is expected that a more complete analysis of these and other patients treated within the scope of this investigation will be made at a later date.

Summary

The results here reported provide further evidence of the therapeutic value of penicillin in subacute bacterial endocarditis.

If the administration of penicillin is continued for 10 days or more almost any system of dosage will occasionally produce excellent results. Relapse is, however, more likely to occur if treatment is not both prolonged and intensive.

From the evidence available it is safer to assume that inadequate treatment is prejudicial to later success.

In previously untreated patients 0.5 mega unit a day for 28 days has given better results than any other system of dosage employed.

The resistance of the infecting organisms as measured by ordinary titration methods appeared to be of no clinical importance within a wide range. Only when the organism was more than 10 times as resistant as the standard test staphylococcus did this measurement appear to be of therapeutic and prognostic significance.

This report is submitted on behalf of a large number of workers who have taken part in this investigation in the fourteen research centres appointed by the Penicillin Clinical Trials Committee.

TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS BY PENICILLIN

PRELIMINARY REPORT ON 18 CASES

BY

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In February, 1945, we were invited by the Medical Research Council to form one of the centres for investigating the value of penicillin for the treatment of subacute bacterial endocarditis. Since February we have treated 18 cases. All our patients have had penicillin with no heparin, and each case has been given 480,000 units daily by intramuscular injections—60,000 units every three hours, night and day. In the first four months this dosage was continued for 21 days—total, 10 million units—and in every case the blood was rendered sterile almost at once, and the temperature usually settled down within a few days of starting treatment. Two cases relapsed, necessitating a further course of penicillin, so it was decided at the beginning of June to give a course of 28 days instead of 21—total, 13.5 million units—as suggested at a meeting of the Endocarditis Research Committee. Since this plan was adopted we have had no more relapses.

In all our cases streptococci of the *viridans* type had been obtained from the blood, and treatment began only after bacteriaemia had been confirmed by positive blood cultures. The only therapeutic measures adopted besides the penicillin were iron or liver preparations for the anaemia and in two cases blood transfusion, vitamin C, and, in one instance, sodium salicylate, antiphlogistine for the relief of localized pain, and mersalyl and digitalis for such cases as showed evidence of congestive failure.

Of these 18 patients four have died, but of these four only one can be considered a failure to respond to penicillin. No. 256 died from cerebral embolism two days after penicillin injections were begun; No. 342 died as a result of a rupture of one of the cusps of the aortic valve; No. 363 died from haemorrhage from enlarged vessels in the oesophagus, which were caused by cirrhosis hepatis; No. 361 failed to show any response to penicillin, and died from pulmonary infarction.

Of the remaining 14 cases two have manifested signs of congestive heart failure. One of these was one of the two cases which relapsed after the 21-days course of penicillin; it has responded well to rest and mersalyl, and now shows no signs of congestive failure. The other case shows early signs of congestive failure, but has refused to come into hospital for further treatment. This patient is still free from infection of the blood. During the course of treatment with penicillin in this case the haemoglobin level fell to 18% as a result of haematemesis.

Thirteen patients have remained free from infection, and have left hospital and are apparently well. One is still in hospital. He has completed his course of penicillin, and shows negative blood cultures but has not yet got a sufficiently stable cardiac mechanism to warrant a claim of uninterrupted convalescence.

No. of Days Treated	No. of Cases	No. Died	No. Relapsed and Re-treated for a further 28 Days	Days Free from Recurrence					
				50–100	100–150	150–200	200–250	250–300	Over 300
21	9	1*	2	—	—	—	—	4	2
28	11†	3	—	3	1	3	1	—	—

* This was No. 256, who died on the second day of the course.
† Including the two which failed on the 21-days course.

Case Summaries

Case 246.—Female aged 12. Admitted 23/1/45. After tooth extraction, two weeks previously, had felt unwell: anorexia, fever, sweats, temperature 103°, pulse 120, apical systolic murmur; haemoglobin (Hb) 88%, basal sedimentation rate (B.S.R.) 20 mm./hr. Treated as rheumatic carditis up to 16/2/45, when temperature started swinging again with profuse sweats; two blood cultures positive. 23/2/45: Began course of penicillin. Temperature normal, only slight sweats; blood culture negative. 1/3/45: Osler's nodes on fingers, scanty red cells in urine. 11/3/45: Central abdominal pain, temperature 102°, pulse 140; subsided in 3 days; probably small mesenteric embolus. 16/3/45: Penicillin discontinued. 5/4/45: Started to get up. 30/5/45: Hb 112%; B.S.R. 5 mm./hr.; a few red cells in urine. 1/6/45: Discharged to convalescent home. Has been seen on several occasions since then. Remained fit; now back at school.

Case 249.—Male aged 29. Admitted 23/2/45. Known congenital heart since age of 2; rheumatic fever at age of 13. Seven months' history of malaise, lassitude, pain in the chest, sweating, swollen ankles; in the same period lost 3 st. (19 kg.) in weight. Clubbing of fingers; spleen palpable; to-and-fro murmurs, maximal in third and fourth interspaces 1/2 in. (1.3 cm.) from sternum; basal crepitations; blood culture positive on two occasions; moderate red cells in urine; Hb 70%; B.S.R. 40 mm./hr. 25/2/45: Started penicillin. 28/2/45: Pain in right side of chest; small pulmonary infarct. Blood culture negative. 2/3/45: Temperature normal. 8/3/45: Marked improvement; appetite good, still occasional night sweats. 18/3/45: Penicillin discontinued. 19/3/45: Positive blood culture. One tooth removed under general anaesthesia; covered by 48 hours' penicillin, 60,000 units three-hourly. Culture of roots revealed *Str. viridans*. Remaining teeth removed in four sessions, covered by penicillin. 13/6/45: Discharged. Has been seen on many occasions since, the last on 2/11/45. Now back at work as a salesman; 2 st. (12.7 kg.) increase in weight; heart unchanged; slight dyspnoea on effort; Hb 106%; B.S.R. 5 mm./hr.

Case 273.—Female aged 26. Admitted 16/3/45. Gave a history of rheumatic fever at age of 7. She had suffered from mild cerebral embolism six weeks before admission and had a swinging temperature, with red cells in urine, aphasia, and oedema of ankles. Café-au-lait colour, extremely pale. Aortic and mitral lesions; nominal aphasia. Hb 36%; B.S.R. 32 mm./hr.; positive blood culture. 21/3/45: Started course of penicillin. 26/3/45: No response to iron or liver preparations; 3 pints (1.7 litres) blood transfusion. Occult blood strongly positive. 5/4/45: Haematemesis—30 oz. (0.85 litre), necessitating further transfusion. Hb only 18%. 7/4/45: Small haematemesis. Patient collapsed; pulse irregular; 3 pints concentrated red cells given. Still profuse red cells in urine. 12/4/45: Occult blood still positive. 13/4/45: Discontinued penicillin. 17/4/45: Hb 46%; macroscopic haematuria. Heart unchanged; spleen palpable; rales at both bases; profuse red cells in urine. 25/4/45: Frank haematuria; blood cultures remained negative; Hb 52%; B.S.R. 30 mm./hr. 22/6/45: Discharged to convalescent home. Has been seen as an out-patient from time to time; remained well until recently, when some oedema of the ankles developed, for which she has refused treatment. Hb 82%; B.S.R. 8 mm./hr.

Case 289.—Female aged 21. Admitted 14/4/45. Two months' history of oedema of ankles and lassitude. Rheumatic fever at age of 8. Night sweats; pain in left lower chest. Very pale; rapid pulse; mitral stenosis; spleen palpable; red cells in urine; Hb 63%; B.S.R. 30 mm./hr.; blood cultures positive. 16/4/45: Started penicillin. 18/4/45: Temperature normal. 9/5/45: Discontinued

penicillin. 11/6/45: Getting up. Hb 94%; scanty red cells in urine; remaining afebrile; blood cultures negative. 18/6/45: Evening temperature 99–100° for several days; blood culture positive on two occasions; tip of spleen palpable. 26/6/45: Further course of penicillin started. 17/7/45: Penicillin discontinued—total 23 million units. 30/7/45: Remained afebrile, with negative blood cultures. 14/8/45: Discharged to convalescent home; Hb 98%; B.S.R. 15 mm./hr. 8/10/45: Readmitted to hospital for treatment of congestive failure. 14/11/45: Good response to treatment. 2/12/45: Discharged. No evidence of heart failure.

Case 293.—Female aged 46. Admitted 14/7/45. Goitre removed at age of 20. Pain in back and legs; occasional sweats. Mitral systolic murmur; petechial spots on hands; café-au-lait colour. Hb 62%; B.S.R. 22 mm./hr.; red cells in urine; positive blood cultures. 19/4/45: Started penicillin. 23/4/45: Temperature normal; appetite improved. 9/5/45: Discontinued penicillin. Still red cells in urine; Osler's node on right hand. 6/7/45: Discharged to convalescent home. 2/11/45: Seen as out-patient; Hb 104%; B.S.R. 3 mm./hr. Doing her own housework with no ill effects.

Case 295.—Male aged 30. Admitted 20/4/45. Rheumatic fever at age of 9. Four weeks' history of pain in left ankle; 10 days acutely ill—fever, rigors, low delirium, confused, irrational, with slow slurred speech. Apical systolic murmur; Hb 90%; B.S.R. 25 mm./hr.; red cells in urine; positive blood culture. 21/4/45: Cerebral embolus resulting in right hemiplegia and aphasia. 22/4/45: Started penicillin. 27/4/45: Some improvement in facial palsy. 13/5/45: Discontinued penicillin. 25/5/45: Speech improved; some movement possible in limbs; blood cultures negative. 4/6/45: Evening temperature raised; two positive blood cultures. 6/6/45: Evening temperature of 101°; further positive blood culture; second course of penicillin. 11/6/45: Four doubtful teeth removed under general anaesthesia. 14/6/45: Still raised evening temperature. 4/7/45: Discontinued penicillin—total, 23 million units. Blood cultures negative; massage and exercises to paralysed limbs. 24/7/45: Getting up in a chair. 27/8/45: Discharged to convalescent home. Blood cultures negative; afebrile; Hb 93%; B.S.R. 16 mm./hr.; walking with a stick. 2/12/45: Seen as an out-patient; gained 2 st. (12.7 kg.) in weight; heart unchanged; no evidence of failure; Hb 108%; B.S.R. 3 mm./hr.

Case 300.—Female aged 40. Admitted 26/4/45. Rheumatic fever at age of 20. Three months' history of loss of appetite, loss of weight, palpitations, tender spots on fingers. Petechial spots and splinter haemorrhages; aortic and mitral lesions; spleen palpable; red cells in urine; Hb 73%; B.S.R. 35 mm./hr.; several positive blood cultures. 28/4/45: Started penicillin. 11/5/45: Slight evening pyrexia; blood culture negative; splinter haemorrhage; red cells in urine. 19/5/45: Discontinued penicillin. 28/5/45: Pain in right shoulder and right arm. 11/6/45: Raised tender red swelling in palm of left hand; blood culture negative; red cells in the urine. 11/7/45: Dental extraction, covered by three days' penicillin. 23/7/45: Discharged to convalescent home. Seen as out-patient on several occasions—last time 2/11/45. Doing housework, weekly washing, etc. Gain in weight. Heart unchanged: no failure. Hb 104%; B.S.R. 4 mm./hr.

Case 302.—Female aged 27. Admitted 26/4/45. Rheumatic history at age of 10 and 23. Pain in left upper chest, lassitude, sweating, loss of weight; café-au-lait colour; splinter haemorrhage; temperature 102°; aortic regurgitation; Hb 54%; B.S.R. 42 mm./hr.; red cells in urine; positive blood culture. Raised tender swelling in palm of right hand. 1/5/45: Started penicillin. 7/5/45: Two further splinter haemorrhages; afebrile; blood culture negative. 14/5/45: Occasional evening pyrexia; Osler's nodes on fingers; red cells in urine. 22/5/45: Discontinued penicillin. 4/6/45: Remained afebrile; blood cultures negative; red cells in urine. 11/6/45: Osler's nodes. 21/6/45: Splenic infarct. 22/6/45: Painful swelling on dorsum of foot; red cells in urine; blood culture negative. 23/7/45: Discharged to convalescent home. Has been seen from time to time. 30/10/45: Heart unchanged; no failure; Hb 90%; B.S.R. 3 mm./hr. Found to be pregnant since discharge; termination advised and carried out.

Case 340.—Female aged 29. Admitted 25/6/45. Rheumatic fever at age of 13. Pain in chest, loss of appetite, breathlessness, palpitations, rigors; drowsy; café-au-lait tinge; petechial spots over the right forearm and splinter haemorrhages beneath the nails. Aortic and mitral lesions; spleen palpable; red cells in urine; Hb 73%; B.S.R. 31 mm./hr.; blood culture positive. 27/6/45: Started penicillin. 28/6/45: Dramatic improvement. 5/7/45: Spleen not palpable; blood cultures negative. 25/7/45: Discontinued penicillin. 7/8/45: Blood culture negative; no embolism; few red cells in urine. 30/8/45: Discharged home; no red cells in urine; Hb 98%; B.S.R. 23 mm./hr. Seen as an out-patient 2/11/45; doing light housework; no evidence of heart failure; heart unchanged; Hb 104%: B.S.R. 3 mm./hr.

Case 341.—Female aged 42. Admitted 10/7/45. Pain in left loin, general aches and pains, rigors, profuse sweats, oedema of ankles. Five teeth removed 6 weeks before admission. Sallow complexion; splinter haemorrhages; petechial spots on both forearms; apical systolic murmur; spleen palpable; red cells in urine; Hb 70%; B.S.R. 33 mm./hr.; blood culture positive. Started penicillin. 12/7/45: General condition improved, no further rigors. 14/7/45: Further crop of petechial haemorrhages; spleen not palpable; profuse red cells in urine. 22/7/45: Severe pain over frontal and maxillary sinuses; relieved 3 days later when several large clots were discharged. 7/8/45: Penicillin discontinued; blood culture negative. 31/8/45: Dental extraction under penicillin cover, several of the teeth growing *Str. viridans*. 2/10/45: Discharged to convalescent home. Has been seen on several occasions since. Leading a comparatively normal life. Hb 97%; occasional red cells in urine; heart unchanged; no evidence of failure; B.S.R. 5 mm./hr.

Case 360.—Male aged 36. Admitted 27/8/45. Lassitude for 3 weeks; persistent pyrexia. No rheumatic history. 19 teeth removed 7 weeks previously. Swelling of ankles; night sweats. Systolic murmur inside apex; screening confirmed maladie de Roger; spleen palpable; Hb 78%; B.S.R. 17 mm./hr.; scanty red cells in urine; positive blood culture. 30/8/45: Started penicillin; rapid response. 26/9/45: Discontinued penicillin. 28/9/45: Heart unchanged; spleen not palpable; blood culture negative; Hb 84%; B.S.R. 7 mm./hr.; few red cells in the urine. 3/11/45: Discharged to convalescent home. 7/12/45: Seen as an out-patient. Gain in weight; no failure; heart unchanged.

Case 364.—Female aged 22. Admitted 10/10/45. No rheumatic history; one month of malaise and fleeting joint pains. Enlarged spleen; mitral stenosis; swelling of ankles; a few petechial spots; positive blood cultures; a few red cells in urine; temperature 101°; Hb 83%; B.S.R. 26 mm./hr. 13/10/45: Started penicillin; general condition much improved. 20/10/45: Osler's node palpable in index finger; splinter haemorrhages under nails of right hand. 10/11/45: Discontinued penicillin. No further evidence of embolism; spleen not palpable. 23/11/45: Blood culture negative; still red cells in the urine; no change in the heart; no failure. 27/11/45: Getting up. 14/12/45: Dental extraction under cover of penicillin. 20/12/45: Discharged. Hb 99%; B.S.R. 14 mm./hr.; no red cells in the urine.

Case 365.—Male aged 29. Admitted 10/10/45. Pain in left groin, swelling of ankles, rheumatic pains in joints. No definite rheumatic history. Febrile; a few petechial spots; mitral stenosis; Hb 76%; B.S.R. 33 mm./hr.; blood cultures positive; red cells in urine. 12/10/45: Started penicillin. 18/10/45: Has remained afebrile since start of penicillin; appetite improved; blood culture negative. 26/10/45: Faint diastolic murmur at aortic area; blood culture negative. 9/11/45: Discontinued penicillin. 22/11/45: Getting up with no ill effects; no failure; heart unchanged. Massage and exercises before discharge. 14/12/45: Dental extraction under penicillin cover. Blood culture negative; Hb 90%; B.S.R. 14 mm./hr. 20/12/45: Discharged.

Case 366.—Male aged 51. Admitted 5/10/45. Had been unwell since influenza in August; fever, lassitude, anorexia. No rheumatic history. Sallow complexion; splinter haemorrhages; aortic and mitral lesions; positive blood cultures; Hb 73%; B.S.R. 22 mm./hr.; red cells in urine. 8/10/45: Started penicillin. 15/10/45: Temperature normal; "has not felt as well for five years"; blood culture negative. 27/10/45: Dull ache in centre of sternum on inspiration, spreads to left breast—pulmonary infarct. Later very restless, sweating, dyspnoeic; marked engorgement in neck veins; apex beat further out to left; systolic apical murmur had assumed a harsher quality; oedema of lung bases; liver tender; rapid auricular fibrillation; immediate intravenous digitalization. 28/10/45: Pulse regular at 130/min., definite improvement in general condition; failure subsided. 29/10/45: Pulse normal, though rapid rhythm. 5/11/45: Penicillin discontinued. 13/11/45: Pulse regular, 90/min.; heart smaller; no evidence of failure. 27/11/45: Afebrile; blood cultures remained negative. Hb 75%; B.S.R. 20 mm./hr. 31/12/45: Massage and exercises before discharge.

Case 256.—Female aged 56. Admitted 1/3/45, after having had 2 million units of penicillin in two courses, which did not appear to influence the endocarditis. Six months' history of oedema, dyspnoea, lassitude. Aortic and mitral lesions; pain in left ankle; positive blood culture; red cells in urine; Hb 63%. 3/3/45: Started penicillin. 5/3/45: Fatal cerebral embolism. *Necropsy:* Vegetations in left auricle, mitral and aortic vaives; infarcts of kidney and spleen.

Case 342.—Male aged 34. Admitted 16/7/45. Pain in left chest; spots on legs; lassitude, increasing dyspnoea; night sweats; oedema of ankles. Clubbing; pale; spleen palpable; petechial rash on legs; Hb 48%; B.S.R. 30 mm./hr.; red cells in urine; positive blood culture; left pleural effusion. 26/7/45: Started penicillin. 1/8/45: Extreme cardiac asthma with further enlargement of the heart; marked aortic regurgitation; rales in both lungs; increasing pulmonary congestion. 13/8/45: Oedema of lungs less; heart still grossly enlarged; frequent extrasystoles; blood culture negative; red cells in urine; spleen not palpable; Hb 60%; B.S.R. 30 mm./hr. 23/8/45: Discontinued penicillin. 29/8/45: Increasing severity and duration of cardiac asthma. 2/9/45: Further increase in oedema

of lungs in spite of all diuretic measures. 6/9/45: Patient became orthopnoeic and died suddenly. *Necropsy*: Large ulceration through the aortic cusps.

Case 361.—Female aged 21. Admitted 11/8/45. No rheumatic history. Oedema of ankles; lassitude; upper abdominal pain; fever; increasing dyspnoea; petechiae on abdominal walls. Yellowish skin; aortic and mitral lesions; spleen not palpable; red cells in urine; positive blood culture; Hb 66%; B.S.R. 20 mm./hr. 16/8/45: Started penicillin. 20/8/45: Penicillin does not appear to have affected the temperature at all. Central abdominal pain; tenderness over McBurney's point. Course of sulphacetamide for urinary infection, which cleared up. 8/9/45: Boost doses of penicillin 100,000 units did not influence the high temperature. 12/9/45: Discontinued penicillin. 17/9/45: Remaining febrile; red cells in urine. 27/9/45: Finished course of sulphamezathine for bronchopneumonia. Still some consolidation in the left base; blood cultures positive. 1/10/45: Aspirin 10 gr. (0.65 g.) four-hourly—no effect on temperature. 6/10/45: Pain in left chest and area of consolidation. Died next day. *Necropsy:* Large friable vegetations on mitral and aortic cusps; recent infarct left lower lobe.

Case 363.—Male aged 29. Admitted 3/10/45. Two months' history of loss of appetite, increasing dyspnoea, occasional palpitations, tenderness of fingers. Admitted to military hospital 5 weeks ago after three-pint (1.7-litres) haematemesis. Very pale; splinter haemorrhages; Osler's nodes; spleen palpable; red cells in urine; positive blood cultures; mitral stenosis; Hb 65%; B.S.R. 21 mm./hr.; occult blood positive. 4/10/45: Started penicillin. 7/10/45: Temperature normal; general condition much improved. 8/10/45: Febrile; blood culture negative. 9/10/45: Rigor. 15/10/45: Spleen further enlarged; another crop of tender spots on pulps of fingers. 18/10/45: Haematemesis 30 oz. (0.85 litre) bright red blood; replaced by 2 pints (1.14 litres) packed red cells by drip transfusion. 20/10/45: No signs of failure; abdomen less distended; spleen still palpable, not tender. 24/10/45: Haematemesis of 30 oz. bright red blood. Pulse 110/min.; not sweating or shocked. This was followed by further haematemeses of 20 oz. (568 ml.) bright red blood, later 15 oz. (426 ml.) and 10 oz. (284 ml.). Became shocked, pale, sweating; pulse 160/min., hardly perceptible. Immediate intravenous drip, packed red cells; improved until pulse came down to 90/min. Two hours later further haematemeses of 32 oz. (0.9 litre). In the next 24 hours vomited another 30 oz. of darker blood. Drip discontinued after 10 pints (5.7 litres). 26/10/45: Marked improvement; no evidence of failure; Hb 75%. 28/10/45: Again became shocked; pain and massive distension in upper abdomen; further drip. 29/10/45: Patient died, not having recovered from final haemorrhage. *Necropsy:* Early coarse cirrhosis of the liver; large patent varicose veins in the oesophagus; 2½ pints (1.4 litres) of free blood in the stomach, with a clot representing about 3 pints (1.7 litres) more. Small vegetations on mitral valve, not much larger than rheumatic vegetations.

Bacteriology

Blood Cultures.—As has already been mentioned, streptococci of the *viridans* type were isolated from all cases before treatment was started. Qualitative and quantitative methods were used—that is to say, at least 5 ml. of citrated blood was inoculated into 50 ml. of meat extract peptone broth, and a further 2 ml. was used to make two poured-plate cultures. The latter method proved more useful in that, besides providing an estimate of the numbers of bacteria in the blood stream, it gave positive results on several occasions when the fluid culture showed no growth. In each of the cases described here a positive result was obtained with the first blood culture taken after admission, though on one occasion (Case 273) only the fluid culture gave growth. In two subsequent cultures from this case only one colony per ml. was found, so that the failure of the first plate cultures was presumably due to the small number of organisms in the blood. This case illustrates the small variation in the degree of bacteriaemia which we found to be the rule in the six cases in which repeated blood cultures were taken before treatment. There were, however, considerable variations in the number of colonies per ml. from patient to patient. Of 30 plate cultures taken before treatment two were negative, eight had 1 to 6 colonies, five 10 to 20 colonies, nine 28 to 60 colonies, five 100 to 250 colonies, and one (Case 256) had 2,000 colonies per ml. A high bacteriaemia seemed to have some prognostic significance in that the patients who subsequently died had colony counts of 50, 60, 100, and 2,000 per ml.

Starting from the second to the sixth day, three to six blood cultures were taken during the course of treatment, and all were negative except in three cases, two of which were the only cases that subsequently relapsed. It would thus appear that a positive blood culture during the course of penicillin treatment may be an indication that relapse is likely to occur. In Case 249 a positive blood culture was obtained on the day after stopping penicillin treatment, but this was regarded as due to a transient invasion probably from infected teeth, because there were no clinical symptoms of active infection, and since then blood cultures have been consistently negative.

Characters of the Isolated Streptococci.—The streptococcal strains isolated from these cases before treatment all displayed alpha-haemolysis typical of the *Str. viridans* group, with the exception of one strain (Case 342) in which haemolysis was slight and more of the beta type. Of these strains 14, excluding that from Case 342, have been maintained for further study, and preliminary work shows that they can be divided into two main fermentation groups. The first group, comprising six strains, ferment lactose, and in their range of fermentation reactions correspond well with *Str. salivarius*, described by Andrewes and Horder (1906) as the most common type of *Str. viridans* in the mouth and nasopharynx, and of frequent occurrence in subacute bacterial endocarditis. The second group, comprising eight strains, do not ferment lactose and are less readily identified with known strains. Okell and Elliott (1935), however, have found streptococci of the *viridans* type that do not ferment lactose in 11 of 36 strains isolated from cases of subacute bacterial endocarditis and in 11 of 26 isolations in blood cultures from cases of dental sepsis. It would therefore appear likely that our strains of the second group can also be mainly associated with *viridans* strains commonly found in the region of the mouth.

Penicillin Sensitivity.—The streptococci from these cases were tested for penicillin sensitivity by the method described by Selbie, Simon, and McIntosh (1945). In general, and like other strains of *Str. viridans* that we have tested, they were rather more resistant to penicillin than most strains of *Str. pyogenes*. Twelve strains were in the range of being not less than half and not more than twice as sensitive as the Oxford staphylococcus, while four strains were 4 times less sensitive and the strains from Cases 363 and 273 were 4 and 8 times more sensitive than the Oxford staphylococcus. There was no apparent correlation between penicillin sensitivity and the fermentation reactions of the organisms or the results of treatment. In the two cases which relapsed there was no difference in sensitivity between the organisms isolated before and after treatment.

Penicillin Blood Levels.—The dosage of penicillin during treatment was controlled by the estimation of penicillin in the blood serum by the method previously described (Selbie, Simon, and McIntosh, 1945). In general, after the intramuscular injection of 60,000 units of penicillin the blood serum inhibited the growth of the Oxford staphylococcus in a dilution of 1/32 to 1/128 at one-quarter to half an hour, and 1/1 to 1/8 at 3 hours. In Case 363, however, penicillin levels were rather low, and in Case 273 the bacteriostatic dilutions remained high, and were 1/32 and 1/64 even at the end of the three-hour period.

Discussion

All cases in this series were clinically shown to have the usual criteria of bacterial endocarditis: fever, heart lesion, and embolic phenomena in at least two different systems. In view of the fact that a transient bacteriaemia can occur in patients with heart lesions who have no bacterial endocarditis, the above signs were demonstrated in addition to positive blood cultures (*Str. viridans*) before a case was treated. In spite of a severe and protracted debilitating illness coupled with the discomfort of up to a month's three-hourly intramuscular injections, all the patients remained extremely cheerful and of bright mentality: the "spes endocarditica" of Horder (1920).

The commonest superficial evidence of embolism was found in the form of splinter haemorrhages beneath the nails, occurring in 15 cases, in contrast to Osler's nodes, which were found in 9 patients. These embolic phenomena occurred most frequently in the first week of treatment, but also in several cases up to one month after treatment. In three cases lesions were noted in the palms of the hands; presumably embolic in nature, they presented suddenly as a tender raised nodule the size of a pea, and made all movements of the fingers painful. In two days the pain was less noticeable, but the fingers of

the affected hand showed some degree of flexion deformity, with complete inability to extend them actively. This was soon overcome with massage and passive movements, as probably due to involvement of palmar fascia.

Palpable splenic enlargement was present at some stage of the illness in 13 cases. In 7 patients the spleen rapidly diminished in size, not being palpable after 10 days' treatment. The degree of enlargement and the time it remained palpable were approximately proportional to the duration of the disease. Although 3 of our patients have shown transient visual disturbances such as blurring of vision, none have had white spots in the retina—so-called Roth spots. There was no optic neuritis or papilloedema. Clubbing of the fingers was present in 15 patients, in three of whom it appeared to be less marked after their discharge from hospital than on admission.

On admission all patients had an anaemia of microcytic hypochromic type which varied between 36% and 82% haemoglobin, mostly between 55% and 70%. In only 6 patients was the leucocyte count above 10,000 cells per c.mm., and one case showed the frequently described increase in large mononuclears, here 1,500 in a total white count of 8,800. An increase in the haemoglobin percentage occurred along with other signs of improvement—e.g., increase in weight, diminished evidence of embolism, fall in sedimentation rate. The B.S.R., estimated by Wintrobe's method corrected for packed-cell volume, was invariably raised at the outset, and showed a slow but steady fall, remaining abnormally high during the stay in hospital, and returning to within normal limits only some three months after treatment.

Microscopical haematuria was found in all cases, macroscopic in two, one of which showed clinical signs of a renal infarct of some magnitude. Ten patients continued to have a small number of red blood cells in the urine—one case five months after the end of treatment. This persistence of blood cells does not appear to be associated with any impairment of renal function at the present state of follow-up. In Bell's (1932) series over 50% of kidneys in endocarditis showed embolic focal nephritis; a smaller percentage had a diffuse acute or chronic glomerulonephritis. Since there may be a considerable time-lag between the onset of these lesions and the time when signs of renal impairment manifest themselves it is probable that, in the future, cases cured of endocarditis will show impairment of renal function.

A typical café-au-lait colour was noted in only 5 patients, probably because the majority started treatment within the first few months of onset. Three patients suffered cerebral damage from embolism—two of these within the first three days of treatment, one before treatment was started. It is worthy of note that the two relapses occurred early—i.e., within six weeks of terminating treatment.

Dental extraction can almost certainly be cited as the determining factor in initiating the infection in 3 patients who first noticed symptoms immediately after this procedure. A further 9 patients showed signs of dental infection. That oral sepsis may be a determining factor in initiating subacute bacterial endocarditis has been amply demonstrated by Okell and Elliott (1935), who found a transient bacteriaemia after teeth extraction in 30 out of 40 cases with marked gum disease, and also obtained positive blood cultures in 12 of 100 cases of oral sepsis without the added trauma of extraction. There can therefore be no doubt that the most stringent oral hygiene is essential in persons with congenital or rheumatic heart affections. In our cases a rigorous search was made for septic foci, and these were eradicated in order to prevent reinfection.

In this series the disease has been completely arrested for periods of two to ten months, as judged by a gain in weight, normal temperature, disappearance of anaemia, absence of leucocytosis, diminution in the number of red cells in the urine, and fall in the sedimentation rate. Three of the four deaths resulted from causes not amenable to chemotherapy—i.e., ruptured aortic valve, cerebral embolism, and cirrhosis of liver.

Until penicillin was used in the treatment of subacute bacterial endocarditis this dread disease carried a mortality of close upon 100%. We now feel definitely more hopeful, or even confident that means of curing this condition are within measurable reach.

Summary

Eighteen cases of proved subacute bacterial endocarditis treated with penicillin are described. There is reasonable hope of permanent cure in 11 instances. There were four deaths, but only one can be called a failure to respond to penicillin. In three cases it is as yet too early to claim permanent recovery.

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SYMPATHECTOMY IN PERIPHERAL ARTERIOSCLEROSIS

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The ischaemia to which the ill effects of arteriosclerosis are due is caused partly by the thickening and narrowing of the vessels and partly by thrombi deposited on the altered intima. The damage may be made worse, sometimes acutely so, by the impaction of emboli from above, and there is also evidence that spasm of the diseased vessels may play some part in aggravating the trouble.

If the mischief were evenly and progressively spread throughout the arterial tree the sequence of mishaps would be coldness, claudication, rubor, rest-pain, persistent deepening cyanosis, and eventually onychia, ulceration, or gangrene. Such a sequence is, in fact, seen in a number of cases, but the complexity of branches, the proneness to disease of certain areas, and the wide differences in the ease with which collateral circulation can be established lead to much divergence in both the order and the severity of symptoms. For instance, an obstruction in the more proximal stretches of the supply may cause only a moderate claudication going on for years without further trouble, whereas an obstruction in the popliteal area not only may cause severe claudication but may gravely imperil the life of the leg. Again, it is not uncommon to find severe digital thrombosis with a palpable posterior tibial pulse and no claudication. These latter cases may be due to the silting up of the vessels by repeated minute emboli and are apt to go to the bad rapidly with few or no premonitory signs. Such wide variations not only make prognosis difficult but render it far from easy to estimate the value of any given line of treatment.

In view of the poor results of medical treatment, with its expectant attitude, we have attempted over a number of years and on many different types of cases to find out what results might be obtained by the practice of sympathectomy on these patients. Division of vasoconstrictor fibres might be expected to lead to an improved supply partly by dilatation of the vessels and partly by improving collateral channels, provided always that the vessels were not too far damaged to permit of a response. Further, if it be true that spasm is a factor, any spastic contribution would be lessened or entirely eliminated.

For the purpose of this paper the word "sympathectomy" means either a cord-ganglionectomy of the lumbar chain, one and a half to two inches (4–5 cm.) in length, centred opposite the third lumbar vertebra, or, for the upper limb, a section of the thoracic chain below the third rib with wide dislodgment of the cut ends.

Scope of the Inquiry

The period over which the work extends is 15 years and the number of patients operated upon is 98. There were only seven women in the series. The consequences of arteriosclerosis are no doubt much less common in women than in men, but the