain isolated on the previous entry was not available but the new strain bore a striking resemblance to it. The degree of sensitivity and the cultural characteristics were the same. This could hardly be a coincidence and the question was raised as to whether the second attack, even after the long interval, was not a recrudescence with organisms which had lain dormant in the damaged valve rather than a new infection with a different strain. This time she again received treatment for 60 days consisting of two daily injections of 600,000 units each of Duracin, a slowly absorbable penicillin preparation. All cultures were subsequently sterile and when last seen in February, 1950, nearly two years later, she was in good condition with no further signs of recurrence.

Several important facts are brought out by this case. First we are in the unsatisfactory position of not being certain whether the second attack was a recrudescence or an entirely fresh infection. It becomes clear that in order to settle such a question in future cases it is essential for laboratories carefully to preserve all endocarditis strains so that should a second attack occur an actual comparison can be made. Secondly it is of interest that in the first attack 400,000 units of penicillin per day in four doses proved subcurative, whereas the same total daily quantity given in eight doses was effective.

In the second patient, a 69 year old man whom we had cured of S. viridans endocarditis in 1945, a prostatectomy done in 1948 was followed by an enterococcal implantation, obviously an entirely new infection.

Discussion and Summary

In the preceding pages we have outlined the development of treatment of bacterial endocarditis with antibiotics. A good deal of stress has been placed on our own work and that of our associates; it has been an exciting experience to observe the improvement in methods and in results since the early days of penicillin therapy six years ago. The following points are especially to be emphasized.

First of all, the great importance of early diagnosis, before huge deforming and destruc-
tive vegetations have grown, cannot be over-
stressed. In early cases therapy often leaves the
patients in essentially as good condition as be-
fore the infection.

Second, it must be recognized that penicillin
does not prevent cardiac failure and that many
patients whose infection has been cured will
die in decompensation or because of an embolic
accident or disturbance of cardiac mechanism.
Renal failure may be a serious problem in some
cases.

Third, there should be emphasized the neces-
sity of making every effort to isolate the causal
bacteria and of performing accurate sensitivity
tests. It is only with this information at hand
that the most promising antibiotic and the
proper dosage can be selected.

Finally it is pointed out that most patients
with highly sensitive strains of S. viridans can
be readily cured by small daily doses of penicil-
lin but that, because of the nature of the lesion,
therapy should be continued for at least four
weeks in order to prevent recrudescences. On
the other hand resistant strains challenge the
ingenuity and resourcefulness of the clinician
and demand huge doses of antibiotics.

While an unsurpassed therapeutic triumph
has already been achieved in the ready cure of
bacterial endocarditis, no doubt even more
effective and more readily administered drugs
will be developed in the future.

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