Prospects for New Antibiotics: Keeping One Step Ahead

DAVID GREENWOOD, DSc, MRCPath
Reader in Microbiology, Department of Microbiology and PHLS Laboratory, University Hospital, Queen’s Medical Centre, Nottingham

So many antimicrobial agents are now available to the physician that it comes as something of a shock to recall that 50 years ago there were none, save quinine and a handful of other, generally rather toxic, antiprotozoal and anthelmintic agents[1]. So far as antibacterial agents were concerned, only the antisyphilitic arsenicals, arsenphenamine (Salvarsan) and neoarsphenamine were available when Domagk’s Prontosil (the activity of which was later shown to be due to sulphanilamide) burst on the scene exactly 50 years ago[2]. Since then, the proliferation of antibacterial agents has advanced to the stage where an embarras de richesce exists, whereas expansion of the armamentarium of antiprotozoal, anthelmintic, antifungal and antiviral agents has progressed extremely slowly.

\section*{\bf{\textit{\beta}-Lactam Antibiotics}}

The astonishing proliferation of antibacterial agents is nowhere more evident than within the \textit{\beta}-lactam group. Originally consisting of benzylpenicillin and a few closely related derivatives, and later widened by the development of semi-synthetic compounds and by the discovery and exploitation of the cephalosporins, the group has blossomed to the extent that over 70 different \textit{\beta}-lactam derivatives are now in clinical use worldwide, of which 40 are on the market in the UK (Table 1). Most of these compounds are directly derived from 6-aminopenicillanic acid or 7-aminocephalosporanic acid, but they include some unusual molecular variants. For example, cefoxitin carries a methoxy group on the \textit{\beta}-lactam ring, a feature that confers stability to \textit{\beta}-lactamases; latamoxef also exhibits this feature and additionally has an oxygen atom in place of sulphur in the fused ring structure; and the \textit{\beta}-lactamase inhibitor, clavulanic acid, exhibits a completely novel structure that also features oxygen in the fused ring.

\section*{Present Progress}

The most significant recent advance has been the development of agents that overcome \textit{\beta}-lactamase mediated resistance in coliform bacteria. The earliest of these compounds, cefoxitin and cefuroxime, display striking enzyme stability, but only moderate intrinsic activity. More recently, a group of structurally related cephalosporins has appeared in which stability to \textit{\beta}-lactamases is combined with high intrinsic activity against a wide range of bacteria. Three of these cephalosporins, cefotaxime, ceftizoxime and ceftazidime, are available in the UK and two others, ceftriaxone and cefmenoxime, are on the market elsewhere; a structurally unrelated \textit{\beta}-lactam agent, the oxa-cephem, latamoxef, shares similar properties and is generally considered together with this group.

The appearance of these highly active compounds undoubtedly represents a useful advance in the treatment of infection, particularly in those patients prone to systemic infection with Gram-negative rods. Moreover, these compounds, and in particular cefotaxime and ceftizoxime, display outstanding activity against the common causes of meningitis, including neonatal meningitis, and this may represent an important area of use. However, the impressively enhanced activity of these antibiotics against Gram-negative bacteria has been achieved at the expense of somewhat reduced antistaphylococcal activity, and none of these agents possess useful activity against \textit{Streptococcus faecalis} (Table 2); certain species of enterobacteria, notably \textit{Enterobacter cloacae}, readily develop resistance[3]. Furthermore, only ceftazidime exhibits therapeutically useful anti-pseudomonal activity, and only latamoxef covers adequately for anaerobes of the \textit{Bacteroides fragilis} group. Thus, all of these agents possess notable gaps in their antibacterial spectrum and, indeed, the amoxycillin/clavulanic acid combination, which embraces staphylococci, enterococci and anaerobes, covers a broader range of organisms.

A few other properties serve to distinguish between the new cephalosporins; cefotaxime is susceptible to hepatic enzymes that may reduce its activity in the body, and latamoxef (as well as cefmenoxime) possesses the methyl-tetrazole side chain which, in several cephalosporins, is associated with hypoprothrombinaemia[4]; ceftriaxone exhibits the unusual property of an extremely long serum half-life (associated with high protein binding) and is preferentially excreted in bile.

\section*{Future Prospects}

Judging from the number of new compounds still being described in the literature, the scope for developing new cephalosporins is far from exhausted. However, the most
intriguing innovations concern β-lactam agents that exhibit fundamental changes in the central part of the molecule, rather than simple side chain modifications. Four compounds have received particular attention: aztreonam, one of a family of compounds known collectively as monobactams, in which the β-lactam ring is not associated with another fused ring system; imipenem, a carbapenem derivative in which carbon replaces the sulphur of the thiazolidine ring of penicillins; temocillin, a penicillin which (like cefoxitin) carries a methoxy group on the β-lactam ring; and sulbactam, a penicillanic acid sulphone which, like clavulanic acid, possesses little intrinsic antibacterial activity, but inhibits most bacterial β-lactamas.

These four compounds exemplify two diametrically opposed approaches to antimicrobial chemotherapy: narrow-spectrum, targeted therapy (aztreonam, temocillin) and the ultra-broad spectrum, cure-all approach (imipenem, sulbactam/ampicillin) (Table 3). Imipenem, indeed, exhibits the broadest antibacterial spectrum of all β-lactam antibiotics and combines this spectrum with impressive intrinsic activity and β-lactamase stability. Ironically, however, the compound is rapidly inactivated in the body by a renal dehydropeptidase and has to be administered with a dehydropeptidase inhibitor[5].

Quinolones

It is perhaps a tribute to the persistence of the pharmaceutical houses that, after years of research effort that yielded compounds offering little or no improvement over

### Table 1. β-lactam agents in clinical use throughout the world.

| Benzylpenicillin and its oral and long-acting derivatives | azidocillin | clometocillin | penemethamate hydriodide | procaine penicillin* |
|----------------------------------------------------------|-------------|---------------|--------------------------|----------------------|
| benzylpenicillin*                                        |             |               |                          | benzathine penicillin*|
| phenoxymethylpenicillin*                                 |             |               |                          | benethamine penicillin*|
| penethicillin*                                           |             |               |                          | clemizole penicillin* |
| penicillin*                                              |             |               |                          | hydrabamine penicillin V|
| propicillin*                                             |             |               |                          | dipenicillin (anicillin)|
| B. Staph, Sir.                                           |             |               |                          |                       |
| Antistaphylococcal penicillins                           |             |               |                          |                       |
| methicillin*                                             |             |               |                          |                       |
| cloxacillin*                                             |             |               |                          |                       |
| floxacillin*                                             |             |               |                          |                       |
| B. Broad-spectrum penicillins                            |             |               |                          |                       |
| ampicillin*                                              |             |               |                          |                       |
| amoxycillin*                                             |             |               |                          |                       |
| cicalcin*                                                |             |               |                          |                       |
| amoxycillin/clavulanate*                                 |             |               |                          |                       |
| epicillin*                                               |             |               |                          |                       |
| Antipseudomonal β-lactam agents                          |             |               |                          |                       |
| carbenicillin*                                           |             |               |                          |                       |
| ticarcillin*                                             |             |               |                          |                       |
| azlocillin*                                              |             |               |                          |                       |
| mezlocillin*                                             |             |               |                          |                       |
| Oral cephalosporins                                      |             |               |                          |                       |
| cephalexin*                                              |             |               |                          |                       |
| cephadine*                                               |             |               |                          |                       |
| cefaclor*                                                |             |               |                          |                       |
| β-lactamase-susceptible injectable cephalosporins         |             |               |                          |                       |
| cephalothin*                                             |             |               |                          |                       |
| cephaloridine*                                           |             |               |                          |                       |
| cephalazin*                                              |             |               |                          |                       |
| β-lactamase-stable cephalosporins                        |             |               |                          |                       |
| cefuroxime*                                             |             |               |                          |                       |
| cefotaxime*                                              |             |               |                          |                       |
| cefotadizime*                                            |             |               |                          |                       |

* = on the market in the UK; † = strictly an oxa-cephem.

### Table 2. Activity in vitro of new cephalosporins against some common bacterial pathogens, including those commonly implicated in bacterial meningitis. R = resistant.

| Organism          | Minimum inhibitory concentration (µg/ml) |
|-------------------|------------------------------------------|
|                   | Cefotaxime | Cefitoxime | Cefatizime | Latamoxef |
| Staph. aureus      | 2          | 2          | 4          | 8         |
| Str. faecalis      | R          | R          | R          | R         |
| Enterobacteria     | 0.06       | 0.03       | 0.12       | 0.12      |
| Ps. aeruginosa     | 16         | 32         | 2          | 16        |
| B. fragilis        | 16         | 16         | 16         | 4         |
| N. meningitidis    | 0.01       | 0.01       | 0.02       | 0.01      |
| Str. pneumoniae    | 0.02       | 0.02       | 0.2        | 0.5       |
| H. influenzae      | 0.01       | 0.01       | 0.06       | 0.06      |
the parent substance, nalidixic acid, they finally succeeded in devising a derivative that displayed greatly improved spectrum and intrinsic activity. This compound was norfloxacin, and its discovery has naturally given rise to a family of closely related compounds, at least one of which, ciprofloxacin, offers a further improvement in activity.

The new quinolones, and ciprofloxacin in particular, display a spectrum of activity rivalling, or even surpassing, that of the new β-lactam agents (Table 4); they are quite well absorbed when administered orally, have a half-life of 3–4 hours, and are excreted in high concentration into the urine. These properties suggest a valuable role for the quinolones in urinary tract infection and norfloxacin is likely to be marketed solely for this indication. Manufacturers of other quinolones have their sights on wider indications, but blood levels are not high (e. 1-4 μg/ml, depending on the compound and the dose) and this may insufficiently exceed the minimal inhibitory concentration of some organisms, notably staphylococci, streptococci and *Pseudomonas aeruginosa* to prevent the development of quinolone resistance, which emerges readily. However, on the credit side, these drugs appear to be extremely well distributed in the body and may be concentrated within cells[6], factors that may be crucial in certain infections. Furthermore, parenteral formulations are becoming available which may provide improved blood levels when needed.

It is still too early to assess the place of these interesting compounds; meanwhile, their appearance has provoked the drug industry into renewed interest in these substances and yet more derivatives are waiting in the wings.

### Other New Antibacterial Agents

Although a trickle of new aminoglycosides continues to appear (amikacin and netilmicin in the UK, sisomicin and dibekacin elsewhere), none offers substantial advantages over gentamicin or tobramycin, except in those units troubled by gentamicin-resistant organisms. Other new derivatives, such as fortimicin B, and various related compounds are under development. Little of note has emerged from the other major antibiotic groups, although macrolides continue to attract some attention. Josamycin, a macrolide described over 20 years ago, is being actively promoted in several countries, but not, as yet, in the UK.

Progress in the development of truly novel antibacterial agents has been extremely slow and such compounds as have been described do not appear to represent major advances. Perhaps the most interesting is the new glycoprotein, teicoplanin, a distant relative of vancomycin, with which it shares a similar narrow spectrum; however, teicoplanin appears considerably more active against staphylococci and streptococci[7]. Other novel compounds that deserve mention are mupirocin (pseudomic acid) and biocazymic. Mupirocin is an antibiotic obtained from *P. fluorescens* which, like teicoplanin, exhibits a spectrum virtually restricted to Gram-positive cocci. It is extensively metabolised when administered systemically, but may be of value in the topical treatment of staphylococcal and streptococcal skin infections[8] or for the elimination of staphylococci from nasal carriers. In contrast, the spectrum of biocazymic is confined to enteric Gram-negative bacilli. Even against these organisms the activity is fairly feeble, but oral administration leads to sufficient concentrations in the lumen of the gut (the drug is not absorbed) to eliminate enteric pathogens, and satisfactory trials have been reported in the treatment[9] and prophylaxis[10] of traveller’s diarrhoea.

### Prospects of Non-Antibacterial Agents

In stark contrast to the abundance of therapeutically useful antibacterial agents, the choice of chemotherapeutic alternatives for non-bacterial infection is severely limited. Antiviral agents in particular are still in their infancy, although the appearance of the anti-herpes drug, acyclovir, has revived hopes of effective antiviral therapy and a number of interesting compounds are under development[11].

Progress in antifungal agents has been largely restricted to the imidazoles. Most of these compounds are suitable only for topical use, but ketoconazole, which is well absorbed when administered orally, has proved useful in systemic mycoses. Recently, attention has turned to triazoles, one of which, itraconazole, seems particularly interesting, as experiments in animals suggest that it may be safe and efficacious in aspergillosis[12].

---

**Table 3. Comparative activity in vitro of some novel β-lactam agents.**

| Organism     | Minimum inhibitory concentration (μg/ml) | Sublactam/ |
|--------------|-----------------------------------------|------------|
|              | Aztreonam | Temocillin | Imipenem | Ampicillin* |
| *Staph. aureus* | R         | R          | 0.02      | 2.0         |
| *Str. faecalis* | R         | R          | 2.0       | 1.0         |
| *H. influenzae* | 0.5       | 0.5        | 0.06      | 1.0         |
| Enterobacteria | 0.06      | 4.0        | 0.12      | 4.0         |
| *P. aeruginosa* | 4.0       | R          | 4.0       | R           |
| *B. fragilis* | R         | R          | 0.12      | 2.0         |

*Expressed as ampicillin activity.

**Table 4. Comparative activity in vitro of nalidixic acid, norfloxacine and ciprofloxacin against selected bacterial pathogens.**

| Organism     | Minimum inhibitory concentration (μg/ml) | Nalidixic acid | Norfloxacine | Ciprofloxacin |
|--------------|-----------------------------------------|----------------|--------------|--------------|
| Staphylococci | 32                                     | 1.0            | 0.5          |              |
| Streptococci | >32                                    | 8.0            | 1.0          |              |
| Enterobacteria (S/nal) | 2.0                  | 0.06           | 0.02         |              |
| Enterobacteria (R/nal) | 256                  | 0.5            | 0.25         |              |
| *P. aeruginosa* | 64                             | 0.5            | 0.25         |              |
| *Bacteroides spp.* | >32                         | 16             | 2.0          |              |
| *L. pneumophila* | NT                             | 0.12           | 0.06         |              |
| *M. tuberculosis* | NT                            | 8.0            | 1.0          |              |

| S/nal = sensitive to nalidixic acid; R/nal = resistant to nalidixic acid; NT = not tested. |
Prospects for new antiprotozoal agents are rather gloomy. Despite the availability for many years of several excellent anti-malarial agents, the inexorable spread of resistance, notably resistance to chloroquine in Plasmodium falciparum, has seriously undermined their usefulness. Years of endeavour at the Walter Reed Army Institute of Research in Washington has yielded one important new antimalarial, mefloquine, but it is feared that resistance to this drug will also emerge readily[13]. A few other novel antimalarials are under study, one of which, qinghaosu (artemisinine) has been used as a herbal remedy in China for centuries[14].

Protozoal diseases such as amoebiasis, giardiasis and trichomoniasis have yielded to 5-nitroimidazoles (metronidazole and its relatives). Resistance has not yet emerged as a major problem and the therapeutic future of these drugs thus seems secure. Among other important protozoal infections of man, leishmaniasis still has to be treated with antimonial and African trypanosomiasis with arsenicals. However, two drugs, nifurtimox and benzimidazole, are now available for the previously untreated Chagas' disease (South American trypanosomiasis), although both have toxicity problems.

Chemotherapy of helminthic infections has benefited from the economic importance of similar diseases in animals and several important anthelminthic agents have found their way into medical use via the veterinary route. Such compounds include the benzimidazoles, thiabendazole and mebendazole (the first really broad-spectrum agents for intestinal worms) and praziquantel, a major advance in the treatment of trematode infections, including schistosomiasis, and also of tapeworm infections.

This fruitful search for medical anthelminthics among veterinary products is continuing: another veterinary benzimidazole derivative, albendazole, is showing promise in hydatid disease[15], and a new anthelminthic antibiotic that is active against a wide variety of animal nematodes (and, curiously, arthropods), ivermectin[16], appears to be of value in onchocerciasis and other filarial infections[17].

It is ironic that developments in the treatment of infections that affect hundreds of millions of people throughout the Third World should depend on the economic importance of animals, but that seems the harsh reality of the market place. Certainly, what is needed on a global scale is not yet another new cephalosporin, but agents active against non-bacterial pathogens.

This article is based on a paper read at the Conference on Infectious Diseases held at the Royal College of Physicians in May 1985.

References

1. Greenwood, D. (1983) In Antimicrobial Chemotherapy, p.5 (ed D. Greenwood.) London: Baillière Tindall.
2. Domagk, G. (1935) Deutsche Medizinische Wochenschrift, 61, 250.
3. Sanders, C. C. (1984) Journal of Antimicrobial Chemotherapy, 13, 1.
4. Smith, C. R. and Lipsky, J. J. (1983) Journal of Antimicrobial Chemotherapy, 11, 496.
5. Kahan, F. M., Kropp, H., Sundelof, J. G. and Birnbaum, J. (1983) Journal of Antimicrobial Chemotherapy, 12, (Suppl. D.) 1.
6. Easmon, C. S. F. and Crane, J. P (1985) Journal of Clinical Pathology, 38, 442.
7. Williams, A. H. and Grüneberg, R. N. (1984) Journal of Antimicrobial Chemotherapy, 14, 441.
8. Sutherland, R., Boon, R. J., Griffin, K. E., Masters, P. J., Slocombe, B. and White, A. R. (1983) Antimicrobial Agents and Chemotherapy, 27, 495.
9. Ericsson, C. D., DuPont, H. L., Sullivan, P., Galindo, E., Evans, D. G. and Evans, D. J. (1983) Annals of Internal Medicine, 98, 20.
10. Ericsson, C. D., DuPont, H. L., Galindo, E. et al. (1985) Gastroenterology, 88, 473.
11. De Clercq, E. (1985) In The Scientific Basis of Antimicrobial Chemotherapy, p.155, (ed D. Greenwood and F. O'Grady.) Cambridge University Press.
12. Van Cutsem, J., Van Gerven, F., Van de Ven, M., Borgers, M. and Janssen, P. (1984) Antimicrobial Agents and Chemotherapy, 26, 527.
13. Peters, W. (1985) In The Scientific Basis of Antimicrobial Chemotherapy, p.95, (ed D. Greenwood and F. O'Grady.) Cambridge University Press.
14. Bruce-Chwatt, L. J. (1982) British Medical Journal, 284, 767.
15. Morris, D. L. (1983) Journal of Antimicrobial Chemotherapy, 11, 494.
16. Campbell, W. C., Fisher, M. H., Stapley, E. O., Albers-Schönberg, G. and Jacob, T. A. (1983) Science, 221, 823.
17. Aziz, M. A., Diallo, S., Diop, I. M., Lariviere, M. and Porta, M. (1982) Lancet, 2, 171.