BACTERIOSTATIC AGENTS IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

BY

H. W. BALME, M.D., M.R.C.P.

First Assistant

AND

A. E. DORMER, M.B., B.S.

Research Assistant

The Medical Unit, St. Bartholomew's Hospital

Antibiotics that are purely bacteriostatic have proved to be disappointing in the treatment of subacute bacterial endocarditis, for it appears to be necessary to sterilize the valve lesions, and for this a bactericidal drug or a bactericidal mixture of drugs is usually required (Garrod, 1953). In both the following cases of subacute bacterial endocarditis treatment with oxytetracycline ("terramycin") or with other bacteriostatic antibiotics seemed at first to be indicated, but even with full dosage the infection was not controlled in either case, although the organisms were sensitive. Effective treatment was thus delayed. When, later, antibiotics with bactericidal action were employed both cases responded promptly.

Case 1

A girl aged 14 was admitted to hospital on October 28, 1952, under the care of Dr. G. W. Hayward. Three years previously she had been treated in Hamburg Military Hospital for subacute bacterial endocarditis due to *Str. viridans* and had received a four-weeks course of penicillin, 50,000 units three-hourly. Thereafter she remained well until a month before her admission here, when she developed febrile symptoms, a few painful spots on the fingers, and later transient stiffness of the neck. At the onset she was given a short course of sulphonamides and then of penicillin, but with the persistence of symptoms she was referred for investigation.

On admission she was febrile, petechiae were present on the right thumb, the spleen was palpable, and she had mitral stenosis. There was no clubbing of the fingers. Investigation showed a moderate normochromic anaemia, normal white count, normal urine without increase in red cells, normal electrocardiogram, and a blood culture positive for *Str. viridans*. This organism was inhibited by 0.04 unit of penicillin and by 0.3 μ g. of oxytetracycline per ml.

On November 1 treatment with penicillin was begun with a dose of 1,200,000 units intramuscularly at 12 noon, the preparation used being "abbocillin," 1.5 ml. of which contains procaine benzyl penicillin, 900,000 units, together with buffered crystalline penicillin potassium, 300,000 units. At 12.15 p.m. a severe reaction started. She vomited, became very flushed, and then developed a rigor. The blood pressure fell and the pulse was for a while imperceptible at the wrist. The temperature rose to 103° F. (39.4° C.), but fell rapidly and by that evening she was feeling fairly well again. A test dose of penicillin was then given, 50,000 units subcutaneously. Fifteen minutes later a weal 2 cm. in diameter developed, with an area of erythema 8 cm. in diameter, at the site of injection; a control of saline given at the same time produced a weal 2 mm. in diameter with no surrounding erythema.

Following this the patient remained afebrile, with repeated negative blood cultures, until November 18, and during this period no further treatment was given. But on that day fever recurred and blood culture again revealed *Str. viridans*,

apparently the same organism that had been isolated previously. Another tender spot appeared on the right hypochondrium.

In view of the severity of her reaction to penicillin it was now decided that she should be treated with oxytetracycline instead, the organism being sensitive to it, and this was started on November 22 in a dosage of 750 mg. six-hourly. This gave a blood level of 24 μ g. of oxytetracycline per ml. when measured four and a half hours after a dose. Within 48 hours the fever settled again, and blood cultures taken on the fourth day of treatment remained sterile. Treatment was continued for six weeks, but on January 1, 1953, two days before the end of the course, fever again recurred and blood culture once more revealed *Str. viridans*. The organism appeared to be the same as that isolated previously, and still showed no resistance to oxytetracycline. During the next two days further petechiae appeared, the spleen became palpable again, and the patient was evidently ill.

It was now obvious that penicillin, to which the patient had earlier shown sensitivity, had to be used, and it was hoped to overcome possible reactions by simultaneous injection of penicillin and an antihistamine (Maslansky and Sanger, 1952). Treatment was therefore started again on January 5, when she received by injection a mixture of crystalline penicillin, 100,000 units, with 50 mg. of mepyramine maleate; this was followed by a slight urticarial reaction. The next day the same mixture was injected six-hourly, a minimal urticarial reaction following the first of these injections; but thereafter no further reactions were experienced. The next day the same mixture was given three-hourly. The following day 250,000 units was given three-hourly and the antihistamine was changed to oral promethazine hydrochloride, 25 mg. six-hourly. On the fifth day the penicillin was increased to 650,000 units three-hourly, at which level treatment was then carried on for six weeks, but the antihistamine was stopped altogether on the sixth day. The infection was promptly controlled once more, and the patient declared she felt better than when being treated with oxytetracycline.

At the end of the course there was no evidence of activity of the disease, and she was discharged on March 6 apparently well. On readmission for dental treatment on June 4, 1953, no evidence of recurrence could be found.

Case 2

A woman aged 25 was admitted as a case of enterococcal endocarditis that had proved resistant to treatment with single and combined antibiotics. Following a septic abortion she had been found to have mitral stenosis, intermittent fever, multiple petechiae and a few larger peripheral emboli, scanty haematuria, and clubbing of the fingers. The spleen was not enlarged. Blood cultures had repeatedly yielded *Str. faecalis* sensitive to chloramphenicol, aureomycin, and oxytetracycline but resistant to penicillin and streptomycin. Treatment, starting on July 19, 1952, had consisted of penicillin, up to 12 mega units daily for six weeks, followed by aureomycin, 2 g. daily for 18 days, then oxytetracycline, 6 g. daily for 23 days, then oxytetracycline and aureomycin together for 7 days, and, finally, oxytetracycline, 6 g., and chloramphenicol, 3 g. daily, for 20 days, all without effect on the fever, on the occurrence of peripheral emboli, or on the general condition of the patient.

On admission here under the care of Professor R. V. Christie on November 20, 1952, the diagnosis of subacute bacterial endocarditis was confirmed. Blood cultures yielded *Str. faecalis* again, inhibited by penicillin, 2.5 μ g. per ml.; streptomycin, 10 μ g. per ml.; aureomycin, 0.3 μ g. per ml.; oxytetracycline, 0.6 μ g. per ml.; and chloramphenicol, 10 μ g. per ml.; but none of these drugs sterilized the inoculum when used singly. The effects on the culture of mixtures of these drugs were then observed, using the following concentrations: penicillin, 1 μ g. per ml.; streptomycin, 10 μ g. per ml.; aureomycin, 5 μ g. per ml.; and oxytetracycline, 5 μ g. per ml. Aureomycin and oxytetracycline alone,

and mixtures of penicillin or of streptomycin with either aureomycin or oxytetracycline, left the bacterial population approximately static. Penicillin and streptomycin when used alone permitted growth to occur, but when they were used together they then formed the only combination discovered that would actually sterilize the inoculum in 24 hours.

Accordingly on November 28 treatment was started with penicillin, 2,500,000 units three-hourly, and streptomycin, 0.5 g. six-hourly, and this was continued for six weeks. Blood samples taken at various times during the day indicated that the penicillin level varied from over 80 to about 20 units per ml., and the streptomycin level remained at about 27 µg. per ml. From December 17 until January 8 probenidol was also given, 0.5 g. six-hourly, but it had little or no effect on the penicillin blood level.

Treatment was stopped on January 8, and thereafter repeated blood cultures have remained sterile. The patient was well when last seen on June 9.

Discussion

In both these cases bacteriostatic antibiotics were first employed in treatment, but, in spite of adequate dosage and although the organisms were fully sensitive, the disease was not controlled by them. This initial failure represented a serious hazard to the patients, for during all the time that infection remains there is an increasing danger of major emboli, renal failure, and irreversible damage to the heart: it has been established that the prognosis depends greatly on the speed with which effective treatment is started (Cates and Christie, 1951). It is not denied that bacteriostatic antibiotics are sometimes effective in this disorder, but the disadvantage of using them when bactericidal drugs are available as an alternative lies in the danger that, should they not work, the time lost whilst using them may well make all the difference to the patient's chances of ultimate recovery.

This being so, it may be as well to examine the reasons why bacteriostatic agents were used at all in the two cases described. In Case 1 the reaction of the patient to her first dose of penicillin was alarming, and the necessity of avoiding a repetition of it was taken as a good indication for a change over to oxytetracycline; but this decision was proved by events to be unwise. It had not been appreciated at this time that desensitization could be so simple a process. Fortunately in her case the delay during the time she was given oxytetracycline instead apparently caused no harm. It may be worth noting, however, that even severe reactions to penicillin do not necessarily preclude the use of the drug, as the technique of desensitization to it can be simple and effective.

In Case 2 treatment with chloramphenicol, aureomycin, or oxytetracycline seemed to be indicated on bacteriological grounds by virtue of the results of the usual sensitivity tests, but, as pointed out by Garrod (1953), the situation is in reality more complex than this. Thus the organism was with difficulty inhibited but not killed by penicillin and streptomycin acting singly; it was more readily inhibited but not killed by chloramphenicol, aureomycin, and oxytetracycline; but it was actually killed by the combined effect of penicillin and streptomycin when acting together. It was not until this situation had been revealed that effective treatment with the bactericidal mixture of penicillin and streptomycin could rationally be instituted.

In these two cases a great contrast was shown between the effectiveness of bactericidal as compared with bacteriostatic drugs. Since it has been shown (Cates and Christie, 1951) that 92% of relapses occur within one month of cessation of treatment it seems likely that both have now been cured, by penicillin in the one case and by penicillin combined with streptomycin in the other, whereas even prolonged treatment with the bacteriostatic antibiotics had previously been ineffective. They thus support the view held by Garrod that effective treatment for subacute bacterial endocarditis usually demands that the drug employed must have bactericidal and not merely bacteriostatic action.

Summary

Two cases of subacute bacterial endocarditis are reported.

The first case was treated with oxytetracycline because of severe reactions to penicillin, but the infection was not controlled by it, although the organism was sensitive. Subsequent use of penicillin, "covered" by antihistamines as described in the text, rapidly cleared the infection.

The second case was treated with chloramphenicol, aureomycin, and oxytetracycline because the organism, *Str. faecalis*, was sensitive to these drugs and resistant to penicillin and to streptomycin. Nevertheless the infection was not controlled by them. When it was subsequently shown that a combination of penicillin and streptomycin acting together was bactericidal whilst the other antibiotics had bacteriostatic action only, treatment with this combination was started, using penicillin in very large doses. The infection was then rapidly controlled.

It is emphasized that the delay caused by first using bacteriostatic antibiotics may well be dangerous because of the likelihood of continued progression of disease, and that every effort must be made from the onset to discover the appropriate bactericidal drug or bactericidal mixture of drugs.

We are indebted to Professor R. V. Christie for his assistance and encouragement in the preparation of this report, to Professor L. P. Garrod for his help and criticism and for the detailed laboratory work, to Dr. G. W. Hayward for permission to publish his case and for his advice with respect to it, and to the house-physicians who looked after the patients and assembled much of the information about them.

REFERENCES

- Cates, J. E., and Christie, R. V. (1951). *Quart. J. Med.*, **20**, 93.
Garrod, L. P. (1953). *British Medical Journal*, **1**, 953.
Maslansky, L., and Sanger, M. D. (1952). *Antibiot. and Chemother.*, **2**, 385.

Medical Memoranda

Oesophagitis Dissecans Superficialis

Sloughing of portions of the oesophageal wall is a recognized consequence of contact with scalding fluids or strong caustic or acid solutions. Plegmonous oesophagitis may uncommonly result from pyogenic infections of the mucous and submucous coats, spreading, perhaps, from a primary infection of the fauces or larynx or originating at the site of a neoplastic ulcer or impaction of a foreign body. Thrush oesophagitis not infrequently gives rise to pseudo-membrane formation, while extension to the upper oesophagus of pharyngeal diphtheritic ulceration has been reported.

There remains for mention a lesion characterized by extensive dissection of the squamous epithelial lining of the oesophagus from its underlying corium in the form of a tubular cast—oesophagitis dissecans superficialis. The following case is recorded on account of the rarity of the condition and the obscurity of its aetiology.

CASE REPORT

A married woman aged 37 was admitted to hospital late at night on October 15, 1951. She had been in her usual good health until about an hour after her evening meal, which had been swallowed without difficulty, when she noticed a sensation of something sticking in her throat. Repeated retching brought the object into her mouth. It was found to be of fleshy substance and apparently attached to the throat. She went to her doctor, and with further