A new type of penicillin resistance of Staphylococcus aureus?

During the last year several reports have appeared from the United States describing patients with severe staphylococcal infections that have been treated unsuccessfully with antibiotics acting on the cell wall, i.e. penicillins, cephalosporins or vancomycin (Mayhall, Medoff & Marr, 1976; Gopal, Bisno & Silverblatt, 1976; Sabath, Wheeler, Laverdiere, Blazevic & Wilkinson, 1977). Recently Sabath et al. have described the detailed properties of such isolates of Staphylococcus aureus. These isolates are said to be penicillin tolerant because, although their growth is inhibited by the usual low levels of antibiotic, when tested for bactericidal effect they are not killed by therapeutic levels of these antibiotics. Sabath et al. have produced evidence that the defect in these bacterial cells is due to the presence of an excess of an inhibitor of autolysin. Individual cells vary in their ability to resist the bactericidal activity of the cell wall antibiotics, so that the proportion of tolerant organisms within such a 'resistant' strain is usually less than 7% of total cocci. However, the presence of the minority of abnormal cells apparently causes a failure of bactericidal effect on the whole culture. Sabath et al. conclude 'Tolerance is thus a common, clinically important form of penicillin resistance, that differs from previously described forms of penicillin resistance, that due to \( \beta \)-lactamase, and that due to "intrinsic" (e.g. methicillin resistance) mechanisms'.

The principal threat and interest to the clinician of these isolates is the possibility that they will prevent successful therapy, particularly in difficult situations. The reports mentioned describe a number of patients in which penicillins, cephalosporins and vancomycin have been associated with therapeutic failure and such tolerant staphylococci subsequently isolated. How justified is the inference by Gopal and Sabath that therapeutic failure is due to tolerance? A close scrutiny of the clinical details indicate that there is no proof at all of the association between tolerance and therapeutic failure.

Many people have pointed out that therapeutic failure can be due to numerable host and bacterial interactions, many of which are not apparent during sensitivity testing in vitro, and we must consider the following possibilities to account for therapeutic failure with anti-staphylococcal antibiotics:

1. The capacity of the cell to produce lactamase. All the cephalosporins and penicillins are to varying extents vulnerable to \( \beta \)-lactamase, although many laboratory methods of testing do not demonstrate this phenomenon (e.g. Lacey & Stokes, 1977).
2. The so-called intrinsic methicillin resistance. Whilst there is no proof that this type of resistance has been responsible for therapeutic failure, this may possibly be involved.
3. Resistance mechanisms of which we are largely unaware that may be manifested in a clinical context but which might not occur in vitro.
4. Problems of accessibility of the antibiotic to the site of infection and other host factors.
5. The so-called 'tolerance' of these strains to cell wall antibiotics.

There is, therefore, no certainty that tolerance is responsible for the therapeutic failure with these drugs. These excellent descriptive reports are marred by rather speculative interpretations without clinical justification. To know whether tolerance is clinically important is of relevance to the debate whether the choice of an antibiotic should be affected by its activity being essentially bacteriostatic or bactericidal.

What approach should laboratories now adopt regarding penicillin tolerance in Staphylococcus aureus? Laboratories may be tempted to test for tolerance after therapeutic failure with a penicillin or a cephalosporin, and to interpret that the tolerance is responsible for the therapeutic failure. This would be unwise until there is clinical proof that the tolerance is responsible for the drug failure. Laboratories with the capacity and expertise to identify and characterize fully such strains should be encouraged to do so with the proviso that all aspects of the patient and properties of bacteria (notably its ability to produce penicillinase) are considered. There is no justification yet to describe this as a new
resistance mechanism. In the same way the assertion that certain strains of staphylococci are 'methicillin resistant' has still to be substantiated.

RICHARD LACEY
West Norfolk and Kings Lynn General Hospital, Kings Lynn Norfolk PE30 5QD, England

References

Problems with neonatal meningitis
Neonatal meningitis remains hard to diagnose, hard to treat and associated with a high mortality and residual morbidity. But the fortunately low incidence of this group of infections—0.26 per 1000 live births in a recent study in the South of England (Goldacre, 1976)—makes it difficult for any one centre to accumulate a large experience, especially as the wide variety of causal organisms, changing resistance patterns and advances in antimicrobial drug therapy lead to frequent changes in policy. Similar difficulties are encountered in evaluating methods of treatment for meningitis caused by Gram-negative rods in older age groups.

For some years most paediatricians have put their faith in combinations of a penicillin, usually ampicillin, with an aminoglycoside, formerly kanamycin, now gentamicin or tobramycin. Since, however, the concentration of aminoglycoside achieved in the CSF by intramuscular or intravenous injection rarely exceeds the MIC against the common causal organisms, intrathecal injection of the aminoglycoside is included in the drug regimen. The value of this aspect of treatment is now open to question.

Kaiser & McGee (1975) provided a series of measurements of the concentration of gentamicin or tobramycin in blood, lumbar CSF and ventricular CSF in patients with subcutaneous reservoirs for intraventricular injection. Their results, although scarcely surprising in the light of the known pathways by which the CSF circulates, showed clearly that lumbar injection gives good levels in the lumbar but not in the ventricular CSF, and that adequate levels at both sites can be achieved only by intraventricular injection. Earlier work with $^{131}$I labelled rose bengal in monkeys (Rieselbach, Morse, Rall, Frei & Freireich, 1962) had clearly demonstrated that the dye is distributed throughout the ventricular system only if a large volume, 25% of the estimated CSF volume, is injected into the lumbar space. Moreover, failure to achieve adequate antibacterial concentrations in the ventricular CSF may be an important drawback in treatment, since ventriculitis is a common component of neonatal meningitis (Salmon, 1972). Moellering & Fisher (1972), for example, describe the ultimate cure of Proteus morganii meningitis in a 16-month-old child by the addition of intraventricular therapy after systemic and lumbar intrathecal administration of gentamicin had failed to sterilize the ventricular CSF.

These doubts about the theoretical validity and practical efficacy of intrathecal treatment by the lumbar route have been strengthened by the results of a remarkable comparative trial organized by McCracken & Mize (1976) in which 117 infants were studied in 18 hospitals in the U.S.A. Treatment was allocated randomly between two groups, both receiving ampicillin and gentamicin systemically and one of them also receiving intrathecal injection of gentamicin by the lumbar route daily for at least 3 days. The overall case fatality was 32%, but no difference between the groups, which were generally similar in their measured characteristics, was noted in mortality, morbidity or duration of positive cultures in the CSF.

To these doubts of the value of lumbar intrathecal treatment must be added the technical difficulty of repeated lumbar punctures in the neonate and the possibility that repeated injections may sometimes enter the subdural rather than, as intended, the subarachnoid space.

Does the CSF concentration of antibiotic matter? Certainly no complete correlation can be established between success in treatment