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# PENICILLIN THERAPY IN ACUTE BACTERIAL ENDOCARDITIS

BY

A. DOLPHIN, M.D., D.P.H., B.Sc.
*Senior Medical Officer*

AND

R. CRUICKSHANK, M.D., M.R.C.P.
*Pathologist*

(From the L.C.C. North-Western Hospital and Group Laboratory, Hampstead)

Disease of the heart valves caused by bacteria which can be recovered from the peripheral blood is generally divided into acute or ulcerative and subacute endocarditis. Acute bacterial endocarditis is usually caused by pyogenic cocci—haemolytic streptococcus, *Staphylococcus aureus*, and the pneumococcus. *Streptococcus viridans* is the causal organism in most cases of subacute bacterial endocarditis, but other non-haemolytic streptococci, *H. influenzae*, diphtheroid organisms, etc., may be concerned. The illness in the first group usually has the features of a septicaemia, with the endocarditis developing during the course of a generalized infection, and it terminates fatally within a few days or weeks. In subacute bacterial endocarditis, which usually has an insidious onset, the illness is characterized by low-grade fever, embolic manifestations, and progressive anaemia, and it runs a course of many weeks or months before death occurs. The results of sulphonamide therapy in both kinds of the disease have been disappointing. Penicillin is now on trial, and this paper reports the good effect of the drug on six patients who had the acute form of the illness. In most cases clear-cut evidence of endocarditis developed after treatment with penicillin had been started for a septicaemia that had not responded to sulphonamides. Before describing our own cases we propose to give a brief review of earlier reports on the treatment of acute and subacute bacterial endocarditis with sulphonamides and penicillin.

## Sulphonamide Therapy

Reports have appeared of cure of *Str. viridans* endocarditis by sulphonamides, but Willius (1942) has stated that careful analysis of the data presented about many of the cases casts justifiable suspicion on the diagnosis. Thus the presence of fever, a cardiac murmur, and a positive blood culture have often been the grounds for the diagnosis of bacterial endocarditis, although other essential signs, such as emboli, splenomegaly, anaemia, and progressive wasting, have been lacking. In many cases the follow-up period has been too short to justify the claims of cure, and, unfortunately, authors have subsequently failed to correct premature conclusions. Katz and Elek (1944) from their own experience and the reports of others concluded that sulphonamides, combined with heparin, were ineffective in the treatment of *Str. viridans* endocarditis.

In acute endocarditis a study of the reported cases does not suggest that sulphonamide therapy has been effective. The English literature of the past ten years records 14 cases of acute endocarditis due to haemolytic streptococci other than Lancefield Group A (9 Group B, 1 Group C, and 4 Group G); in spite of sulphonamide therapy, given in massive doses in 8 cases, all the patients died. Colebrook and Purdie (1937) in a series of streptococcal puerperal infections encountered one case of Group B endocarditis and 2 cases of Group B septicaemia; all three patients died. According to Fry (1938) Group B streptococcal septicaemia complicating post-abortum and post-partum puerperal sepsis is particularly apt to lead to endocarditis. He reported 2 fatal cases of Group B streptococcus endocarditis which occurred in the puerperium. MacDonald (1939) reported 2 fatal cases of Group G streptococcus endocarditis. Hill and Butler (1940) in a series of 12 Group B streptococcus puerperal infections had 2 patients with bacterial endocarditis, both of whom died in spite of sulphonamide therapy. Rosenthal and Stone (1940) gave an account of 2 fatal cases of haemolytic streptococcal endocarditis—one due to Group C and the other to Group B. The Group C infection was treated with 79 g. and the Group B with 162 g. of sulphanilamide without obvious effect. Koletsky (1941) reported a case of Group B streptococcal puerperal endocarditis in which treatment with sulphonamides and numerous blood transfusions failed; death occurred three weeks after delivery. Ramsay and Gillespie (1941), in a series of 16 Group B streptococcal puerperal infections, described 2 patients who had septicaemia and bacterial endocarditis; both died in spite of massive sulphonamide therapy. Among 12 Group G cases there was one patient whose blood culture was positive and who died from bacterial endocarditis although treated with massive doses of sulphonamides. Kehr and Adelman (1942) unsuccessfully treated with 38 g. of sulphanilamide a Group A streptococcal endocarditis in a child aged 2. The drug had no effect on the course of the disease. Keith and Heilman (1943) reported a case of Group G streptococcal endocarditis in a girl aged 8 years with congenital heart disease. During three months in hospital, while on doses of sulphonamide sufficient to give a blood concentration of 14 mg. per 100 c.cm., cultures of her blood remained persistently positive. Cunliffe, Gillam, and Williams (1943) reported a fatal case of endocarditis due to *Staph. albus* (coagulase-positive). Sulphapyridine produced a fall in temperature but no clinical improvement.

The outstanding features in this review of recorded cases are the frequency of Group B streptococcus as a cause of acute endocarditis and the failure of sulphonamide therapy in both the acute and the subacute forms of the disease.

## Penicillin Therapy

Florey and Florey (1943) treated a case of *Str. viridans* endocarditis with 4,760,000 units of penicillin over a period of 30 days. The patient appeared much improved at the end of treatment; but cultures of the blood three weeks later were positive, and after a further three weeks death ensued. Keefer and his associates (1943) treated with penicillin 17 patients who had subacute bacterial endocarditis. Four of them died, 10 were unaffected by the treatment, and 3 improved temporarily. The total dosages of penicillin varied from 240,000 to 1,760,000 units, given for periods ranging from 9 to 26 days. Better results were claimed by Loewe and his colleagues (1944), who used penicillin and heparin (given subcutaneously) in the treatment of 5 patients with subacute bacterial endocarditis; the patients were all well and their blood was still sterile several months after treatment ceased. A clinical trial on a larger scale has lately been reported by Dawson and Hunter (1945); 15 of the 20 treated patients with subacute bacterial endocarditis have been apparently cured of their infection by penicillin, with or without heparin: 12 of them have been in good health for periods of 5 to 22 months. These workers recommend a daily dosage of 200,000 units of penicillin for three weeks as the minimum standard treatment in subacute bacterial endocarditis.

There have been few reports of the effect of penicillin in acute bacterial endocarditis. Keefer and his colleagues (1943) treated 91 patients who had *Staph. aureus* bacteriaemia (quantitative

blood cultures were apparently not done); of 34 fatal cases 9 had bacterial endocarditis, and none of them showed improvement during treatment. None of the recovered patients had bacterial endocarditis and no patient developed bacterial endocarditis after penicillin treatment had begun. Of 6 patients with primary pneumococcal endocarditis who were treated with penicillin 5 died and 1 recovered. Loewe *et al.* (1944) reported cures in one case of haemolytic streptococcus (group not stated) endocarditis and one case of pneumococcal endocarditis. Blood culture of the patient with haemolytic streptococcal endocarditis showed 130 organisms per plate (presumably per c.cm.) immediately before penicillin treatment was begun: 100,000 units of penicillin were given daily for 13 days. There was a dramatic response to the drug, but towards the end of the second week pulmonary oedema developed and digitalization was necessary. The patient with pneumococcal (Type 27) endocarditis was a girl aged 7½ years with congenital heart disease. She failed to respond to massive doses of sulphadiazine (blood concentration 74 mg. per 100 c.cm.), and repeated blood cultures were positive. During penicillin therapy numerous pulmonary infarcts developed, but she recovered sufficiently to return to school.

Thus the results of penicillin therapy in both acute and subacute bacterial endocarditis are encouraging enough to warrant further trial in these usually fatal infections. Penicillin has not hitherto been available for the treatment of subacute bacterial endocarditis in this country, but a co-operative trial is now being sponsored by the M.R.C. Penicillin Clinical Trials Committee (Christie, 1945).

## Original Records

Six cases of acute bacterial endocarditis were treated in the puerperal sepsis unit at the North-Western Hospital and are a consecutive unselected series. Three of the infections were due to haemolytic streptococcus Group B, one was due to haemolytic streptococcus Group A, and two were due to *Staph. aureus*.

### Case I

A multipara, aged 31, with no illness of note in the past history. Her present illness began after an abortion of three months' gestation, and when admitted to the unit she had been ill for one week, during which she had shivering attacks. Her general condition was good and she did not appear ill. The temperature was 99° F., pulse rate 80, and B.P. 110/70. The heart was normal except for a slightly "snappy" first sound at the apex, the lungs and C.N.S. were normal, and there were no local signs of genital tract sepsis. Cultures from the cervix and blood were sterile, the urine was normal, and a blood count showed R.B.C. 4,900,000, Hb 90%, and W.B.C. 12,000.

Five days later the temperature rose to 104° and blood culture showed haemolytic streptococcus Group B (3 organisms per c.cm.). Sulphanilamide was given (blood concentration, 9 mg. per 100 c.cm.), but after three days the drug was discontinued because of vomiting; sulphamezathine was substituted, 6 g. daily for six days. The temperature was normal during sulphonamide therapy except for a moderate rise on three occasions, but the pulse rate remained about 120. An apical systolic murmur appeared; at first faint, after a few days it became loud, rough, maximal at the apex, well conducted into the left axilla, and accompanied by a thrill. At the same time Osler's nodes appeared on the fingers, and the patient complained of pain like a "bruised" feeling in the left leg and foot. On examination the toes and distal half of the foot were deathly pale, and no pulsation could be felt in the left femoral, popliteal, and dorsalis pedis arteries. There was no splenomegaly, petechiae, or haematuria, the W.B.C. was 22,000, and quantitative blood culture showed 170 organisms per c.cm. The temperature was 99° F., but 24 hours later it rose to 101°. The patient was seen by Dr. Terence East, who confirmed the diagnosis of bacterial endocarditis. Penicillin treatment was begun. Except for the first three days, when an intravenous drip was used, the penicillin was given by intramuscular drip, using Eudrip No. 2 apparatus. Treatment was continued for 15 days. During the first seven days of therapy 100,000 units of penicillin were given daily (maximum blood penicillin level, 1:4), but as two blood cultures were positive during this period dosage was increased to 200,000 units daily for the remainder of the treatment, during which time blood cultures proved sterile. The total penicillin given was 2,300,000 units.

Twenty-four hours after treatment was begun the temperature fell to 98° F., and it remained normal afterwards except for an occasional rise to 99° during penicillin therapy. The general condition continued to improve; 12 negative blood cultures were obtained during the two months after treatment, and when the patient was discharged from hospital the sedimentation rate and W.B.C. had been normal for six weeks. There was a loud rough apical systolic murmur, accompanied by a thrill; radiographs of the heart were normal, the patient felt in excellent health, and the left leg showed no disability, although there was diminished pulsation in the left femoral artery.

### Case II

A multipara, aged 42, with an old history of mitral stenosis. She developed puerperal sepsis after an abortion, and received 30 g. of sulphanilamide before her admission to the unit on the fourth day of pyrexia. She appeared ill, with temperature 100° F., B.P. 100/50, and had compensated mitral stenosis. There were no petechiae or Osler's nodes, no local signs of genital tract sepsis, and the abdomen, lungs, and C.N.S. were normal. A blood count showed R.B.C. 2,500,000, Hb 46%, and W.B.C. 7,000. Lancefield Group B streptococcus was cultured from the cervix and quantitative blood culture showed 35 haemolytic streptococci per c.cm.

Sulphamezathine, 6 g daily, was given for five days, but the patient's general condition deteriorated; she sweated profusely, had remittent fever up to 105° F., and the pulse rate averaged 140. Quantitative blood culture showed 127 organisms per c.cm. immediately before penicillin treatment was started on the ninth day of disease. Treatment continued for 11 days. During the first six days the drug was given by intramuscular drip, 100,000 units daily (blood penicillin level, 1:4), and afterwards by 6-hourly intramuscular injections of 15,000 units. The total penicillin given was 960,000 units.

Twelve hours after penicillin treatment started the temperature fell from 105° F. to 97°, remained normal for two days, and then rose to 102°, after which it fell by lysis. The general condition improved, but on the third day of treatment a few petechiae appeared on the neck. Next day there was numbness and pain of sudden onset in the right foot; the toes and distal part of the foot became deathly pale, and no pulsation could be felt in the right popliteal and dorsalis pedis arteries. Gangrene did not develop, although pulsation could not be felt in the vessels for about six weeks. Since the patient's heart had not been fibrillating or in flutter it was considered improbable that the arterial obstruction was due to a thrombus arising in the left auricle. Five negative blood cultures were obtained during penicillin therapy and four negative blood cultures during the next two months. Five days after the penicillin was discontinued an intensely itchy generalized urticarial rash developed—probably an allergic reaction to the drug, since other possible causes were eliminated. The temperature and sedimentation rate have been normal for four months, but convalescence has been slow because of a considerable reduction in her cardiac reserve. This was due to recent myocardial and endocardial damage superimposed on old heart disease.

### Case III

A primipara, aged 27. The duration of her illness was not exactly known, but apparently she was ill for two days before admission to the unit. Her general condition was then poor, she was drowsy and non-cooperative, the temperature was 101° F., and B.P. 110/70. There were no petechiae or Osler's nodes, and the lungs, abdomen, and C.N.S., apart from the drowsiness, were normal. A blood count showed R.B.C. 3,500,000, Hb 64%, and W.B.C. 19,000. The uterus was slightly enlarged, but there were no definite signs of sepsis. Lancefield Group B streptococcus was cultured from the throat, cervix, and blood (quantitative blood culture showed 109 organisms per c.cm.). Sulphanilamide treatment was begun (blood concentration, 9.5 mg. of free drug per 100 c.cm.), but blood culture after two days' treatment showed 15 organisms per c.cm., and after a further two days, during which time the general condition of the patient deteriorated, it was decided to discontinue sulphanilamide and begin penicillin therapy. Except for a short initial period when an intravenous drip was used, the penicillin was given by 3-hourly intramuscular injections of 15,000 units. Treatment was continued for 10 days, and the total penicillin given was 1,157,000 units.

Osler's nodes appeared on the fingers on the same day as penicillin treatment began, and on the second day of treatment the patient had sudden pain and numbness in the left foot and leg; on examination the foot was deathly pale, and pulsation could not be felt in the left popliteal and left dorsalis pedis arteries. The temperature, except for an occasional fall to normal, remained about 100° F. until three days after penicillin treatment was stopped, when it remained about 99° F., probably owing to gangrene, which had developed in the left foot. Blood cultures performed on the second, fifth, and seventh days of treatment, and on the ninth day after treatment had ceased, were sterile.

At this stage the patient was transferred to St. Thomas's Hospital for surgical treatment of the gangrenous foot. The temperature was normal for the next three weeks, when suppuration developed in the left foot. The temperature rose to 104.4° F., the leucocyte count was 15,000, and a swab from the left foot gave a growth of *Staph. aureus* and *albus* and haemolytic streptococci (not grouped). Blood cultures were sterile. After a course of sulphathiazole the temperature was normal again in seven days. The patient had another

pyrexial bout four days later, probably associated with the septic foot. On the 41st day after transfer she had a mid-thigh amputation, developed signs of bronchopneumonia, and died five days after operation.

At necropsy the heart showed mitral stenosis and hypertrophy of the left ventricle. The mitral cusps were adherent to each other and a little thickened; there were a few warty vegetations along the line of closure. The spleen was much enlarged and showed a number of septic infarcts, containing many streptococci. The material was not cultured. There were numerous small old infarcts in the kidneys. The left femoral artery contained old thrombus at its proximal end. It may be concluded that this patient had an acute bacterial endocarditis which was apparently cured by penicillin therapy, and that she died of bronchopneumonia following a major operation.

### Case IV

A primipara, aged 31, with an old history of mitral stenosis. She developed puerperal sepsis after full-term delivery and was admitted to the unit on the sixth day of illness. Her general condition was fairly good; temperature 103° F., pulse rate 136, and B.P. 110/60. The heart was not enlarged; there was an apical systolic murmur, but no presystolic murmur and no thrill. There were no local signs of genital tract sepsis, and the lungs and C.N.S. were normal. A blood count showed R.B.C. 3,650,000, Hb 38%, and W.B.C. 16,000. Cultures from the cervix and blood were sterile. The urine contained no pus or red cells, but culture revealed Group A haemolytic streptococcus. Sulphanilamide treatment was given for six days (total drug, 28 g.). On the fourth day of treatment the temperature fell to 97° F. in the morning, but rose to 100° in the evening, after which a remittent fever developed, sometimes reaching 103°. A second blood culture 10 days after admission showed Group A streptococcus, and a second course of chemotherapy with sulphapyridine was started. While the drug was being given the blood cultures remained positive, and quantitative blood culture at the end of the course of sulphapyridine showed 129 organisms per c.cm. The patient's general condition was then worse; there was an apical systolic murmur as before, but no diastolic murmurs, the pulse rate was 144, and petechiae were present on the neck and tender red areas on the fingers. The spleen was not enlarged, but haematuria appeared for the first time; Hb was 55% and the W.B.C. 30,000. Penicillin treatment was begun 13 days after obtaining the first positive blood culture. The drug was given at first by 3-hourly intramuscular injections of 15,000 units, but later the interval between doses was increased. Treatment was continued for 14 days, and the total dose of penicillin was 960,000 units.

Within 24 hours of beginning penicillin treatment there was considerable clinical improvement; repeated blood cultures proved sterile, the temperature fell from 104.6° F. to 100° and remained around this level until treatment ceased, when it fell to normal. The pulse rate fell more slowly, and four days after treatment was begun a diastolic murmur was heard at the aortic area and along the left sternal border. Progress was maintained, and when the patient left hospital three months later the sedimentation rate was normal, Hb was 88%, there was a slightly diminished cardiac reserve, systolic and diastolic murmurs were heard at the aortic and mitral areas, the B.P. was 130/60, and she had a collapsing pulse.

After she left hospital the patient was seen by Dr. Jenner Hoskin, who reported: "She now has aortic regurgitation and double mitral disease, which in my opinion is rheumatic in origin. In my opinion the heart has suffered materially from the recent illness, which has definitely aggravated the valvular damage."

### Case V

A multipara, aged 29, with no illnesses of note in the past history. She was admitted to the unit two days after she had aborted. She was only slightly ill; temperature 99° F., heart normal except for tachycardia of 116, B.P. 130/80. Cervical swab culture showed *Staph. aureus*; blood culture was sterile. Within 24 hours of admission to hospital she had severe haemorrhage, and manual evacuation of the uterus was performed. During the next seven days she received 47 g. of sulphanilamide. Eleven days after operation the temperature rose to 104° and blood culture showed *Staph. aureus*. A second course of sulphonamides was begun, being continued for eight days (30 g. of sulphathiazole by intravenous drip and 42 g. orally; 28 g. of sulphapyridine orally); the maximum drug concentration attained in the blood was 3.7 mg. of sulphapyridine per 100 c.cm. The general condition deteriorated; four blood cultures taken during chemotherapy were positive, and quantitative cultures on the sixth, seventh, and eighth days of treatment showed respectively 75, 120, and 703 organisms per c.cm. Penicillin treatment was then begun. The clinical picture was that of severe septicaemia without evidence of endocarditis.

Penicillin was given by 3-hourly intramuscular injections of 15,000 units for five days, then 3-hourly intramuscular injections of 10,000 units for two days; total penicillin, 790,000 units. The general condition improved considerably with the treatment, and blood cultures were sterile; but three days after treatment was stopped a rigor occurred, quantitative blood culture showed 167 organisms per c.cm., heart failure with pulmonary oedema developed, and a loud harsh pulmonary systolic murmur was heard. A second course of penicillin was given; the total dose was 879,000 units, administered during nine days by intermittent intramuscular injection. The patient's general condition again improved considerably; blood cultures were sterile on four occasions, the cardiac failure became progressively less, but six different specimens of urine contained numerous red cells. Three days after the second course of penicillin had ended acute heart failure again developed, but it responded to oxygen and diuretics; there was no pyrexia during this attack, but the pulse rate remained about 120. Six days later the temperature rose to 103° and quantitative blood culture showed 186 organisms per c.cm. No extracardiac origin was found for the septicaemia; and endocarditis, although suspected as the most probable cause for the relapses and the haematuria, was not diagnosed definitely because of the absence of petechiae, splenomegaly, and cardiac murmurs other than the pulmonary systolic. A blood count showed R.B.C. 4,100,000, Hb 68%, and W.B.C. 15,000.

A third course of penicillin was given (375,000 units during eight days by intermittent intramuscular injections). Two days after this course was begun a soft, blowing diastolic murmur which followed immediately on the second sound was heard at the aortic area and along the left sternal border. The urine contained numerous red cells, and when cultured showed some *Staph. aureus*. Blood cultures during this third course of penicillin and all subsequent blood cultures were sterile. The patient continued to improve, but her discharge from hospital was delayed by chronic cystitis. She left hospital fit and well five months after her third course of penicillin had finished. Her cardiac reserve was then normal, but the aortic diastolic murmur was still well marked.

The patient was seen at the hospital 12 months later; she has been fit and well meanwhile, and has become pregnant again. She still has a diastolic murmur at the cardiac base and along the left sternal border, but it is less loud than it was before. Her B.P. is 140/70, radiographs of the heart show no abnormality, and her Wassermann reaction is negative.

### Case VI

This patient, a multipara aged 31, was admitted with post-abortum puerperal sepsis and *Staph. aureus* septicaemia. She had received 31 g. of sulphonamides (13 g. of sulphamezathine and 18 g. of sulphapyridine) before admission to the unit on the seventh day of disease. She was extremely ill; temperature 100.6°, pulse 128; she was cyanosed and dyspnoeic, and had some basal pulmonary rales. Auscultation revealed an apical rumbling diastolic and an apical systolic murmur. There were numerous petechiae, especially on the neck and arms, and the spleen was slightly enlarged. *Staph. aureus* was cultured from the cervix and blood; quantitative blood culture showed 3,800 organisms per c.cm. (a repeat culture 24 hours later showed 4,820 organisms per c.cm.). The urine contained numerous red cells and some pus cells, and culture revealed *Staph. aureus*. The Hb was 58% and W.B.C. 33,000.

Penicillin treatment was started on the ninth day of disease (second day after admission) and continued for 12 days; during the first three days 120,000 units were given daily by 3-hourly I.M. injections of 15,000 units; but as the drug was slowly excreted because of chronic nephritis (urea clearance test, 16% of normal) the intervals between doses were gradually lengthened, until finally 15,000 units were given once daily, because excretion of a dose of 15,000 units was not completed until 36 hours afterwards. Total penicillin, 646,000 units. Within 24 hours of starting treatment the patient's condition improved. The temperature fell from 103° F. to normal, and it remained normal for six days, but afterwards became intermittent, sometimes reaching 100°. Blood cultures taken during penicillin treatment were sterile, but the clinical improvement was not maintained. She developed uraemia on the fifth day of treatment and became progressively worse. Death from uraemia occurred on the 21st day of disease.

The report on the necropsy was as follows: "Tricuspid valve thickened. Mitral stenosis and recent small vegetations on the valve. Cloudy swelling of the liver. The spleen contained several large infarcts and some smaller ones, most of them septic (cultures from the infarcts gave growths of *B. proteus*; Gram-positive cocci were seen in the smears, but it was not possible to determine if they were *Staph. aureus* or not). Kidneys: chronic nephritis and small infarcts in the enlarged left kidney. The uterus was slightly enlarged and without apparent sepsis. The brain had a large subdural haemorrhage; no embolism, and the arteries were normal."

### Laboratory Tests

The infecting organisms in all these cases were sensitive to penicillin by *in vitro* tests. Blood and urinary levels of penicillin were determined by the methods of Fleming (1944). Penicillinase was added to blood cultures in fluid media. Quantitative blood cultures were made repeatedly in all cases by adding 1 c.cm. of blood to a tube containing 10–12 c.cm. of melted

agar and pouring into a Petri dish at the bedside. We consider quantitative blood culture to be very valuable as a prognostic aid in both staphylococcal and streptococcal septicaemia, and records of cure of "septicaemia" without this check should be accepted with caution (see McLellan and Goldbloom, 1942). The presence or absence of inhibitory penicillin in the quantitative blood-culture plate was determined by streaking a culture of *Staph. aureus* on one corner of the plate before incubation.

### Diagnosis of Acute Bacterial Endocarditis

Thayer (1931) wrote that in acute streptococcal and staphylococcal endocarditis the short duration of the illness and the intense septicaemia so dominate the picture that the clinical signs of petechiae, emboli, etc., associated with *Str. viridans* endocarditis uncommonly occur and the endocarditis is often indeterminable clinically. In his series petechiae and emboli occurred in only 25% of acute haemolytic streptococcal infections, and were unusual in *Staph. aureus* cases (13.8%) unless the disease was subacute, when emboli and nephritis were commonly seen after some weeks. In staphylococcal infections the spleen was generally not palpable (felt in only 12.5% of cases); suppurative arthritis occurred in 6% of cases, clubbed fingers were not observed, and red corpuscles were found in the urine only four times among 32 cases. Pericarditis was uncommon (11% of cases) in acute streptococcal endocarditis; it occurred in 13.3% of staphylococcal infections, in which it was always purulent. It was particularly noted that streptococci, both haemolytic and *viridans*, attacked the sites of congenital malformations or previously damaged valves; in his series there was evidence of pre-existing valve damage in 58% of acute streptococcal and in 71% of *Str. viridans* infections. *Staph. aureus* showed no predilection for diseased valves, and although it most commonly attacked the left side of the heart the tricuspid valve was often affected.

Until grouping of haemolytic streptococci was possible endocarditis caused by Lancefield B, C, and G organisms was not distinguishable from that caused by Group A strains, but recent reports on endocarditis caused by these organisms confirm our experience in the puerperal sepsis unit that petechiae and Osler's nodes occur infrequently in Group B and G endocarditis and that obstruction of large arteries, especially of the lower limbs, is commonly found in Group B infections. Thus, this phenomenon occurred in all three Group B cases in the present series, while of the nine Group B cases found in the literature one patient developed complete gangrene of one foot and partial gangrene of the other, one developed hemiplegia, and one developed obstruction of an iliac artery. The only Group C endocarditis (confirmed at necropsy) found in the literature developed obstruction of both iliac arteries due to an aortic embolism. The frequency of embolism in the large vessels in Group B endocarditis may be associated with the character of the vegetations. Fry, and also Ramsay and Gillespie, noted that in this condition the endocardial vegetations were large and friable, owing perhaps to the fact that Group B streptococci do not produce fibrinolysin as Group A strains do, so that the thrombus deposited on the damaged valve is not dissolved away. Massive vegetations have also been noted in Group C and G endocarditis, and occur, of course, in staphylococcal and pneumococcal endocarditis. However, in the latter infections the course of the disease is usually so acute that embolic signs may not have time to develop.

In the light of the recorded findings it may be profitable to recapitulate the criteria on which a diagnosis of acute bacterial endocarditis was made in our series of six cases. In the first three patients the repeated isolation of Group B streptococcus from the blood stream, associated with clinical evidence of a generalized infection and, with one exception, the absence of an extracardiac focus, would be strong presumptive evidence of endocarditis even before signs of valvular damage were apparent. Although a diagnosis of endocarditis was made in only one of the three cases before penicillin treatment was begun, all three developed unequivocal signs of endocardial involvement with embolic phenomena; in one the diagnosis was confirmed at necropsy. In only one of the three patients was there definite evidence of antecedent valvular damage (following acute rheumatic fever), so that Group B streptococci may attack healthy heart valves—a finding which accords with the experience of other workers. The occurrence of signs of obstruction in the large leg vessels in all three cases (followed by gangrene of the foot in one case) was probably due to arterial embolism from the friable endocardial vegetations. There was no evidence of cardiac failure or auricular fibrillation, which also predispose to arterial block.

Of the two patients with staphylococcal septicaemia, signs of endocarditis were present in one of them on admission. Although the diagnosis was confirmed at necropsy, the small size of the vegetations and the repeatedly negative blood cultures during penicillin therapy are evidence that the staphylococcal infection had been controlled. Treatment, however, had been begun too late (blood culture showed nearly 5,000 organisms per c.cm.); irremediable damage had been done, and the patient died in uraemia. The other patient with staphylococcal endocarditis had two septicaemic relapses, and evidence of endocardial damage in the form of an aortic diastolic murmur was noted for the first time during the second relapse, although haematuria, anaemia, and persistent tachycardia were present earlier. The aortic diastolic murmur, the haematuria, and negative evidence of antecedent syphilitic or rheumatic infection were accepted as proof of the development of bacterial endocarditis. Although the valvular lesion is still present, the patient is fit and well 10 months after she was discharged from hospital.

The patient with Group A streptococcal septicaemia developed signs of fresh endocardial damage during the course of her illness. She was admitted with a history of mitral stenosis and had an apical systolic but no diastolic or aortic murmur. Blood cultures were persistently positive despite intensive sulphonamide therapy, and tachycardia, anaemia, and progressive wasting were present. About the time penicillin therapy was begun Osler's nodes and haematuria occurred, and four days later an aortic diastolic murmur appeared. When discharged from hospital, and again when seen by a cardiologist about one month later, she had aortic regurgitation in addition to mitral stenosis.

The beneficial response which these patients with acute bacterial endocarditis have shown to moderate dosage of penicillin is interesting in view of the failure of similar dosage in subacute bacterial endocarditis. Part of the explanation may lie in a greater sensitivity of the infecting organism to penicillin; or perhaps the more bulky and friable vegetations may allow the penicillin to permeate the clot more easily. Although three of the patients are now well and one improved 6 to 12 months after penicillin therapy was stopped, it is impossible to say what the long-term prognosis may be. With gross valvular damage, a heavy strain is put upon their cardiac reserve and they are obviously at the mercy of any infective condition—e.g., dental sepsis—that may lead to bacteriaemia and a fresh endocardial infection.

### Summary

Six cases of acute bacterial endocarditis—three due to haemolytic streptococcus Group B, two to *Staph. aureus*, and one to haemolytic streptococcus Group A—were treated with moderate doses of penicillin. Four of the patients are alive 6 to 12 months after penicillin therapy was stopped; three are well and one has improved.*

Attention is directed to the frequency of infection of healthy heart valves by Group B streptococcus, which not uncommonly causes mild genital-tract sepsis, particularly after abortion.

The criteria for the diagnosis of acute bacterial endocarditis which may occur during the course of a generalized infection are discussed.

### * ADDENDUM

Since this paper was completed, patient No. II of the series has died, six months after penicillin treatment had ceased. During this period the temperature was normal, blood cultures were sterile on four occasions, and the sedimentation rate was normal. She had severe mitral disease. Chronic congestive failure, which responded to mercurial diuretics for a time, developed. Death was due to pulmonary oedema following acute left heart failure.

At the necropsy dilatation and hypertrophy of both auricles and right ventricle and dilatation of the left ventricle were found. The tricuspid orifice was enlarged and the cusps slightly thickened. The mitral orifice was rather small, the valves thickened and contracted, and there were two large perforations of the cusps. A small vegetation on the mitral valve gave a growth of *B. coli* and enterococcus on culture. The kidneys were rather large and congested, and one kidney had scars from two infarcts. It may be concluded that this

patient had an acute bacterial endocarditis which was apparently cured by penicillin therapy, and that she died from acute heart failure.

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# STAPHYLOCOCCUS PYOGENES SEPTICAEMIA TREATED WITH PENICILLIN

## REPORT OF TWO CASES

BY

**LEONARD HOWELLS, M.D., B.Sc., M.R.C.P.**
*Lieut.-Col., R.A.M.C.; Officer in Charge, Medical Division of a General Hospital*

**R. R. HUGHES, M.D., M.R.C.P.**
*Major, R.A.M.C.; Medical Specialist*

AND

**R. RANKIN, M.B., B.Sc., Ch.B.**
*Capt., R.A.M.C.; Graded Pathologist*

The following is an account of two cases of *Staphylococcus pyogenes* septicaemia treated with penicillin.

### Case I

The patient was a marine aged 22. On Sept. 28, 1944, he developed headache, sweating, slight cough, and pain in the back; he remained on duty all night and was sent to the sick-bay the next day. On the 30th he was admitted to hospital still complaining of the above symptoms. On examination he was rather apathetic, temperature 101.6°, pulse rate 100, and respiratory rate 22 a minute; his throat was slightly injected, but no other abnormality was found.

By Oct. 1 his condition had deteriorated; his temperature was swinging to 102° F., and the pulse and respiratory rates were rising. He was confused, restless, and irritable, his heart apex beat was in the mid-clavicular line in the fifth left intercostal space, there was some neck rigidity, and Kernig's sign was slightly positive. In view of these findings a clinical diagnosis of meningococcal meningitis was made. Lumbar puncture was done under pentothal anaesthesia; the cerebrospinal fluid pressure was 200 mm., and the fluid was slightly murky in appearance; on laboratory examination it was found to contain 40 red blood cells and 9 white blood cells per c.mm. and 40 mg. of protein (no excess of globulin), 70 mg. of glucose, and 700 mg. of chlorides per 100 c.cm. The urine was loaded with albumin (0.75 g. Esbach), and on microscopical examination scanty epithelial cells, leucocytes, and granular casts were found. Blood examination showed a haemoglobin of 89%, red blood cells 4,750,000 per c.mm., and white blood cells 14,000 per c.mm., with 85% polymorphonuclears.

On Oct. 2 the patient was still confused and irritable, with a temperature swinging to 102° F. and raised pulse and respiratory rates. On examination the neck rigidity and Kernig's sign were more pronounced, the fundi were normal, all tendon reflexes were absent, and plantar responses showed voluntary withdrawal of both feet. The heart was enlarged, with the apex beat 4½ in. from the midline in the fifth left intercostal space, a systolic murmur was heard at the apex and base of the heart, and the blood pressure was 140/60. The white cell count had now risen to 23,600 per c.mm., with 84% polymorphs, the blood urea was 55 mg per 100 c.cm., the urine was still loaded with albumin, and leucocytes and granular casts were still present.

During the day the patient's pulse rate had been rising steadily, and at 22.00 hours had reached 142 a minute. At this time he suddenly developed a left hemiparesis involving the limbs and face, and on examination his heart was found to be more dilated and the systolic murmur still present. In view of these developments it was now felt that a clinical diagnosis of infective endocarditis could be made; although this had not yet been confirmed by blood culture the dangerously ill condition of the patient made immediate specific treatment essential. Penicillin therapy was therefore started; he was given 100,000 units at 23.30 hours, followed by 40,000 units intramuscularly 3-hourly day and night.

By 09.00 hours on Oct. 3 he had been given 220,000 units of penicillin. His general condition had improved somewhat and his pulse rate had fallen to 108 a minute, but he was still in a state of low muttering delirium, his neck rigidity was more marked, and his hemiplegia was unchanged. The urine was loaded with albumin, the blood urea was 80 mg. per 100 c.cm., and the cerebrospinal fluid now contained 376 red blood cells per c.mm. Blood and cerebrospinal fluid cultures were made on this date and later; both were reported to contain *Staph. pyogenes*. The bacteriological report was as follows: "A smooth-growing well-pigmented strain of *Staph. pyogenes* was isolated after 36 hours. The organism was coagulase-positive, moderately haemolytic, and showed a sensitivity to sodium penicillin equalling that of the standard 'Oxford' strain." When re-examined at 19.00 hours his general condition was unchanged. He was still delirious, the neck rigidity and hemiparesis were still pronounced although he could now use his left arm a little, his heart apex beat was 1 in. outside the left mid-clavicular line in the fifth intercostal space, and a soft short apical diastolic murmur could be heard. The spleen was not palpable.

On Oct. 4 there was an improvement in the patient's general condition, his temperature had settled to the region of 99° F., and his pulse rate was steadily falling. He was, however, still delirious and the neck rigidity and hemiparesis were severe; the heart apex beat was well outside the left mid-clavicular line, and the soft apical diastolic murmur could still be heard. The blood urea was 60 mg. per 100 c.cm. On the 5th the patient's temperature was normal and his pulse and respiratory rates were falling rapidly. He was still very ill, but his condition had improved in the past 24 hours and he was having short lucid intervals. A crop of purpuric spots had appeared on the toes of both feet. The cerebrospinal fluid pressure was 250 mm.; the fluid contained 167 red blood cells per c.mm., and on culture was sterile. By 20.30 hours he had been given 1,020,000 units of penicillin; his condition was rapidly improving; he was fully conscious, with only occasional short periods of confusion, and was able to use his left hand to hold a feeding-cup.

By Oct. 6 the patient's condition had very much improved and he had been afebrile for the past 24 hours. He was still having occasional slight delirium and his neck rigidity was more pronounced; his hemiparesis was improving and he was now moving his left arm and leg a good deal. There was a left extensor plantar response. The heart apex beat was still well outside the mid-clavicular line in the fifth left intercostal space; there was a soft localized aortic systolic and a harsh apical diastolic murmur. The liver and spleen were not palpable. The blood urea was 55 mg. per 100 c.cm., the urine still contained albumin, and there were some leucocytes and an occasional granular cast in the deposit.

On Oct. 7 he was using his left arm and leg a good deal although weakness persisted; his condition was otherwise unchanged, and he was delirious at times. The next day an aortic diastolic murmur was heard for the first time. The white blood count was 14,150 per c.mm. with 81% polymorphs. A course of sulphapyridine was started with an initial dose of 2 g., followed by 2 g. four hours later, then 1 g. 4-hourly by mouth.

On Oct. 9 his general condition was very good, his appetite was satisfactory, and he was sleeping well with only very few short periods of delirium. He was still having an occasional rise of temperature to 99 or 100° F. On examination the heart apex beat was in the mid-clavicular line in the fifth left intercostal space; there was no palpable thrill. Auscultation revealed a rough aortic systolic murmur which was conducted along the subclavian and carotid arteries, and also a soft short aortic diastolic murmur conducted down the left border of the sternum. The pulse was collapsing, the blood pressure 140/40, and a pistol-shot murmur was audible over the femoral arteries. The spleen was not palpable. He was now using the left arm normally, but there were a slight weakness of the left lower face, a spastic left leg, and a left extensor plantar response. The abdominal reflexes were present but diminished on the left side. The blood urea had now fallen to 45 mg. per 100 c.cm. Radiographs showed definite enlargement of the heart to the left, with the general configuration of an early aortic lesion. There was also some hyperaemia at the base of the right lung.

The patient's condition was still improving on Oct. 10 and his neurological signs had almost completely cleared. On this date a