PENICILLIN IN SUBACUTE BACTERIAL ENDOCARDITIS

REPORT TO THE MEDICAL RESEARCH COUNCIL ON 147 PATIENTS TREATED IN 14 CENTRES APPOINTED BY THE PENICILLIN CLINICAL TRIALS COMMITTEE

BY

Prof. RONALD V. CHRISTIE, M.D., D.Sc., F.R.C.P.

Secretary of the Committee

Only 18 months ago few patients suffering from bacterial endocarditis had been treated with penicillin in this country, and the results both here and in the U.S.A. were far from encouraging. Early in 1945 reports were received from America which suggested that better results might be obtained with larger doses given for longer periods. An attempt to determine the best system of dosage was clearly indicated, both to save life and to prevent wastage of a valuable drug still in short supply. Since subacute bacterial endocarditis is an uncommon disease, it was decided that this could be best achieved by a co-ordinated effort, and in February, 1945, an announcement was made in this *Journal* of the formation of research centres in Belfast, Bristol, Edinburgh, Leeds, Liverpool, London (St. Mary's, Middlesex, and St. Bartholomew's Hospitals), Manchester, and Sheffield. In April four further centres were formed, in Birmingham, Cardiff, Glasgow, and Newcastle. The response to this announcement can be gauged from the fact that by the end of September, 1945, the treatment of 147 patients had been completed. Since that date many more have been treated, but these will be included in a later report, as an adequate follow-up is essential in assessing the results of any treatment of this disease.

Therapeutic Results

Penicillin was given either by three-hourly injection or by continuous intramuscular infusion. No difference in the therapeutic results could be demonstrated, and opinion on the merits of these two methods is divided. Most are agreed, however, that both methods should be available if the treatment of subacute bacterial endocarditis is to be undertaken.

In the first group to be treated the dose was planned to show the relative importance of duration of treatment and the total amount of penicillin given. An answer to this question is given in Table I, which summarizes the results in 46 patients, all of

TABLE I.—Patients receiving a Total of 5 million Units of Penicillin, given in Courses lasting 5, 10, and 20 Days

Dose	Died	Relapsed	"Cured"	Average Follow-up
1 mega unit for 5 days ..	6 (13%)	14 (70%)	0	—
0.5 mega unit for 10 days	2 (17%)	7 (58%)	3 (25%)	217 days
0.25 mega unit for 20 days	4 (33%)	3 (23%)	7 (50%)	249 ..

Figures in brackets in Tables I-IV represent number of patients in whom dosage was only approximately as stated.

whom received 5 mega (million) units of penicillin but over different periods of time: 20 patients were given 1 mega unit a day for five days, and all relapsed or died; 12 received 0.5 mega unit a day for 10 days, and of these 3 were apparently cured; 14 were given 0.25 mega unit a day for 20 days, and of these 7 have remained well. These patients have been under observation for over 6 months, and since relapses, if they occur, almost invariably take place within 6 weeks of treatment (Table V) the conclusion appears to be justified that, within these limits of dosage, the duration of treatment is of much greater importance than the total amount of penicillin given: increased dosage is no substitute for prolonged treatment.

The results of treatment in a further series of 66 patients are shown in Table II; all received penicillin for 28 days, but the

TABLE II.—Patients Treated for 28 Days with a Daily Dose of 0.1, 0.25, and 0.5 Mega Unit

Dose	Died	Relapsed	"Cured"	Average Follow-up
0.1 mega unit a day ..	3 (32%)	5 (50%)	6 (43%)	198 days
0.25 mega unit a day ..	13 (50%)	4 (15%)	17 (65%)	117 ..
0.5 mega unit a day ..	7 (39%)	0	11 (61%)	114 ..

dose was varied, one group receiving 0.1 mega unit a day, another 0.25 mega unit a day, and another 0.5 mega unit a day. In the first group 43% recovered, in the second group 50%, and in the third group 61% have remained cured after an average follow-up of 4 months. It should not be forgotten that, no matter how effective penicillin may prove to be in the treatment of this disease, a significant death rate will remain from causes such as heart failure, uraemia, and major emboli. These deaths, many of which occurred during treatment, have little or no bearing on the efficacy of penicillin, and when this is borne in mind the therapeutic results shown in Table II are all the more remarkable—11 out of 18 patients receiving 0.5 mega unit a day for 28 days have remained cured. In only 1 of the 7 patients who died was there any evidence that the penicillin had failed to control the septicaemia, and the infecting organism in this case was more than 32 times as resistant to penicillin as the standard Oxford staphylococcus. For previously untreated patients 0.5 mega unit a day for 28 days seems to be a most satisfactory system of dosage.

Another small group of 12 patients received 0.5 mega unit a day for 21 days; of these, 1 died, 2 relapsed, and 9 have remained well after an average follow-up of 244 days.

Lastly, there were 11 patients who received a system of dosage which did not fall into any of the categories described above: 5 of these died, 1 relapsed, and 5 have remained well for an average period of 172 days.

Effect of Inadequate Treatment

It is of considerable practical importance to know whether inadequate treatment, as well as wasting time and penicillin, is prejudicial to later success. The results of treatment in patients who had already received a short course of penicillin are given in Table III. A comparison of this table with Tables I and II

TABLE III.—Patients Previously Treated with a Short Course of Penicillin, of 5-10 Days' Duration

Dose	Died	Relapsed	"Cured"	Average Follow-up
1 mega unit for 5 days ..	0	1	0	—
0.5 mega unit for 10 days	0	0	2	220 days
0.1 mega unit for 28 days	0	2	1	232 ..
0.25 mega unit for 20 days	4 (33%)	1 (8%)	3 (23%)	260 ..
0.25 mega unit for 28 days	0	3 (23%)	6 (46%)	162 ..
0.5 mega unit for 28 days	0	0	3	175 ..
Total	4 (15%)	7 (27%)	15 (58%)	

does not suggest that previous treatment with a short course is prejudicial to later success in the patients who survive.

The results of treatment in patients who had already received a long course of penicillin are given in Table IV. A comparison

TABLE IV.—Patients Previously Treated with a Course of Penicillin of 20–28 Days' Duration

Dose	Died	Relapsed	"Cured"	Average Follow-up
1 mega unit for 5 days	0	1	0	—
0.5 mega unit for 10 days	0	1	0	—
0.1 mega unit for 28 days	0	0	1 (1)	214 days
0.25 mega unit for 20 days	1 (1)	1 (1)	1 (1)	200 "
0.25 mega unit for 28 days	2	3	2	107 "
0.5 mega unit for 20 days	0	1 (1)	0	—
0.5 mega unit for 28 days	2	6	4	134 "
Total	5 (19%)	13 (50%)	8 (31%)	

of this table with Tables I and II shows that if a patient does not respond to a long course of treatment he is less likely to respond to a second course. There are two possible explanations. Lack of response to the first course may indicate natural resistance to penicillin therapy, so that this forms a selected group of resistant cases. Alternatively, the explanation may be that an ineffectual course of treatment may increase the resistance to penicillin.

Repeated estimations of the resistance of the infecting organisms to penicillin were made in this series, but no convincing evidence of changes in sensitivity was found. Sixteen patients received more than one long course (20 days or more) of treatment, and in only two of these was there any evidence of a change in sensitivity; in both there was a threefold increase in resistance to penicillin as measured by the ordinary dilution methods. Clinical evidence bearing on the question of acquired resistance to penicillin is also meagre, and is confined to two small groups. The first group was of 7 patients in whom septicaemia was uncontrolled during treatment; in 2 it was uncontrolled from the start, but in the other 5 the infection had been previously controlled by a similar or smaller daily dose of penicillin, suggesting that resistance to penicillin had increased; in all of these 5 patients the first course, which seemed at the time to be effective, involved a daily dose of only 0.1 to 0.25 mega unit. In the second group there were 5 patients who relapsed after a second long course of penicillin; in all, the dosage of penicillin was greater in the second than in the first course, and yet the interval before relapse was decreased rather than increased.

This evidence is, to say the least, not incompatible with acquired resistance to penicillin. Delay in controlling the infection also exposes the patient to the many dangerous complications of this disease, and it is therefore safer, from the patient's point of view, to assume that inadequate treatment is prejudicial to later success.

Relapses

Short courses of treatment, of 10 days or less, are usually followed by relapse within a few days. Even after long courses most relapses occur within 30 days of cessation of treatment, and relapse after 50 days is extremely rare (Table V). The con-

TABLE V.—Relapses after Treatment

Interval between Treatment and Relapse	Relapse After Treatment Lasting 20 Days or More	Relapse After Treatment Lasting 10 Days or Less
0–10 days	14	17
11–20 "	7	3
21–30 "	6	2
31–40 "	0	1
41–50 "	2	0
51–60 "	0	1
Over 60 "	1 (130 days)	

clusions drawn from Tables I–IV, in which the period of follow-up varied from 107 to 260 days, are therefore not unreasonable. There is still, of course, the chance of reinfection, but this was proved in only one patient of this series; this patient relapsed, and *Streptococcus faecalis* was recovered from the blood 161 days after apparent cure from an infection with *Str. viridans*.

The treatment of relapses presents a special and often difficult problem. Of 16 patients who relapsed after a course of penicillin which lasted longer than 20 days, all but 4 relapsed or died after a second course which was either more prolonged

or of higher dosage than the first. Four patients have received more than two long courses of penicillin, but only one of these has finally responded: she relapsed after 0.5 mega unit for 10 days, again after 0.1 mega unit for 28 days, and again after 0.5 mega unit for 28 days, but has now remained well for 60 days after a fourth course of 0.5 mega unit a day for 42 days. It is this system of dosage—0.5 mega unit a day for 6 or 8 weeks—that we propose usually to adopt in patients who have relapsed.

The Infecting Organism

Of the 147 patients included in this series 146 were infected with streptococci and one with a strain of *Haemophilus influenzae* which was almost completely resistant to penicillin. Of the streptococci 136 are described as *Str. viridans*, 8 as a non-haemolytic streptococcus, 1 as an anaerobic streptococcus, and 1 as a micro-aerophilic streptococcus. The sensitivity to penicillin was measured by the ordinary dilution methods and compared with the standard Oxford staphylococcus. To facilitate tabulation this has been expressed as a coefficient of resistance, and it is clear from Table VI that there is a surprising

TABLE VI.—A Comparison of the Results of Treatment with the Sensitivity of the Organism to Penicillin. (Resistance is expressed as a multiple of the resistance of the standard Oxford staphylococcus.) None of these patients had previously been given a long course of treatment

Dose		Coefficient of Resistance to Penicillin				
		1 or Less	2	3–5	8–10	32–64
0.1 mega unit a day for 28 days	Died	1	2			
	Relapsed	6	1			
	Cured	6			1	
0.25 mega unit a day for 20 days	Died	1		2		
	Relapsed	4				
	Cured	7	1	1		
0.25 mega unit a day for 28 days	Died	6	2	2		
	Relapsed	3	1	1		
	Cured	14	3	2	1	
0.5 mega unit a day for 20 days	Died		1	1		
	Relapsed	4	2	1		1
	Cured	3	1			2
0.5 mega unit a day for 28 days	Died					
	Relapsed	8	3	2	1	
	Cured					
Total	Died	11	5	4	1	2
	Relapsed	13	3	2	3	
	Cured	39	9	6		1

lack of correlation between this coefficient and the results of treatment. There were 16 patients infected with comparatively insensitive streptococci having a coefficient of resistance between 3 and 10; 5 of these have died, 9 have been apparently cured, and only 2 have relapsed. These results compare favourably with those in patients infected with more sensitive organisms. There were three patients infected with streptococci more than 32 times as resistant as the Oxford staphylococcus, and this degree of insensitivity may be of therapeutic significance. One of these three was cured after receiving 0.5 mega unit a day for 21 days, but in the other two septicaemia remained uncontrolled while they were receiving 0.5 mega unit a day, and both ultimately died. A fourth patient was infected with an extremely resistant strain of *H. influenzae*, and he relapsed 6 days after receiving 0.5 mega unit a day for 23 days.

These results suggest that the resistance of the organism to penicillin as measured by ordinary titration methods is of no clinical significance within a wide range. Only when the organism was more than 10 times as resistant as the Oxford staphylococcus did this measurement appear to be of therapeutic and prognostic importance. This unexpected result may only reflect some inherent inaccuracy in the methods employed in measuring sensitivity, but this does not affect its clinical importance, since these methods are in general use.

Comments

Of the 147 patients treated in this series, 50 have died and 81 have been apparently cured, but it should not be forgotten that the systems of dosage at first used were inadequate. Of the remaining 16 patients, some are still under treatment and in a few treatment has been discontinued for one reason or another.

This report is concerned only with evidence which has a bearing on the treatment of subacute bacterial endocarditis. It

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

GEORGE E. S. WARD, M.D., F.R.C.P.

Senior Physician, Middlesex Hospital

R. I. MEANOCK, M.B., B.S.

Registrar, Middlesex Hospital

F. R. SELBIE, M.D., Ph.D.

Assistant Pathologist, Bland-Sutton Institute of Pathology

AND

R. D. SIMON, B.Sc.

Research Assistant, Bland-Sutton Institute of Pathology

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 bacteraemia 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 con-

gestive 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 *S. 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