*Medical Memoranda***Failure of Cephaloridine in a Case of
Staphylococcal Endocarditis***Brit. med. J.*, 1966, 2, 1244

When cephaloridine was introduced in 1964 it was said to be more active than cephalothin against staphylococci, whether penicillinase-forming or not, and to be suitable in all staphylococcal infections, where it would provide an alternative to methicillin or cloxacillin (Muggleton *et al.*, 1964; *Brit. med. J.*, 1964). In another paper cephaloridine is described as active against penicillin-resistant strains of *Staphylococcus aureus*, and, for practical purposes, unaffected by penicillinase (Murdoch *et al.*, 1964).

Barber and Waterworth (1964) thought that its high anti-staphylococcal activity, high resistance to penicillinase, and lack of plasma-binding suggested that it might be more effective than any of the new penicillins against penicillinase-producing staphylococci. However, they drew attention to the fact that of the antibiotics tested cephaloridine showed the greatest decrease in activity when a large inoculum was used.

More recently Benner *et al.* (1965) have observed marked differences in the susceptibility of penicillinase-producing staphylococci to cephalothin and cephaloridine: when a large inoculum was used with cephaloridine there was in some cases a hundredfold increase in the minimal inhibitory concentration value, whereas with cephalothin there was a maximal increase of tenfold. The differences were shown to be due to the much greater susceptibility of cephaloridine to inactivation by penicillinase. Ridley and Phillips (1965) have also shown that strains of *Staph. aureus* possessing multiple resistance or resistance to methicillin can be much more resistant than others to cephaloridine, and have a greater capacity to destroy this antibiotic.

These findings must bring into question the value of cephaloridine in the treatment of infections due to penicillinase-producing staphylococci, and our experience in the following case cannot be regarded as encouraging.

CASE REPORT

A woman aged 48 came under our care after a febrile illness at home for the preceding three weeks. She was known to have aortic incompetence following an attack of bacterial endocarditis, due to a penicillin-sensitive staphylococcus, seven years earlier, which had been treated successfully with penicillin and streptomycin.

When she was admitted her temperature was 105° F. (40.6° C.), and there was a marked tachycardia. Signs of aortic incompetence were observed, and the spleen was palpable. A presumptive diagnosis of bacterial endocarditis was confirmed by the isolation of a penicillin-resistant staphylococcus from the blood.

Preliminary sensitivity tests suggested that the organism was sensitive to cephaloridine, and, as the patient had suffered shortly before admission from what appeared to be a genuine allergic reaction to ampicillin, it was decided to withhold the synthetic penicillins and to begin treatment with cephaloridine (0.5 g. four-hourly intramuscularly) pending more detailed bactericidal sensitivity tests of combinations of antibiotics.

After 48 hours blood was collected for culture and antibiotic assay immediately before a further injection was due; though the level of cephaloridine in the blood was 8 µg./ml., the staphylococcus was again isolated.

As there was thought to have been some improvement in the patient's general condition, though little change had occurred in the pyrexia or tachycardia, the dosage of cephaloridine was increased to 1 g. six-hourly. Three days later a further specimen of blood

collected immediately before an injection gave another positive culture in spite of a blood cephaloridine level of 12.5 µg./ml.

Next day there were signs of a cerebral embolus and of cardiac failure with increasing aortic incompetence, and death ensued 24 hours later after eight days of cephaloridine therapy.

Necropsy (Dr. C. F. Ross).—This revealed infarcts in the cerebrum, liver, spleen, and kidneys. The heart showed that ulcerative endocarditis had destroyed much of the aortic valve except for the non-coronary cusp, which was thickened and had a central hole, interpreted as a healed lesion from the attack in 1957. A similar hole was seen in the right coronary cusp. The vegetations were large and friable, up to 8 mm. in diameter. The rest of the organs showed nothing worthy of remark. A staphylococcus was isolated from the spleen; sections of this organ showed infarction, with large colonies of staphylococci but no suppuration. No organisms were seen in the infarcts of other organs.

Bacteriology.—The organism isolated from the blood cultures during life and from the spleen at necropsy was a coagulase-positive *Staph. aureus*. Preliminary sensitivity tests with discs indicated sensitivity to tetracycline, erythromycin, novobiocin, streptomycin, cloxacillin, fusidic acid, cephaloridine, lincomycin, neomycin, and vancomycin, but resistance to penicillin.

From the size of the inhibition zone (3 cm. diameter) obtained with the 5-µg. cephaloridine disc it was assumed that the strain was fully sensitive to this antibiotic. However, though subsequent tests showed the minimal inhibitory concentration with a small inoculum to be 0.12 µg./ml. of cephaloridine, it rose to 4 µg./ml. when a large inoculum was used. Moreover, the antibiotic was not bactericidal at this level, survivors being obtained from tubes containing 25 µg./ml. There was no variation in the antibiotic sensitivity of the subsequent isolates.

Tests carried out by the cellophane-transfer method showed that cephaloridine in combination with streptomycin or kanamycin was bactericidal.

COMMENT

It is well recognized that a bactericidal antibiotic, or combination of antibiotics, is required for the successful treatment of bacterial endocarditis. Nevertheless, pending the result of tests to select an appropriate antibiotic or combination, it is usually possible to halt the progress of the disease by administering in adequate dosage any antibiotic capable of inhibiting the growth of the infecting organism.

The fact that cephaloridine signally failed in this respect in spite of a level in the blood some three times greater than the minimal inhibitory concentration for the infecting organism must raise doubts about its suitability for the treatment of severe infections due to penicillinase-producing staphylococci. It may well be that cephalothin is the more useful antibiotic in such cases.

We are indebted to Miss Hazel Pugh, A.I.M.L.T., for technical assistance and to Miss Pamela Waterworth, F.I.M.L.T., of the Bacteriology Department, Postgraduate Medical School, for carrying out the cellophane-transfer tests.

H. A. BURGESS, M.B., B.S.,
General Practitioner and Medical Officer, Weybridge
and Walton-on-Thames Hospitals.
R. J. EVANS, M.D., F.C.PATH.,
Consultant Pathologist, N.W. Surrey Group.

REFERENCES

- Barber, M., and Waterworth, P. M. (1964). *Brit. med. J.*, 2, 344.
Benner, E. J., Bennett, J. V., Brodie, J. L., and Kirby, W. M. M. (1965). *J. Bact.*, 90, 1599.
Brit. med. J., 1964, 2, 1211.
Muggleton, P. W., O'Callaghan, C. H., and Stevens, W. K. (1964). *Brit. med. J.*, 2, 1234.
Murdoch, J. McC., Spiers, C. F., Geddes, A. M., and Wallace, E. T. (1964). *Brit. med. J.*, 2, 1238.
Ridley, M., and Phillips, I. (1965). *Nature (Lond.)*, 208, 1076.