ment techniques suggests that a clinical director drawn from the ranks of the surgeons or anaesthetists might provide more direct and effective support. For the foreseeable future the most intransigent problem that the new managers will face, however, will be shortage of staff. This report properly pointed out that operation department assistants and nurses should be interchangeable, as should theatre and anaesthetic work—and that with parity of work should come parity of pay.

The problems of operating theatres are neatly quantifiable and thus may be soluble; but theatres and beds are almost totally interdependent, and if the problems of providing beds are not solved reforms in the theatre suite will be wasted. Ensuring a steady flow of patients is a much more taxing problem than improving the usage of theatres, and it depends on factors such as waiting lists, admissions, case mix, and staffing. The Bevan report made a stab at suggesting some

solutions, including more computerisation and more day case surgery. The possibility that overall there might not be enough surgical beds in the NHS at present was not addressed.

Operating theatres—like the whole of the NHS after the white paper—will need to be heavily managed. Whether history will show that the huge injection of cash, technology, human effort, and angst will be worth while in clinical, financial, and human terms remains to be seen.

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1 National Audit Office. *The use of operating theatres in the National Health Service, report by the Comptroller and Auditor General*. London: HMSO, 1987.

2 NHS Management Executive. *The management and utilisation of operating departments*. London: HMSO, 1989. (Chairman P G Bevan.)

The penicillins today

Use is now well defined by clinical trials

Pneumococci, streptococci, gonococci, and meningococci have been the major targets for penicillin for half a century. Resistance has long excluded *Staphylococcus aureus* from this list of pyogenic cocci with predictable susceptibility to penicillin. The extent of penicillin resistance in gonococci reached a peak in 1983 and has since declined.¹ Pneumococci are still generally susceptible, despite the worrying identification of strains with either reduced susceptibility (minimum inhibitory concentration $>0.1-2$ mg/l), or, less common still, overt resistance (minimum inhibitory concentration >2 mg/l).² The highest incidence of these resistant pneumococci is in the Iberian peninsula—a popular holiday destination for many Britons.³ Penicillin resistance among meningococci has been identified in Spain, South Africa, and Britain.⁴⁻⁶

Despite these concerns the indications for penicillin G remain infections caused by pneumococci, meningococci, *Streptococcus pyogenes* and other non-enterococcal streptococci, microaerophilic streptococci such as *Streptococcus milleri*, and gonorrhoea when susceptibility can be confirmed. The continued susceptibility of *Treponema pallidum* is reassuring, though when syphilis complicates HIV infection more prolonged treatment is necessary.⁷ Acute leptospirosis⁸ and established Lyme borreliosis⁹ are other indications. Most oral and anaerobic bacteria, including both the actinomycetes and the clostridia, remain susceptible to penicillin.¹⁰

The isolation of the 6-aminopenicillanic acid nucleus in 1957 was an important milestone in the development of the penicillins. The first fruit of this discovery was ampicillin. Other aminopenicillins, analogues, esters, and prodrugs followed: amoxycillin, pivampicillin, bacampicillin, and talampicillin to name but a few. The extensive indications for the aminopenicillins include infections of the middle ear, paranasal sinuses, and lower respiratory tract; meningitis caused by meningococci, pneumococci, *Haemophilus influenzae*, susceptible Gram negative enteric bacilli, *Strep agalactiae*, and *Listeria monocytogenes*; systemic salmonellosis, including enteric fever; and serious enterococcal sepsis and urinary tract infections. Despite their established safety, including for use in pregnancy, drug resistance has relegated the aminopenicillins to second line treatment for urinary tract

infections, and the increase in the number of strains of *H influenzae* and *Branhamella catarrhalis* producing β -lactamase raises questions concerning the continuing efficacy of these drugs to treat such infections.

The discovery that resistance to penicillin is caused by enzymatic hydrolysis of the β -lactam ring by *Staph aureus* stimulated the development of the penicillinase-resistant penicillins such as methicillin, nafcillin, and the isoxazolyl penicillins—oxacillin, cloxacillin, dicloxacillin, and flucloxacillin. These compounds are the mainstay of antistaphylococcal treatment, with flucloxacillin popular in Europe and nafcillin, oxacillin, and dicloxacillin in North America. These have generally been assumed to be of comparable clinical efficacy. Recent experimental data suggest, however, that dicloxacillin and (especially) methicillin are more stable to *Staph aureus* β -lactamase.¹¹ Strains of *Staph aureus* with reduced affinity of the binding protein 2' are resistant to these and all other penicillins.¹² And coagulase negative staphylococci, which are now a major cause of hospital sepsis, are also often resistant to these penicillins.¹³

Penicillinase is one of a large and expanding family of β -lactamases that has eroded the therapeutic efficacy of the penicillins.¹⁴ Resistance is now recognised in about 40% of *Escherichia coli*,¹⁵ 6% of *H influenzae* (8% among type b isolates),¹⁶ some 5% of gonococci,¹ and up to 70% of *B catarrhalis*,¹⁷ while *Staph aureus* that are sensitive to penicillin are collectors' items. Recognition that antistaphylococcal penicillins such as cloxacillin and bind penicillinase suggested a chemotherapeutic solution to the protection of the β -lactam ring, and this has been realised in β -lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam. While lacking useful antibacterial activity they confer broad spectrum, yet individually variable, resistance to Gram negative β -lactamases.¹⁸ Where resistance is the result of impaired cell wall penetration, however, these β -lactamase inhibitors are of no therapeutic benefit. Clavulanate is licensed in combination with both an aminopenicillin, co-amoxiclav (augmentin), and ticarcillin. Sulbactam is licensed in other countries as the mutual prodrug sultamicillin. Co-amoxiclav is available in a fixed ratio of amoxycillin and clavulanate of 2:1 for oral administration and as a 5:1 ratio for parenteral use; ticarcillin-

clavulanate is available only in the ratio 15:1. The pharmacokinetic features of the component drugs must be matched to maintain adequate tissue concentrations.

Gram negative enteric pathogens dominated hospital infections from the 1960s to the 1980s. The antipseudomonal penicillins carbenicillin, ticarcillin, and sulbenicillin met this challenge and extended the spectrum of the penicillins. Their activity against *Klebsiella* species, however, is poor and is only modest against *Pseudomonas aeruginosa*. The well established safety of the penicillins, however, permitted dosages of up to 30 g a day—though this may result in excessive sodium loading¹⁹ and interference with platelet aggregation.²⁰ Efficacy in the febrile patient with neutropenia is a stringent test of the “therapeutic muscle” of any anti-infective drug; the α carboxypenicillins have been successful when combined with an aminoglycoside and provide broad spectrum cover and activity that is often synergic against selected pathogens such as *P. aeruginosa*.²¹ When used in combination, however, they must be given at separate times and sites to avoid inactivation of the aminoglycoside by the penicillin—an action that is most pronounced for carbenicillin and gentamicin.²²

The ureidopenicillins—azlocillin, mezlocillin, and piperacillin—are active against many Gram negative and Gram positive bacteria including enterococci but excluding many staphylococci. This activity is unfortunately dependent on the inoculum²³ and is not compensated for by relatively poor resistance to β -lactamase hydrolysis.²⁴ Only azlocillin and piperacillin show definite activity against *P. aeruginosa*, but again large doses are necessary. The poor results reported when these agents were given as monotherapy in febrile, neutropenic patients require them to be given in combination with an aminoglycoside.^{25, 26} As such they have proved a popular regimen.

As our understanding of structure-activity determinants has improved β -lactam compounds have been designed that

are highly resistant to many common plasmid and chromosomally mediated β -lactamases. Such compounds include many of the extended spectrum (third generation) cephalosporins, the carbapenem imipenem,²⁷ and, among the penicillins, temocillin.²⁸ Temocillin is now marketed and has a spectrum of activity limited to most medically important Gram negative bacteria but excluding *P. aeruginosa*. Its half life is 4.5 hours; thus it can be given twice daily.²⁹ Its place in treatment has yet to be established, but it is unlikely to be used alone except in infections known to be due to susceptible pathogens.

Research has also led to an appreciation that certain β -lactam drugs have the ability to induce production of β -lactamase in selected pathogens such as *Enterobacter* species, *Serratia* species, and *Pseudomonas* species.³⁰ This varies by organism and β -lactam; it is most pronounced for drugs such as cefoxitin and certain third generation cephalosporins and lower for drugs such as temocillin.³¹ The clinical impact of inducible resistance varies widely and depends on the selection of derepressed mutants.³²

In summary, the interaction between a penicillin and its target pathogen is complex. The final outcome depends on several phenomena, including pharmacokinetic behaviour, cell wall penetration, and binding to specific target proteins, which may be neutralised by β -lactamase activity. Though many of these features have been defined in vitro, the clinical use of the penicillins has been established through carefully designed and executed trials. Such trials are essential to establish the efficacy and safety of a drug and to define its place in chemotherapy.³³

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