Subacute Bacterial Endocarditis: Medical Staff Conference

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Dr. Quinn: This morning we will present two interesting cases and discuss some of the principles of diagnosis and results of treatment of bacterial endocarditis. Dr. Brunner will present the first case.

Dr. Brunner: A 16-year-old girl was admitted to the Henry Ford Hospital on August 17, 1955. She had experienced daily chills and fever associated with headaches, malaise, sore throat, nausea, and vomiting for eight days. Six days prior to admission she noted swelling and pain in the left ankle that persisted for four days. Five days prior to admission she noted a bluish tender area on the palmar surface of the tip of the left middle finger. She received an indefinite amount of penicillin both orally and by injection during the eight days prior to admission to the hospital. Her history revealed the presence of a heart murmur since an attack of rheumatic fever at the age of 11 years. In May and June, 1955, the patient was seen on two occasions with attacks of supraventricular tachycardia that subsided spontaneously. A diagnosis of inactive rheumatic heart disease with mitral stenosis and insufficiency was made at that time.

Physical examination revealed that her temperature was 41.2 C (106.2 F) and that the pulse rate was 120 per minute and regular. There were 20 respirations per minute, and the blood pressure 115/64 mm. Hg. She was a well-developed and well-nourished young female and appeared acutely ill. There was a single bluish tender lesion, 6 mm. in area and slightly elevated, on the tip of the left middle finger. Several palpebral conjunctival and subungual petechial hemorrhages were present. The heart was enlarged to the left, the point of maximal impulse being in the left sixth interspace 11.5 cm. from the midsternal line. The precordium was heaving, and a diastolic thrill was noted at the apex. A grade 4 harsh, high-pitched systolic murmur and an apical diastolic rumble were heard on auscultation. The spleen tip was palpable 4 cm. below the left costal margin. The remainder of the physical examination was negative.

Laboratory tests revealed that the hemoglobin level was 11.4 gm. per 100 cc.; there were 3,600,000 red blood cells and 15,760 white blood cells per cubic millimeter. There were 73% polymorphonuclear leukocytes, 22% lymphocytes, and 4% monocytes. The sedimentation rate was 41 mm. per hour (Wintrobe), and the hematocrit was 37%. The urine was normal except for a trace of albumin. An electrocardiogram disclosed evidence
of left ventricular enlargement. Cardiac fluoroscopy showed left auricular enlargement. Seven blood cultures taken on the third and fourth hospital days were all positive for an organism identified as Neisseria sicca. The organism was inhibited in vitro by 2.5 units of penicillin per cubic milliliter and by less than 0.56 units of penicillin combined with 5 mcg. of streptomycin per cubic milliliter.

The patient's course is shown in the first slide (Fig. 1). On the fourth hospital day, intramuscular administration of one million units of procaine penicillin twice daily was started. On the sixth hospital day parenteral administration of penicillin was discontinued and oral administration of 2 million units of penicillin V every four hours was begun. Within 48 hours of the initiation of penicillin therapy the patient became afebrile and showed marked symptomatic improvement. The tachycardia decreased, and the systolic murmur decreased in intensity. On the 15th day of treatment she developed a headache and her temperature rose to 40.4 C (104.5 F). New petechial hemorrhages were noted on the soft palate and in the conjunctiva. During the ensuing four days her temperature remained elevated, although blood cultures obtained at this time were all sterile. The results of the in vitro sensitivity test became available at this time, and 0.5 gm. of streptomycin plus 0.5 gm. of dihydro-streptomycin given intramuscularly twice daily was added to the course of therapy. She promptly became afebrile, and no new petechiae were noted. The combined therapy was continued for six weeks. Frequent blood cultures during treatment and twice weekly for one month after treatment was discontinued were sterile. The patient was last seen 11 weeks after cessation of treatment and has maintained clinical and bacteriological remission.

Dr. Quinn: Dr. Gale will present the next case.

Dr. Gale: An 18-year-old man was admitted to the Henry Ford Hospital on September 14, 1955. Three and one-half weeks prior to admission he had developed a toothache and was found to have a deeply carious tooth, without evidence of apical abscess. He
was given 300,000 units of procaine penicillin G with 0.25 gm. of streptomycin sulfate and 0.25 gm. of dihydrostreptomycin sulfate one hour preoperatively, and the tooth was extracted. For the next 5 days, 200,000 units of penicillin G was given orally three times daily, followed by 200,000 units twice daily for 10 additional days. One week before admission he noted the onset of fever, with temperature of up to 39.7 C (103.5 F) accompanied by mild malaise. This persisted until September 12, when he presented himself to the outpatient clinic and a blood culture was drawn.

His history disclosed a known heart murmur since the age of 6 months. At the age of 10 he developed daily fever, with temperature ranging from 37.8 to 39.5 C (100 to 103F) and a cough that persisted for 10 months. He was first admitted to the Henry Ford Hospital on July 23, 1947, with this complaint. Numerous blood cultures were sterile. A diagnosis of bacterial endocarditis without bacteremia was made, and he was treated with 100,000 units of aqueous penicillin, administered intramuscularly every three hours for 50 days. He was asymptomatic until January 27, 1954, when he developed fever, chills, cough, and migratory arthralgia. Numerous blood cultures were sterile. A diagnosis of bacterial endocarditis without demonstrable bacteremia was made, and he was treated with 4 million units of aqueous penicillin and 1 gm. of streptomycin daily for four weeks. He became afebrile and asymptomatic. On April 10, 1954, he was admitted for the third time with recurrence of fever. Again blood cultures were sterile, and he received tetracycline orally for 21 days with prompt remission of fever. Data obtained from cardiac catheterization in January, 1955, were consistent with a diagnosis of infundibular pulmonary stenosis.

Physical examination revealed that his temperature was 40 C (104 F), his pulse rate 100 per minute, and respiration rate 24 per minute. The blood pressure was 110/70 mm. Hg. He appeared moderately ill with a flushed face. No petechial hemorrhages were noted. The heart was not enlarged to percussion. The rhythm was regular. A grade 4 harsh systolic murmur was audible along the left sternal border, loudest at the third left interspace. A systolic thrill was palpable in this area. The pulmonic second sound was absent. No diastolic murmur was heard. The spleen was not palpable.

Laboratory tests revealed that the hemoglobin level was 15.9 gm. per 100 cc., and there were 5,950,000 red blood cells and 9,700 white blood cells per cubic millimeter. There were 82% neutrophils, 12% lymphocytes, 5% monocytes, and 1% basophils. The urinalysis was negative. Roentgenogram of the chest disclosed slight prominence of the left cardiac border. Three blood cultures obtained during the first two days of hospitalization were positive for alpha-hemolytic streptococci. The organism was sensitive in vitro to 0.04 units of penicillin per cubic milliliter. The patient’s course is shown in slide 2 (Fig. 2). He was given 2 million units of penicillin V orally every four hours for six weeks. His temperature fell to normal on the second day of treatment, and his symptoms subsided promptly. Biweekly blood cultures made during treatment and for one month after discontinuing therapy with penicillin remained sterile. The patient has been followed for three months since completion of therapy, and there has been no clinical or bacteriological evidence of relapse.

Dr. Quinn: These two cases present some of the usual but contrasting aspects of bacterial endocarditis. The first patient had pre-existing rheumatic heart disease, the second congenital heart disease. One presented with a three weeks illness with undiagnosed
fever and inadequate antibiotic therapy; the other presented with persistent fever following “adequate” chemoprophylaxis at the time of dental extraction. Classical signs of bacterial endocarditis i.e. splenomegaly, emboli; etc. were found in the patient with acquired heart disease but absent in the patient with the congenital cardiac lesion. Both patients, however, presented with persistant fever and in both multiple blood cultures were positive. Dr. Green would you comment further about these cases.

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Figure 2
Course of patient with subacute bacterial endocarditis due to alpha-hemolytic streptococcus. (case 2.)

Dr. Green: The second case was of considerable interest in that this boy received quite adequate, or at least what we think is quite adequate, prophylaxis at the time of his dental extraction. This raises the interesting question, “Did his bacterial endocarditis exist prior to the dental extraction?” I am afraid that we do not know the answer to that. It is also of interest that this boy’s pulmonary stenosis is infundibular in location in that it has previously been thought to be very rare for pulmonary stenosis to develop bacterial endocarditis unless it was valvular. However, we now have two cases of infundibular pulmonary stenosis who have had classical bacterial endocarditis so I do not think we can hold to this any more. The organism is of interest in the first case, in that Nisseria sicca is, certainly in our experience, a very unusual organism and I think that it was fortunate that we did have adequate penicillin sensitivity test.

Dr. Quinn: I think the panel will agree that Nisseria sicca is generally regarded as a non-pathogen and had we not had seven positive cultures and classical signs of bacterial endocarditis clinically, this organism would be open to question as a cause of this patient’s illness.

Another contrasting point in these two cases relates to the sensitivity of the organism. The Nisseria sicca was inhibited in vitro by the tube dilution method by 2.5 units of penicillin per cubic milliliter. Later when we conducted in vitro test with a combina-
tion of penicillin and streptomycin the organism was inhibited by less than 0.5 units of penicillin combined with five micrograms of streptomycin. Thus, this would be classified as a moderately resistant organism. The streptococcus viridans isolated in the second case was sensitive in vitro to 0.04 units of penicillin per cubic milliliter.

I think this is the point to talk a little about prophylaxis with regard to dental extraction, as this point has been raised. It has been recommended by the Committee on Prevention of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association that one of the following two regimens of penicillin prophylaxis of subacute bacterial endocarditis be used in patients with rheumatic heart disease or congenital heart disease at the time of dental extraction. The first dose schedule recommended is the injection of 600,000 units of aqueous penicillin G and one injection of 600,000 units of procaine penicillin in oil with 2% aluminum monostearate given 30 minutes before the dental extraction. The alternate plan consists of the administration of oral penicillin G, 250,000 to 500,000 units four times a day, for one day before and four days after the dental extraction.

It has not been established just what the value or risk of such a procedure is in a patient who has had this kind of treatment. In a patient with rheumatic heart disease or congenital heart disease, the likelihood of developing bacterial endocarditis after a single tooth is extracted is estimated to be about one in five hundred. This probably explains why an adequate study has never really been done to find out exactly what should be used. I think that most everyone agrees it is sound clinical judgment and theoretically correct to employ such prophylaxis. Exactly what drug to use or how long to use it or in what dosage has not, however, been established by adequate study. There are, interestingly enough, four reported cases of bacterial endocarditis following tooth extraction in which prophylactic antibiotic therapy was used. Three of these received small or moderate doses of penicillin and developed endocarditis despite this. The fourth reported case was treated more intensely with something like a million units of penicillin daily for six days. This patient's subsequent endocarditis proved to be due to a penicillin resistant organism. Thus, the possibility arises that if you treat too intensely and eliminate the sensitive organisms one may end up with endocarditis due to a resistant organism. I will ask each member of the panel what their current practice is on the prophylaxis of bacterial endocarditis.

Dr. Drake: At the present time, we believe that prophylaxis should consist of the following: In the first place, a quick-acting preparation such as Dr. Quinn mentioned should precede the actual extraction and then for at least four or five days following the patient should receive either orally or by injection, a penicillin preparation supplemented by streptomycin.

Dr. Green: Our practice is very much the same and I have nothing to add except that I think in prophylaxis of enterococcus endocarditis, we have felt it necessary to cover with larger doses of penicillin during times of therapeutic abortion or similar procedures in areas where the enterococcus is prevalent.

Dr. Colville: I think that we would agree with that method. The important thing to stress here is the fact that you cannot prevent bacteremia with prophylactic penicillin in one hundred per cent of the cases. You can cut it down but some patients will still develop bacteremia. Therefore, the only additional suggestion one might make is that
we continue the prophylaxis for approximately a week in the hopes that if these organisms find a suitable focus and begin to multiply, the penicillin will then be active. As you know, penicillin is not active against an organism that is not in the active growth phase.

Dr. Quinn: The next point which we would like to discuss in relationship to diagnosis is the matter of blood cultures. Just how many cultures should be taken, how long one should wait before treatment is started, etc.? I wonder if Dr. Colville would discuss this.

Dr. Colville: I think the point to stress about blood cultures is that multiple cultures are essential. A single blood culture on occasion may be more confusing than no culture. Supposing this single culture reveals an organism such as a coagulase negative staphylococcus? Normally this organism inhabits the skin and nasal mucous membranes and may be a contaminant in a blood culture. On the other hand, it may represent the offending organism in bacterial endocarditis. It is difficult to commit a patient to a long, strenuous, and expensive course of therapy on the basis of such tenuous evidence. If multiple cultures reveal the same organism, the evidence for treatment is much more secure.

How long should we delay before instituting therapy? In one series of 140 adequately studied cases, 90 per cent of the cultures that were positive occurred within the first three days of the disease, that is, after the patient appeared in the hospital, and only 1 per cent after the first five days. Therefore, one would think that if you are going to get positive blood cultures, you should in the vast majority of cases, get them within the first three days. I certainly do not think that there is much to be lost by delaying treatment for three to five days to get blood cultures, since such a delay does not alter the results of treatment.

Failures to obtain positive cultures may occur because of the lack of putting the blood into appropriate media, incubating the culture long enough and the actual technique of taking the culture.

With reference to multiple sites for blood culturing, I might say that as far as I am concerned, venous blood is apparently as good as arterial blood with the exception, and this is purely a personal experience, that bone marrow will occasionally give positive cultures when peripheral blood does not. I know Dr. Drake has a comment about arterial and venous blood cultures.

Dr. Drake: Yes, I would like to give what seems to be a minority opinion here in favor of arterial blood cultures. I have seen them successful in several instances that I can remember where the repeated venous culturing had failed. It seems to me that any capillary system will, to some extent, act as a filter and that theoretically, if not practically, the arterial blood culture should offer some advantage, and I believe does.

Dr. Quinn: Do we all agree that perhaps the bone marrow has its special value in patients who have had a dose or two of penicillin before we see them and we might be able to culture the organism there easier than out of the blood?

Dr. Drake: Yes, I would agree with that.

Dr. Quinn: I am sure we would all agree that if the patient has a cerebral hemorrhage or is in severe congestive failure, we should not wait the two or three days but we can then get 5 or 6 cultures in a few hours and proceed with treatment. Now let us classify
these organisms that are isolated according to their sensitivity. We will turn to Dr. Colville again and ask him also to discuss sensitivity tests in bacterial endocarditis.

Dr. Colville: I think at the onset the comment should be that all sensitivity tests are only rough guides. We all know of cases where we have in vitro a highly sensitive organism which does not respond satisfactorily to what would appear to be adequate antibiotic therapy. However, sensitivity tests are a guide and the accumulated experience enables one to predict the results of treatment with some degree of accuracy on the basis of these studies.

I would like to say something about methods first. I think that tube dilution methods are certainly the most accurate. Clinical experience in bacterial endocarditis has been correlated with the tube dilution inhibition study method rather than with the disk sensitivity which is the popular and easier method, and the one which is carried out in almost all hospitals. Tube dilution is an all or none response. The organism is either completely inhibited or it is not inhibited at all, as we read the tests. One gets a fairly accurate reading, can carry the dilutions down into very minute amounts and the end point is clear cut. With the disk sensitivity method as presently employed, one uses the filter paper disk which is saturated with antimicrobial agent and put on a plate. On the basis of the size of the zone of inhibition, a report of moderately or highly sensitive or resistant organism is made. This is a very crude index. Therefore, I would think that in subacute bacterial endocarditis, for accuracy's sake, we would want tube dilution studies in all of these cases. Secondly, with tube dilution methods one is able to do a synergism, antagonism and additive type of study. This is not possible with a disk system.

With reference to penicillin, I think one could say that organisms which are sensitive to less than 0.10 of a unit of penicillin per milliliter in vitro may be considered to be generally sensitive. Those from 0.1 to 0.9 of a unit are moderately resistant and one unit and above are highly resistant. With streptomycin, a sensitive organism is inhibited by less than 10 micrograms. With the tetracyclines, the evidence is quite confusing, but one would think that a sensitive organism is inhibited by less than 2 to 2.5 micrograms per ml. With bacitracin and erythromycins, I do not think that there is enough evidence accumulated to say what the sensitivity means.

Dr. Quinn: I think this point of tube dilution is most important. We first of all have to realize the practicality of this test, that is, to do tube dilutions on all specimens sent to the bacteriological laboratory would be an impossibility. Many hours are taken to do these tests. I certainly feel that in all cases of septicemia where documented clinical experience is available to guide your treatment by tube dilution sensitivity tests this is the only method one can rely on. We have felt that the disks sometimes were less than valuable, even misleading, i.e., in the second case presented the alpha streptococcus originally isolated was found to be only moderately sensitive to penicillin by the disk method but highly sensitive by the tube dilution method. In cases other than bacterial endocarditis, if one is well versed in the clinical experience with various antibiotics and what they can do, singly or in combination, one can frequently get along without sensitivity tests. I am not excluding them, but I think one must be very careful with interpretation of sensitivity tests especially if the disk method is employed. Dr. Green, do you have some comments in this regard?
**Dr. Green:** The only other comment would be that in certain cases of penicillin resistant organisms such as the enterococcus, I think it is a very wise idea, although it is a time consuming job for the laboratory, to set up combination sensitivities with penicillin and streptomycin in the same tube. We have found this extremely helpful in a number of cases with resistant organisms that look impossible to treat with penicillin alone but were sensitive to quite easily obtainable clinical level with the combination.

I think that it is important to remember that if you are dealing with an enterococcus you should use a combination of penicillin and streptomycin. This is true even if the tube dilution method shows a penicillin sensitive enterococcus. One can almost predict with assurity that treatment is going to fail if only penicillin is used unless you employ massive doses.

**Dr. Quinn:** The next step would seem to be to decide just what drug to use, and I think it is generally agreed that penicillin is the drug of choice in most cases of bacterial endocarditis. Secondly, the amount of penicillin given has to be large. Thirdly, the duration of treatment must be prolonged. I do not think anyone would disagree with these three points. There would be, however, some difference of opinion about just how much penicillin to use or just how long to use it, and we would like to explore this just a little bit. To approach this matter I will ask Dr. Drake to classify endocarditis according to what he might call sensitive and resistant forms, thinking not just of the causative organism but also of other things like duration if illness, etc.

**Dr. Drake:** Actually, we might define a resistant case of endocarditis as one which fails to respond in the expected manner to treatment. There are several factors which contribute to resistance. One of these is the long duration of the illness prior to diagnosis and therefore institution of therapy. This is quite important. Another, of course, is the isolation of a virulent organism or a resistant organism in the laboratory. Another factor is the failure to isolate any organism at all. In these circumstances, of course, there is a delay in the institution of the proper therapy. Still another factor is the presence of inadequate early attempted therapy which may sometimes turn a case into quite a resistant one from a therapeutic standpoint. Lastly we might mention the development of some complication during the course of therapy such as heart failure.

**Dr. Quinn:** Do you think that these factors have something to do with the dose and also with the duration that you would treat a patient?

**Dr. Drake:** Yes, I do, but only in a general way, in that they would tend to make one start out with adequate doses and continue the therapy for an extended period of time. The exact limits on that we will set later.

**Dr. Quinn:** Well, let's get into this matter of short term versus long term treatment. We will turn to Dr. Colville again and ask him to tell us a little about penicillin blood levels. Although these have been depreciated a certain amount, I think that perhaps they are rather important and give us some idea as to what dosage or what route of treatment we might employ.

**Dr. Colville:** The blood levels obtained with any penicillin agent depend upon the type of agent used, the amount given and the route by which it is given. To briefly summarize one could say that using crystallin penicillin intravenously one expects a very high peak
rapidly. This is achieved by giving a large intravenous dose over a short period of time. Studies in animals have indicated that if one gives a million units of penicillin intravenously in five seconds the blood level in the aorta at about 12-15 seconds will approximate about 200 or 300 units per cubic milliliter. There is a very rapid fall of the blood concentration, and at the end of an hour the levels will be below one unit.

When one gives penicillin by continuous intravenous drip, in contrast to the sudden peaking type of dose, one achieves a relatively constant level that will roughly approximate one unit in the serum for every million units given intravenously per 24 hours. Therefore, if we gave 24,000,000 units a day, we might expect a continuous level in the region of 24 units. This is provided, of course, that the patient has competent renal function and no blocking agent has been used.

Intramuscular crystallin penicillin produces a curve similar to the rapid intravenous route. The peak is reached in 15 to 20 minutes, with values of 20 to 100 units after a large dose followed by a rapid fall to less than two units at the end of four hours. Parenteral repository forms such as aqueous procaine penicillin G or procaine penicillin G in oil give levels that never reach the high peaks of intramuscular or intravenous crystallin penicillin. With a 600,000 unit dose, the peak might be in the region of 5 to 10 units at the end of an hour. This falls off gradually, so that by 24 hours the penicillin is only just detectable in the serum.

Oral penicillin has been generally discouraged and I think for a very good reason. It has been shown that the absorption is erratic in that only 10-15% of crystallin penicillin G is absorbed from the gastrointestinal tract. However, it has been demonstrated that levels just as high as those from intramuscular, subcutaneous or any other parenteral route can be obtained if you use enough of this agent. More recently we have had experience that you have seen on these slides with penicillin V or phenoxymethyl penicillin. This agent is apparently better absorbed from the gastrointestinal tract and over longer periods of time. Based on what we know at present, about 30% or possibly 35% of this preparation is absorbed from the gastrointestinal tract, and we do get appreciable blood levels. These levels are somewhat in between those seen with intramuscular procaine penicillin G and intramuscular crystallin penicillin G in that we get the peak at about the same time, at a half hour to an hour, and obtain a level similar to that with procaine penicillin but we see a rapid fall off so that levels are down quite low at the end of four hours with this type of medication.

*Dr. Quinn:* To summarize and get the opinion of other panel members, it would seem to me that about 12,000,000 units of penicillin V orally in 6 divided doses daily will give us a level of around 8 units in the serum. About the same level would be obtained with 600,000 units of procaine penicillin intramuscularly every six hours. If you also give probenecide you will get levels about twice that high with either of these agents. This would be roughly equivalent to a continuous intravenous dose of about six to eight million units per 24 hours. It is a little hard to compare this with rapid intravenous or intramuscular crystallin penicillin because one gets a peak and it falls right off, but it would seem to me that about 500,000 units of aqueous crystallin penicillin G intramuscularly every three hours would simulate this dose. I would, therefore, propose the following four treatment schemes as equivalent for use in treating a sensitive or a moderately sensitive case of subacute bacterial endocarditis: Oral penicillin V, 12,000,000
units daily; aqueous procaine penicillin G 600,000 units every six hours; a continuous intravenous drip of 8,000,000 units of crystallin penicillin G per day; or, intramuscular administration of crystallin penicillin G, 500,000 units every three hours. Do the other panel members agree that these schemes are more or less equivalent?

Dr. Drake: Yes, I feel they are more or less equivalent. Most of our cases that Dr. Green and I have recently gone over, have been treated either with the intermittent intramuscular, using the doses that Dr. Quinn mentioned, or the continuous intravenous route employing approximately between ten and twenty million units a day. We have not in that scheme, routinely at least, employed anything extra to give peaks. We have attempted no treatment with the oral product.

Dr. Quinn: Do you feel these schemes are satisfactory for the resistant cases or do we have to give higher doses?

Dr. Drake: Well, that was for the sensitive cases. You would have to go higher with the resistant ones.

Dr. Quinn: Now having defined several dose schedules we should discuss the matter of duration of treatment. I would recommend to all of you an editorial in the July, 1955 issue of the American Journal of Medicine on the duration of treatment which we will not have time to cover, but certainly it is most important that you not stop treatment early. Giving a large dose over a short period will give you more treatment failures than giving smaller doses over a long period. In general, the sensitive cases are treated for two to four weeks with these dose schemes we have mentioned, and the resistant cases are treated for not less than six weeks with dose levels about two or more times greater than these. Now, I wonder about the importance of streptomycin routinely in these cases. Do you have any feelings about that, Dr. Colville?

Dr. Colville: I would differ a little in opinion here in that I think eight million units intravenously continuously would be a better dose than twelve million units intermittently orally. Since absorption of penicillin by the oral route is somewhat unpredictable, I think you would do better with the intravenous route unless you were prepared to do blood levels and make sure that adequate levels were being achieved with the oral medication.

If there is any evidence of resistance occurring during therapy or if the patient does not respond, then certainly streptomycin should be added. Otherwise, I should think that penicillin alone in a case due to sensitive organisms should be adequate.

Dr. Quinn: I think that a lot of people follow Dr. Hunter’s and Dr. Dowling’s recommendation that 600,000 units of aqueous procaine penicillin G four times a day along with streptomycin for two weeks will cure about 90% of cases due to streptococcus viridans. When dealing with an enterococcus and perhaps with most non-hemolytic streptococci one should use streptomycin along with the penicillin and continue treatment for four to six weeks. As an alternate plan with streptococcus viridans, penicillin alone is adequate but should be given for six weeks. Staphylococcal endocarditis poses many problems, and we will not have time to discuss treatment of this type.

Dr. Green and Dr. Drake have reviewed the Henry Ford Hospital experience and Dr. Green is going to briefly summarize this.
Dr. Green: We have available for study 61 consecutive cases of endocarditis since the advent of penicillin which we have been able to follow from 2 to 12 years. Of this group, there are 25 cases where recovery has been complete without any detectable aggravation of heart disease and these patients at the present time are virtually asymptomatic. These patients had a total of 28 episodes of bacterial endocarditis without any recurrences; that is, the three cases with a second attack were all reinfections. The following types of heart disease were observed; rheumatic occurred in 19 of these, of which 11 were mitral only, 5 were combined aortic and mitral and 3 were aortic alone. The 7 congenital heart cases included infundibular pulmonary stenosis, intraventricular septal defect and patent ductus. The most common organism was, of course, the penicillin sensitive or only slightly resistant type of streptococcus viridans and we had eighteen cases due to this organism; one enterococcus which was penicillin resistant in vitro to five units per cubic milliter; a penicillin sensitive staphylococcus occurred in 5 cases; and, we had 5 with negative blood cultures. In general, all the patients in this group had organisms for which appropriate levels could be reached clinically. One enterococcus was finally cured with one billion units of penicillin and streptomycin over a period of ninety days. As contrasted with the entire series, the congenital group seemed to do fairly well unless perhaps there was aortic valve involvement or a resistant organism.

We have a second group of ten patients who are symptomatically well but showed some residual effect such as progression of cardiac murmurs or something that was felt to be fairly definitely related to the bacterial endocarditis. We cannot be sure that these patients developed these findings on the basis of the bacterial endocarditis since the progress of rheumatic heart disease is such a variable thing. All of these cases were caused by streptococcus viridans which was more or less sensitive to penicillin, except one which had a negative culture and one enterococcus which was again only slightly sensitive to penicillin. The distribution of the structural heart disease in this group was entirely rheumatic except for one congenital aortic stenosis in which a murmur of aortic insufficiency appeared early in the course. There was one patient with no evidence of structural heart disease.

There are five patients in the third group who have survived the infection but are considerably aggravated. They have congestive failure or other fairly serious symptoms at the present time. Three of these cases were due to streptococcus viridans, one had a negative blood culture and there was one moderately resistant enterococcus. All had rheumatic heart disease, four with mitral involvement alone, and one with aortic stenosis.

Out of the total of 61 infections which we have followed, 21 patients have subsequently died. All of these had rheumatic heart disease except for one congenital bicuspid aortic valve with aortic insufficiency, one patient who had luetic aortitis with aortic insufficiency and one child with ventricular septal defect who had a resistant staphylococcus and developed a mycotic abscess at the root of the great vessels. A total of 10 of the 21 fatal cases had aortic valve involvement which may be of some importance. The following organisms were observed in the fatal group; streptococcus viridans in 8 cases; 3 were only moderately sensitive to penicillin and 5 were undetermined; enterococcus occurred in 3 cases; the staphylococcus occurred in 6 cases. Interestingly enough in the staphylococcus group, 5 were penicillin resistant (in contrast to none in the non-fatal group) and the sixth fatal case was only slightly sensitive.
Nonhemolytic streptococcus occurred in 2 cases and 2 were blood culture negative.

Of this fatal group, 2 patients were terminal on admission and died in the first few days of treatment. The following causes of death were observed: early progressive cardiac failure with uncontrolled infection in 5 cases; progressive early heart failure with infection apparently controlled, 5 cases; subarachnoid hemorrhage with emboli, 2 cases, in one of which the infection in the heart was controlled; ruptured mycotic aneurysm, 2 cases; sudden death at 2 months with infection cleared, 1 case; uremia with infection cleared, 1 case; 1 incidental death of carcinoma of the kidney; and late congestive failure occurred in 3 cases.

In terms of our present knowledge, we felt that treatment was grossly inadequate in 6 cases but these occurred very early in the series after the introduction of penicillin. If we correct our mortality and eliminate all those patients who died after a year of freedom from symptoms and those who died within the first three or four days of hospitalization, our mortality is 21%.

From this data, we would have to conclude that resistant organisms present a most serious prognostic implication as well as advanced cardiac disease with failure and long continued advanced infection at the time of the diagnosis. In only six patients in this series was there evidence of failure to eliminate the intracardiac infection. However, the highest incidence of fatal complications occurred in this group where infection was more difficult to bring under control and progression of structural heart disease was more flagrant in this group.

Dr. Quinn: Dr. Drake would you discuss the several points the panel proposed just before this meeting?

Dr. Drake: One of the points you asked me to bring up was the question of relapse versus reinfection. Normally we arbitrarily set a time limit of one year. After one year we term a case a reinfection; before one year, a relapse. This is purely arbitrary and other people have selected time limits as short as two months. This presumes, however, that the same organism is involved. If a different organism comes into the picture then it is a reinfection no matter when it occurs.

Also, you wish some clarification on acute versus subacute. Formerly, before penicillin, the acute bacterial endocarditis was defined, arbitrarily again, by a time limit of the duration of the infection, usually about six weeks. With the advent of the antibiotics, however, this became obsolete. Actually an acute endocarditis is merely a complication or an event occurring in the course of some other acute pyogenic infection, while subacute bacterial endocarditis is actually an entity in itself. In the acute form of the disease, you can usually recognize and locate the pyogenic focus. The organism is usually more virulent and there need not be any underlying heart disease.

Also, you asked me to bring up something in regard to fibrillation and congestive heart failure. There used to be an axiom that fibrillation and congestive heart failure do not occur, or occur only rarely in connection with bacterial endocarditis. Some even went so far as to say that the presence of one of the two complications mentioned was a protection against bacterial endocarditis. The first statement is true and the second is decidedly not so. It is true that the incidence of fibrillation and congestive failure
preceding bacterial endocarditis is low. It is quoted in the literature as being about three per cent. I think our series ran about ten per cent, but there is no protection offered by the presence of fibrillation. Actually what happens is something like this — in the course of rheumatic heart disease, the individual has recurrent episodes of thrombotic vegetations which are usually non-infected and which heal in the course of time. Actually, with the frequent occurrence of transient bacteremia which we know occurs, it is a wonder that they do not get infected more often and there must be here some host factor which protects the individual. With repeated healing, there comes increased scarring of the valves and progression of the rheumatic disease. Now, fibrillation, by and large, is a manifestation of an advanced rheumatic heart disease, and when this stage is reached the individual in the main has demonstrated his ability fairly well to resist infection of his vegetations. There are exceptions, of course, and these exceptions represent ten per cent of our series.

Dr. Quinn: Now just to go back to the two cases which were presented this morning. The second case is certainly a patient with a sensitive organism with none of the complications, who clinically was in the sensitive group and who responded very nicely to penicillin alone in the average dose which we mentioned over a period of six weeks. The first patient was complicated in that she had a resistant organism. She had had almost a month of antibiotic therapy before she was admitted. She had an unusual organism. She had had several bouts of fibrillation. She suffered relapse clinically, and it was necessary to use a combination of penicillin and streptomycin in this case.

I would like to close the panel discussion by asking how we can improve our results even above the corrected rate of eighty per cent? What single or several factors might help us to improve this?

Dr. Drake: I think that the greatest single factor brought out by the panel today is that we should employ the improved culture technique which was mentioned.

Dr. Green: I think that proper education of every patient who is a possible host to this infection is a very important point. Many rheumatic heart disease patients do not know about subacute bacterial endocarditis. The physician needs constant awareness of this disease since index of suspicion is very important in early diagnosis.

Dr. Quinn: My own feeling is that one must try to recognize and treat these cases promptly. We do not have to wait always for positive cultures or classical clinical signs. Any patient with valvular or congenital heart disease that has a fever for more than a week has to be seriously considered as having endocarditis. A patient with rheumatic heart disease, for example, who comes in with acute pyelitis should be considered as a possible endocarditis case until proved otherwise. We must have a high index of suspicion.