Subacute Bacterial Endocarditis

A Report on 57 Patients Treated with Massive Doses of Penicillin

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SUMMARY

Fifty-seven patients with subacute bacterial endocarditis were treated with doses of penicillin varying from 500,000 to 20,000,000 units per day. Diagnosis was confirmed in some cases by growths on blood culture, in others by postmortem examination. In those cases in which the diagnosis was established by blood culture, the in vitro sensitivity of the organism to penicillin was determined and penicillin then was administered by continuous intramuscular infusion in a dosage calculated to produce blood levels of penicillin four to five times that required for in vitro inhibition. Penicillin was given for a period of 21 days, and blood cultures were made periodically during and after treatment.

Of the 57 patients, 38 were cured (66.7 per cent), and 19 died (33.3 per cent).

Of the 19 who died, three did so within 48 hours of hospitalization and seven died despite adequate treatment. Of these seven, three died of cerebral emboli, two because of resistance to penicillin and streptomycin, one because of congestive heart failure, and one of undetermined cause. The remaining nine who died were considered to have been inadequately treated in that there was (1) failure to obtain sensitivity, (2) inadequate dosage of penicillin, (3) delay in starting treatment, or (4) failure to recognize mixed infections.

There were five patients with repeatedly sterile blood cultures during life. In all of these cases, streptococcus viridans was recovered at postmortem examination. In an attempt to determine how long therapy should justly be withheld in patients with repeatedly sterile blood cultures, 140 cases of subacute bacterial endocarditis in which positive blood cultures had been obtained were reviewed. From the review it was determined that if blood cultures taken during the first two days are reported sterile, the chance of subsequent cultures proving positive is minimal. Therefore, for patients in whom the diagnosis seems otherwise obvious, delaying treatment for more than two days is not justified even though the blood culture be sterile. In cases in which blood cultures are repeatedly sterile, a dosage of 6,000,000 to 10,000,000 units of penicillin daily for 21 days is advisable.

High bacterial resistance to penicillin and streptomycin was found in four fatal cases. In one of these, the infecting organism was streptococcus viridans, and in three it was staphylococcus albus. There was one patient with pneumococcal meningitis complicated by unrecognized streptococcal viridans bacterial endocarditis.

OVER a four-year period (1944 to 1948) 57 cases of subacute bacterial endocarditis were treated with doses of penicillin varying from 500,000 to 20,000,000 units per day. An attempt was made to standardize the management of this disease, and except for minor variations, the following routine was usually followed.

DETERMINATION OF PENICILLIN DOSAGE

Once a positive blood culture was obtained, the in vitro sensitivity of the organism to penicillin was determined. It has been found that approximately 90 per cent of the strains of streptococcus viridans are inhibited in vitro by 0.1 units of penicillin per cc. of culture, and that the remaining 10 per cent may require up to 25 or more units per cc. for inhibition.

After the in vitro sensitivity had been determined, penicillin was given by continuous intramuscular infusion in a dosage calculated to produce blood levels of penicillin four to five times that required for in vitro inhibition. The dosage and average blood level obtained are listed in Table 1.

The correlation between the in vitro sensitivity and the clinical results was good in those cases in which the organism was found to be sensitive to less than 0.5 units per cc. of culture. With the more resistant organisms, the correlation between the in vitro sensitivity and clinical results was not quite as consistent.

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TABLE 1.—*Blood Levels of Penicillin Obtained with Various Doses of the Drug*

Dosage per Day Units	Average Blood Level of Penicillin (Units per cc. of Blood)
200,000	.05
300,000	.10
500,000	.20
1,000,000	.50
2,000,000	1.20
For each additional 1,000,000	Increases by .50 to 1.00

METHOD OF ADMINISTRATION OF PENICILLIN

The penicillin was, with a few exceptions, given by continuous intramuscular infusion. Studies by Hirsch and Dowling[1] showed that penicillin given by intermittent injection did not maintain blood levels as high as did continuous intramuscular infusion. These investigators also observed that with a continuous intramuscular infusion, blood levels similar to those obtained by continuous intravenous administration could be obtained, and that 50 per cent less penicillin was required. Other obvious advantages of a continuous intramuscular infusion are that it can be used when nursing staffs are inadequate, when hospitalization is impossible, and when patients object to multiple intermittent injections.

PERIOD OF ADMINISTRATION

Penicillin was administered in almost all cases for a period of 21 days. Blood cultures were taken prior to treatment, at weekly intervals during treatment, and at weekly intervals for two months after therapy had been discontinued. Thereafter blood cultures were taken whenever reinfection was suspected. In event of relapse after completion of therapy, the sensitivity of the organism was redetermined and penicillin administered in twice the dosage ordinarily employed.

SELECTION OF CASES, RESULTS OF THERAPY

The 57 cases of subacute bacterial endocarditis upon which this report is based were either those in which positive blood cultures were obtained during life, or cases with repeated sterile blood cultures during life but in which, at postmortem, positive cultures were obtained from the bacterial vegetations on the heart valves and elsewhere. Thirty-eight of the patients (66.6 per cent) were cured and 19 (33.3 per cent) died.

The 19 cases in which the patient died were very carefully reviewed and analyzed as to the cause of death and as to possible errors in management (Table 2).

Some of the difficulties and errors in the management of subacute bacterial endocarditis which were observed in the present series will be discussed in detail along with the presentation of illustrative case histories.

One of the most difficult problems in the management of subacute bacterial endocarditis is presented by the finding of repeatedly sterile blood cultures in patients in whom the diagnosis appears otherwise obvious. In the present series, there were five such cases. In all five, positive cultures of streptococcus viridans were obtained at postmortem examination from the vegetations on the heart valves. The case histories and pertinent postmortem findings in these cases are presented.

CASE REPORTS

CASE 1: A 45-year-old white male was admitted to the hospital complaining of nausea, vomiting and ankle edema of three weeks' duration. "Heart trouble" was first discovered at the age of 18 but since that time the patient had been in good health until the present entry.

He was pale and appeared to be acutely ill. The temperature was 100.4° F., the pulse rate 140 per minute and respirations 24 per minute. The blood pressure was 110 mm. of mercury systolic and 70 mm. diastolic. There was pronounced pallor of the skin and mucous membranes. There was grade III enlargement of the heart on percussion. The point of maximum intensity could not be determined. A grade IV mitral systolic murmur and a grade III aortic systolic murmur were heard and a systolic thrill was present over the aortic area. The rhythm was that of auricular fibrillation. The liver edge was felt three fingers' breadth beneath the right costal margin. Clubbing of fingers and toes was noted.

The erythrocyte count was 2,200,000; the hemoglobin was 7 gm. per 100 cc., a value of 38 per cent. Leukocytes numbered 4,800 with 68 per cent polymorphonuclear cells. The urine contained 1 plus albumin and many erythrocytes. The nonprotein nitrogen level was 55 mg. per 100 cc. and the total plasma protein was 7.1 gm. per 100 cc.

The diagnosis upon admission was subacute endocarditis superimposed upon aortic stenosis of rheumatic origin. The patient's course was febrile and showers of petechiae appeared shortly after admission. On the tenth hospital day after six sterile blood cultures had been reported, the patient was started on 20,000 units of penicillin intramuscularly every two hours. The course was progressively downhill and

TABLE 2.—*Subacute Bacterial Endocarditis: Causes of Death and Errors in Management in 19 Cases*

	No. of Cases	Cause of Death
I. Death within 48 hours of hospitalization	3	Cerebral embolus (1), undetermined (2).
II. Treatment adequate	7	Cerebral embolus (3), resistance to penicillin and streptomycin (2), congestive heart failure (1), undetermined (1).
III. Treatment inadequate	9	
a. Treatment denied, heart badly damaged, required 20 or more million units of penicillin daily.		Congestive heart failure (1).
b. Failure to determine sensitivity, inadequate dosage, and delay in onset of treatment.		Septicemia (2), carcinoma of the colon with severe anemia and cachexia (1).
c. Failure to recognize mixed infection.		Heart failure (1).
d. Delayed and inadequate treatment in patients with repeatedly sterile blood cultures in whom diagnosis was otherwise obvious.		Cerebral embolus (1), congestive heart failure (1), myocardial abscess (1), undetermined (1).

despite penicillin and frequent blood transfusions, the patient suddenly became comatose and died on the 36th hospital day.

At postmortem, the heart weighed 600 gm. and was covered with a shaggy exudate. The aortic valve was stenotic, consisted of two cusps and was almost completely replaced by vegetations. The surfaces of both kidneys had numerous petechial hemorrhages and microscopically were typical of focal embolic glomerulonephritis. Multiple small cerebral emboli were also present. Postmortem culture of the vegetations of the aortic valve revealed streptococcus viridans.

Discussion: This patient, starting on the tenth hospital day after six sterile blood cultures, was given 240,000 units of penicillin daily for 21 days. At postmortem, it was obvious that the bacterial endocarditis had not been arrested. Treatment is considered to have been inadequate in that too small a dosage of penicillin was employed.

CASE 2: A 25-year-old white male was admitted to the Los Angeles County General Hospital complaining of chills and fever of two days' duration; dyspnea, orthopnea, hemoptysis and ankle edema were present. Heart disease was first detected in 1940 when the patient had been rejected by the army.

He was acutely ill, dyspneic, orthopneic, and cyanotic, and numerous petechiae were found on the anterior surfaces of both thighs. The temperature was 102° F., the pulse rate 120 per minute, the respirations 44 per minute, and the blood pressure 104 mm. of mercury systolic and 46 mm. diastolic. Numerous rales were present at both lung bases. Cardiac enlargement was present, the point of maximum intensity being felt in the fifth interspace at the anterior axillary line. Grade III aortic and mitral systolic murmurs were reported. Gallop rhythm was present. The liver edge was felt two fingers below the right costal margin.

The hemoglobin content of the blood was 5 gm. per 100 cc. Leukocytes numbered 12,200. The sedimentation rate was normal. The urine contained 2 plus albumin. The nonprotein nitrogen was 95 mg. per 100 cc. Reactions to both Wassermann and Kahn tests were positive.

The electrocardiogram showed left ventricular hypertrophy and the orthocardiogram 2-3 plus left ventricular enlargement.

After admission the patient continued to have a low grade fever accompanied by intermittent showers of petechiae. Fourteen repeated blood cultures were all reported sterile. In spite of the failure to recover an organism, the diagnosis was thought to be subacute bacterial endocarditis and penicillin was given in a dosage of 300,000 units per day for the first two weeks of hospitalization, at which time it was increased to 200,000 units every two hours. Additional therapy consisted of blood transfusions, low salt diet, mercurial diuretics, and digitalis. Despite this vigorous therapy, the course was progressively downhill and the patient died on the 27th hospital day.

At postmortem the heart weighed 550 gm. There was a bicuspid aortic valve, the free margin of which was thickened and had numerous recent friable vegetations. The mitral valve appeared normal. There was also a 3 mm. defect in the membranous portion of the interventricular septum. Examination of the brain showed gross subarachnoid hemorrhage which was ascribed as secondary to septic emboli. Postmortem culture of the bacterial vegetations revealed streptococcus viridans.

Discussion: The diagnosis of this case appeared obvious and penicillin was started shortly after admission of the patient to the hospital. The dosage of penicillin was 300,000 units per day for the first two weeks of hospitalization and 2,400,000 daily thereafter. The fatal outcome illustrates that although this dosage might well have been adequate for most cases of subacute bacterial endocarditis, it was inadequate for this patient.

CASE 3: A 47-year-old white male entered the hospital complaining of malaise, cough, chills, and fever, and ankle edema of two to three weeks' duration. He also gave a history of syncopal attacks since May 1942, at which time a complete heart block was first observed.

He was a well-developed and well-nourished white male who appeared neither acutely nor chronically ill. The temperature was 100° F., the pulse rate was 50 per minute and the respirations 20 per minute. The blood pressure was 112 mm. of mercury systolic and 60 mm. diastolic. There were several minute erythematous lesions on the anterior surface of both thighs. The lungs were clear. There was grade II cardiac enlargement, the point of maximum intensity being felt in the fifth intercostal space, 1 cm. to the left of the midclavicular line. There was a systolic thrill over the aortic area and a grade IV aortic systolic murmur transmitted into the neck. The liver edge was palpable two fingers below the right costal margin. The spleen was palpable one finger beneath the left costal margin.

The erythrocyte count was 4,500,000, and the hemoglobin content was 13.5 gm. per 100 cc. Leukocytes numbered 9,600 with 80 per cent polymorphonuclear cells. Results of urinalysis were negative. Seventeen blood cultures were all sterile. A urine culture was positive for staphylococcus albus and a gamma streptococcus. The electrocardiogram showed complete heart block.

Despite repeated sterile blood cultures, the diagnosis was thought to be subacute bacterial endocarditis engrafted on rheumatic aortic stenosis. On the 14th hospital day, penicillin was started in a dosage of 1,500,000 units daily by continuous intramuscular drip and continued for ten days. The patient then left the hospital at his own request.

The patient was readmitted nine days later complaining of malaise, chills, fever and ankle edema. He appeared pale, dyspneic and apprehensive. The temperature was 100° F., the pulse rate 36 per minute and the respirations 30 per minute. There were moist rales at both lung bases. The heart was enlarged and the thrill and systolic murmur over the aortic area were unchanged. The liver and spleen were both palpable two fingers beneath the right and left costal margins respectively.

The hemoglobin content was 10 gm. per 100 cc. of blood. Leukocytes numbered 5,200 with 55 per cent polymorphonuclear cells. The sedimentation rate was 10 mm. in one hour. Five blood cultures at this time were all sterile.

The day following admission, the patient suddenly became cyanotic, had a convulsion, and died. It was thought that he had had cardiac arrest.

The postmortem findings were: The heart weighed 700 gm. The aortic valve was stenosed, bicuspid and calcified, and small adhesions were present on the free margin. The mitral valve was normal. The liver was enlarged, and the cut surface had a nutmeg appearance. The spleen was also enlarged and had several old infarcts.

Postmortem cultures of the heart valve and of the spleen were both positive for streptococcus viridans.

Discussion: After 17 sterile blood cultures, penicillin therapy was started on the 14th day of hospitalization. After 19 days of treatment the patient left the hospital at his own request. It is impossible to speculate as to what the outcome would have

been had the course of penicillin therapy been completed. It was felt, nevertheless, that penicillin therapy had been delayed too long.

CASE 4: A 39-year-old truck driver first entered the Los Angeles County General Hospital in 1944 because of hemoptysis. At this time he was found to have rheumatic heart disease with mitral stenosis and auricular fibrillation. In May 1945, there was an episode of congestive heart failure accompanied by pneumonitis. In December 1946, the patient reentered complaining of chills, fever, cough, and chest pain of one week's duration. He was not in acute distress and did not have dyspnea, orthopnea or cyanosis. The temperature was 100.4° F., the pulse rate 90 per minute and the respirations 24 per minute. Blood pressure was 120 mm. of mercury systolic and 74 mm. diastolic. There were moist rales at both lung bases. The heart was enlarged and fibrillating; the point of maximum intensity was in the sixth intercostal space at the anterior axillary line. Systolic and diastolic murmurs were heard at both mitral and aortic areas. The liver was enlarged three fingers below the right costal margin.

The hemoglobin content was six gm. per 100 cc. of blood. Leukocytes numbered 4,300 with 76 per cent polymorphonuclear cells. The urine contained 4 plus albumen and many erythrocytes. Results of Wassermann and Kahn tests were doubtful. Fourteen blood cultures were all reported sterile. Retrograde and intravenous urograms were all reported negative.

The patient was readmitted three months later with congestive heart failure and again had hematuria. Penicillin was given for six days in a dosage of 125,000 units every three hours. One week after hospitalization the patient became comatose and died within a few hours.

The postmortem findings were: The heart weighed 520 gm. A fish mouth mitral stenosis was present and friable vegetations were present upon the anterior leaflet of the mitral valve. The kidneys weighed 450 gm. The capsules stripped with ease, showing a surface studded with minute petechiae. Microscopic examination of the kidneys showed incomplete destruction with shrinkage of some of the glomeruli. Necrosis of the glomerular tufts was also present. Examination of the lungs showed pulmonary infarction in the left lower lobe. A small amount of subarachnoid hemorrhage was found over the right frontal convolution of the brain. Postmortem culture of the heart valve showed streptococcus viridans.

Discussion: Penicillin therapy was withheld until the final hospital admission. At this time subacute bacterial endocarditis was considered a strong diagnostic possibility despite 14 negative blood cultures. In this case, therapy was obviously delayed too long, and the dosage of penicillin employed was inadequate.

CASE 5: A 61-year-old white housewife, well nourished and well developed, entered complaining of chills and fever of two weeks' duration. The patient had a history of heart disease since 1925. In 1930, at the age of 42, she had had an attack of acute rheumatic fever with polyarthritis for one year. During the year prior to admission, she had noticed progressive enlargement of the fingertips and increasing substernal distress.

There was pronounced cyanosis of lips and fingernails. Dyspnea and orthopnea were not present. The temperature was 100.2° F., the pulse rate was 92 per minute and the respirations 18 per minute. The blood pressure was 120 mm. of mercury systolic and 90 mm. diastolic. Clubbing of the fingers and toes was present. Crepitant rales were heard at both lung bases. There was grade II cardiac enlargement and a grade III systolic murmur was heard all over the precordium, loudest over the aortic area, and transmitted into the neck. The aortic second sound was poor. The rhythm was irregular.

Erythrocytes numbered 5.4 million per cc. The hemoglobin content was 14.5 gm. per 100 cc. The leukocyte count was 10,800 with 76 per cent polymorphonuclear cells. Results of urinalysis were negative. Thirteen blood cultures were all reported sterile.

Ten days after admission, despite 13 sterile blood cultures, a presumptive diagnosis of subacute bacterial endocarditis was made. Penicillin was given in a dosage of one million units daily by continuous intramuscular infusion for the next 21 days. The course continued febrile, and on the 65th hospital day the patient suddenly died.

The postmortem findings were: The heart weighed 500 gm. The leaflets of the aortic valve were thickened, the commissures were fused, and large calcified vegetations were present on the free margins. Between the left posterior and anterior cusps of the aortic valve there was a small opening which communicated with a small abscess cavity (1 by 1 by 1 cm.) in the adjacent adventitia. Between the right posterior and left posterior aortic valve cusps there was a large abscess cavity (4 by 4 by 4 cm.) which extended into the adventitia between the aorta and the left auricle. Both cavities were filled with purulent material. There was an old myocardial infarction present in the posterior superior portion of the interventricular septum. In addition, recent myocardial infarcts were present in the anterolateral wall of the left ventricle and in the apical portion of the interventricular septum.

Postmortem culture of the purulent material in the abscess cavities revealed streptococcus viridans.

Discussion: This patient, with repeatedly sterile blood cultures and a presumptive diagnosis of subacute bacterial endocarditis, received a dosage of penicillin which would have been adequate in most cases. At postmortem, myocardial abscesses were found, and one can only speculate as to whether more vigorous and prompt therapy might have altered the result in this case.

Loewe and Eiber[2] discussed the problem of repeatedly sterile blood cultures in 11 patients in whom the diagnosis of subacute bacterial endocarditis appeared otherwise obvious. Ten of the 11 patients were successfully treated, nine with penicillin and heparin and one with streptomycin. Loewe and Eiber concluded that in such cases treatment should not be withheld in an attempt to obtain a positive blood culture, but that intensive penicillin therapy should be started as soon as possible, and the therapeutic response be used as confirmation of the diagnosis.

In an attempt to decide how long therapy may be justifiably delayed, the author reviewed 140 cases of subacute bacterial endocarditis in which positive blood cultures had been obtained (Table 3). In 129 cases, or 92 per cent, cultures taken during the first day were reported positive, and 137, or 97.8 per cent, taken within the first two days were found positive. From this it appears that if a positive culture ever is to be obtained, it will be found in cultures taken in the first two days in the great majority of cases. The obvious conclusion, then, is

TABLE 3.—*Time Occurrence of Positive Blood Cultures of Subacute Bacterial Endocarditis*

Organism	1st Day	2nd Day	3rd Day	4th Day	5th Day	56th Day
Streptococcus viridans	125 cases	6 cases	1 case		1 case (78 negatives previously)	1 case
Staphylococcus albus	4 cases					
Gonococcus			2 cases			
Total	129	8	1		1	1

that the beginning of treatment should not be delayed more than two days even in the face of sterile cultures.

PENICILLIN DOSAGE WHEN CULTURES ARE STERILE

The problem of what dosage of penicillin to employ in cases of subacute bacterial endocarditis with negative blood cultures is a very difficult one. Unfortunately, sensitivity tests were not performed in the cases in this series in which the organism was cultured at postmortem. Since it is known that 90 per cent of streptococcus viridans organisms are inhibited by 0.1 unit of penicillin per cc. of culture, and since 300,000 units of penicillin will maintain a blood level of 0.1 unit per cc. of blood, it is believed wise to maintain a blood level of 0.5 unit per cc. of blood. This can be done with a dosage of 1,000,000 units of penicillin daily in the average case. Because in the 10 per cent of cases remaining the streptococcus viridans are very resistant and since it is believed the organisms that are difficult to recover on culture are more resistant, a blood level five to ten units should be maintained in those cases in which blood cultures are sterile. Therefore, a daily dosage of penicillin of six to ten million units daily is advisable.

BACTERIAL RESISTANCE

In four of the cases in the present series in which the patient died, the infecting organism had a pronounced in vitro resistance to penicillin and streptomycin. In one of these cases, the organism was streptococcus viridans, and in the remaining three cases, staphylococcus albus.

A report of one of these cases is presented to illustrate increasing bacterial resistance following an initial unsuccessful course of penicillin.

CASE REPORT

CASE 6: A 70-year-old white male was admitted to the Los Angeles County General Hospital with history of a urinary infection following a transurethral prostatic resection about one year previously. He was in good health until 11 weeks prior to admission when weakness, anorexia, dyspnea and ankle edema were observed. Examination revealed rheumatic heart disease with aortic insufficiency. Blood cultures were positive for streptococcus viridans. The sensitivity of the organism was 0.39 units of penicillin per cc. of culture. Penicillin was given in a dosage of 4,000,000 units daily for four weeks and at the end of that time the blood cultures were negative. Three weeks later, the blood cultures were again positive, and the patient was rehospitalized.

The temperature was 99.2° F., the pulse rate was 108 per minute and the respirations were 20 per minute. The blood pressure was 150 mm. of mercury systolic and 56 mm. diastolic in the right arm and 148 mm. systolic and 48 mm. diastolic in the left. There was pallor of the skin and mucous membranes. The heart was enlarged to percussion, and the point of maximum intensity was felt in the fifth intercostal space 1 centimeter to the left of the midclavicular line. Grade III systolic and diastolic murmurs were present at both the primary and secondary aortic areas. Sinus tachycardia was noted. The liver edge was felt two fingers below the right costal margin.

The hemoglobin content was 9 gm. per 100 cc. of blood. Leukocytes numbered 3,700 with 64 per cent polymorphonuclear cells. The urine contained 10 to 15 erythrocytes per high power field. Blood cultures were positive for streptococcus viridans.

An orthocardiogram showed minimal left ventricular enlargement, and at fluoroscopy the aortic pulsations were noted to be collapsing in type. The electrocardiogram showed left ventricular hypertrophy.

Sensitivity tests showed that the infecting organism was quite resistant, requiring 25 units of penicillin or 31 micrograms of streptomycin per cc. of culture to inhibit growth. On the tenth hospital day, treatment was started with penicillin, 20,000,000 units daily by continuous drip, streptomycin, 400 mg. intramuscularly every three hours, and Stataccin® (caronamide) 2 gm. every three hours. In addition, frequent blood transfusions were given. Penicillin and streptomycin blood levels on the second and third days of treatment were:

	2nd day of treatment	3rd day of treatment
Penicillin level	500 units per cc.	1,000 units per cc.
Streptomycin level	2 micrograms per cc.	5 micrograms per cc.

It was found that a 1:64 dilution of serum from the patient on either of the above days was sufficient to inhibit the organism in vitro.

The patient became confused, disoriented and finally comatose. He died on the 20th hospital day.

Permission for a postmortem examination was not obtained.

As to the three cases in which the infecting organism was highly resistant staphylococcus albus: In one case the point of sensitivity to penicillin in vitro was found to be 12 units of the drug per cc. of culture, and sensitivity to streptomycin was shown at 250 micrograms per cc. Because of the extreme myocardial damage present in the patient and the extremely large dosage of penicillin required (20,000,000 or more units daily), treatment was withheld. In the second case seven blood cultures were positive for hemolytic staphylococcus albus with an in vitro sensitivity to 6 units of penicillin or 30 micrograms of streptomycin per cc. of culture. In this case penicillin was started 48 hours prior to the death of the patient, so the effect of therapy cannot be evaluated. In the third case, growth of the organism continued in vitro even with a penicillin concentration of 100 units per cc. of culture. Streptomycin was found to inhibit growth in a concentration of 25 micrograms per cc. of culture. To have attained that level in the blood of

the patient would have required 3 gm. of streptomycin every three hours, a prohibitive dosage. This case is reported in detail:

CASE 7: A 56-year-old white female was first admitted complaining of chills, fever and weakness of ten months' duration. In February 1946, when the patient had first noticed fever and weakness, the cause had been diagnosed as gastroenteritis and the patient had been given 200,000 units of penicillin daily by intramuscular injection for one week but the weakness and fever persisted. In October 1946, physical examination revealed rheumatic heart disease with mitral insufficiency and mitral stenosis, splenomegaly and numerous petechiae. Blood cultures were said to be negative at that time, but the diagnosis of subacute bacterial endocarditis was thought to be a certainty. Penicillin was given in a dosage of 2,400,000 units daily for three weeks. At the end of this period, the fever still persisted and the patient was referred to the Los Angeles County General Hospital for further study and treatment.

At the time of admission, the temperature was 100.2° F., the pulse rate was 112 per minute, and respirations were 20 per minute. The blood pressure was 150 mm. of mercury systolic and 80 mm. diastolic. There were several petechiae over the lower middle back. An old retinal hemorrhage was noted in the fundus of one eye. There were moist rales at both lung bases. Grade I cardiac enlargement was noted, the point of maximum intensity being felt at the fifth intercostal space just outside the midclavicular line. Systolic and diastolic murmurs were heard at both the aortic and mitral areas. The liver edge was felt five fingers below the right costal margin, and the spleen was also palpable.

Erythrocytes numbered 3,500,000, and the hemoglobin content was 11 gm. per 100 cc. of blood. The urine contained many erythrocytes.

An electrocardiogram showed low voltage, and an orthocardiogram revealed a typical "mitral" heart with left auricular enlargement being demonstrated at the right oblique.

One week after admission, a blood culture was reported positive for staphylococcus albus, and six subsequent daily cultures were positive for the same organism. Sensitivity tests showed that the organism was penicillin-fast (no inhibition of growth in 100 units of penicillin per cc. of culture). Streptomycin was found to inhibit growth at a level of 25 micrograms per cc. of culture. It was calculated that this would require 3 gm. of streptomycin every three hours to obtain a therapeutic level in the patient. The patient's course was progressively downhill and the fever persisted despite 1,000,000 units of penicillin daily, accompanied by sulfadiazine. On the 29th hospital day the patient suddenly became stuporous. She died shortly thereafter. Permission for a postmortem examination could not be obtained.

PRESENCE OF MIXED INFECTION

The occurrence of mixed or double infection is infrequent. However, failure to recognize its presence may prove disastrous. In the present series, one patient who was initially admitted for pneumococcal meningitis had a positive blood culture for streptococcus viridans on the 20th hospital day. The diagnosis of subacute bacterial endocarditis was considered by some members of the attending staff at that time, but no specific therapy was instituted. Twenty-five days later the patient died, and postmortem examination revealed subacute bacterial endocarditis involving the mitral valve. This case is reported in detail:

CASE 8: A 44-year-old white male truck driver was admitted complaining of fever and of stiffness of the neck and hiccoughs of three days' duration. Four months prior to admission the patient had had an attack of acute rheumatic fever accompanied by congestive heart failure. Since that time he had had dyspnea on exertion and digitalis had been given.

The temperature at the time of admission was 100.6° F., the pulse rate was 120 per minute, the respirations were 24 per minute, and the blood pressure was 110 mm. of mercury systolic and 50 diastolic. The neck was stiff, and pain was elicited on flexion of the neck. There were a few moist rales at the base of the left lung. Grade II cardiac enlargement was present, the point of maximum intensity being felt in the fifth intercostal space 1 cm. outside the midclavicular line. There were systolic and diastolic murmurs at both the aortic and mitral areas, and auricular fibrillation was noted. The edge of the liver was palpable two fingers below the right costal margin. The tip of the spleen was also palpable. Babinski's reaction was present bilaterally, and a positive Kernig's sign was obtained.

A spinal tap was done, and the pressure was 225 mm. of water. The fluid was cloudy and contained 1,980 cells (90 per cent polymorphonuclear). Pneumococci were found in the smear. Erythrocytes of the blood numbered 4,200,000 and leukocytes 13,300. The urine was normal. The Kahn test reaction was positive.

An electrocardiogram showed auricular fibrillation.

The initial diagnosis was pneumococcal meningitis, and the therapy consisted of penicillin, 40,000 units every three hours for 20 days, and sulfadiazine. On the 20th hospital day, a blood culture was reported positive for streptococcus viridans. A diagnosis of subacute bacterial endocarditis was considered but no definite therapy was started. During the next 25 days the course was gradually downhill, and the patient finally died of congestive heart failure.

At postmortem examination the heart weighed 550 gm., the aortic valve was deformed, and the anterior leaflet had numerous bacterial vegetations. The meninges were thickened and infiltrated with round cells. There was also a small mycotic aneurysm of the right posterior inferior cerebellar artery.

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REFERENCES

1. Hirsch, H. L., and Dowling, H. F.: Observations in the continuous intramuscular method of administering penicillin, Am. Jour. Med. Sc., 210:435, 1945.

2. Loewe, L., and Eiber, H. B.: Subacute bacterial endocarditis of undetermined etiology, Am. Heart J., 34:349, 1947.