activity and inhibition of leucocyte chemotaxis are other possible mechanisms by which they exert their effect (Hurwitz, 1979; Stoughton, 1979). Initially the antibiotics were used systemically but there is an increasing range of topical antibiotic preparations for use in acne and provided the vehicles used permit entry of the drug deep into the follicles they represent a logical step forward in treatment. Clindamycin, erythromycin and the tetracyclines are the most useful topical antibiotics (Frank, 1977; Stoughton, 1979). Topical preparations containing corticosteroids cannot be generally recommended for the treatment of acne but there is no doubt that in carefully selected cases of severe inflammatory disease a short course of systemic corticosteroids may bring much needed relief to the patient and reduce potential scarring when all else has failed (Scholtz, 1977). In addition, the injection of small amounts of corticosteroids into particularly troublesome nodulocystic lesions may be of value (Scholtz, 1977).

In conclusion, many patients with non-inflammatory acne will respond well to topical therapy with such agents as benzoyl peroxide or retinoic acid, whilst those with predominantly inflammatory disease are best managed initially with systemic antibiotics, combined with appropriate topical therapy. Later on such cases may well be maintained with locally applied agents alone. Thus, today's treatment concentrates on the later stages of pathogenesis, but perhaps tomorrow will reveal a more fundamental and yet still safe approach.

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References


Towards better antimicrobial treatment of sexually transmitted diseases

The report of the sexually transmitted diseases (S.T.D.) surveillance in the U.K. in 1978 (British Medical Journal, 24 November 1979, p. 1375) shows that although both syphilis and gonorrhoea have been increasing since 1973 the highest increase has been in the incidence of non-specific urethritis which is now the commonest sexually transmitted disease in males in the U.K. In the U.S.A. the increase in sexually transmitted diseases has been even greater and they are a major problem in the Far East and Africa where accurate figures are unavailable.

Until recently, penicillins were the treatment of choice for gonorrhoea. However, the emergence in the late 1950s of strains of Neisseria gonorrhoeae showing decrease in penicillin susceptibility and their subsequent increase in frequency and degree of resistance has necessitated continual re-evaluation of therapy with penicillins. Such strains often show a diminished sensitivity to other antibiotics used in the treatment of gonorrhoeae: tetracycline, erythromycin and chloramphenicol, and are usually resistant to streptomycin (Reyn, 1961). Penicillins are still
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Effective, but the dose required for optimal cure rates has needed to be progressively raised. Presently 4 8 mega units of procaine penicillin as a single dose i.m. with 1 g of probenecid orally is given in many centres and is nearing the tolerable limit. The emergence of the β-lactamase producing strains and their continuing relative high prevalence in some parts of the world (Ngeow & Thong, 1979) has further limited the effectiveness of penicillins.

The antibiotics that have proved to be effective in this situation are spectinomycin and the new β-lactamase stable cephalosporins, but they are much more expensive. Spectinomycin is effective as a single i.m. dose of 2 g which gives a serum level of 100 mg/l after 1 h (Porter & Rutherford, 1977). The MIC of spectinomycin is 5 20 mg/l for most strains. Resistance is rare but could emerge with increasing use of the drug, and therefore it should be used only for treatment of infection by known β-lactamase producing gonococci or of patients acquiring their infections in areas of high prevalence of such strains.

The β-lactamase stable cephalosporins, cefuroxime, cefoxitin, cefamandole and cefotaxime, have also been successful. Cefuroxime is the most active of these, and, like ampicillin, is more active than benzyl penicillin against insensitive strains. Cefoxitin is only as active as benzyl penicillin against these strains, and cefamandole is four times less active (Phillips et al., 1976). Cefoxitin and cefotaxime are painful on i.m. injection. Unlike spectinomycin these cephalosporins should eradicate incubating syphilis.

Chlamydia trachomatis is the causative agent in 50% of cases of non-specific urethritis in men, and in 35% of their female sexual contacts (Tait et al., 1980). Chlamydia are also found in approximately 25% of cases of gonococcal urethritis in males (Oriel et al., 1976), and 53% of gonococcal cervicitis in females (Hobson & Rees, 1978). Chlamydia cause pelvic inflammatory disease in females. Conjunctivitis is common in infants born to infected mothers and is very often associated with respiratory tract infection (Rees et al., 1980) seen as pneumonia in the U.S. (Beem & Saxon, 1977) but not in the U.K. Oxytetracycline 1 g a day orally for 2 weeks gives an 80% cure rate (Oriel, 1978). Erythromycin stearate, at the same dose, is an adequate alternative when tetracycline is contra-indicated.

The causes of failure with oxytetracycline have not been elucidated. In vitro it is bactericidal against Chlam. trachomatis with an MIC of 0.06 mg/l which does not vary significantly with different strains or serotypes (Kuo, Wang & Grayston, 1977; Treharne et al., 1977). Therefore although non-compliance and re-infection would explain some failures, other factors such as sequestration of the organism and difficulty of penetration of tetracycline may be present.

As the facilities for the isolation of Chlam. trachomatis are still limited to a few centres, and because of the high incidence of concurrent infection with both gonococci and chlamydiae, the current approach to the treatment of S.T.D. should be reviewed. The objectives should be to eradicate the two micro-organisms simultaneously and eradicate incubating syphilis. In vitro studies show that benzyl penicillin has an MIC of 1 mg/l against Chlam. trachomatis and induces the formation of abnormal inclusions (Johnson & Hobson, 1977), which recover their viability after repeated passage in antibiotic free medium (Ridgway, Owen & Neil, 1978). Also, single doses of benzyl penicillin are only infrequently effective against Chlam. trachomatis. Women, concurrently infected with chlamydia and gonococci after treatment with a single large dose of penicillin are still positive for chlamydia in 73% of cases (D. Hobson, personal communication). Neither the effect of multiple doses of penicillins, nor the minimal duration for an effective course of tetracycline have been established.

Tetracyclines would be inadequate for the treatment of gonorrhoea in areas where the prevalence of penicillin- and tetracycline-insensitive gonococci is high. In Liverpool the incidence of such strains is 20% and this is associated with a failure rate of approximately 35% in women treated with a multiple dose regime of oxytetracycline.

Unfortunately the antibiotics used for the treatment of infection with penicillin resistant gonococci, spectinomycin and cefuroxime and other cephalosporins are relatively inactive against Chlam. trachomatis in vitro. MICs for Chlam. trachomatis are 64, 256 and 2048 mg/l respectively for spectinomycin, cefuroxime and cefotaxime (Ridgway et al., 1978; Ridgway & Oriel, 1979).

Minocycline is slightly more active than oxytetracycline against Chlam. trachomatis (MIC 0.03 mg/l, Ridgway et al., 1978) and has been used successfully in the treatment of
patients with Chlam. trachomatis urethritis (Prentice, Taylor-Robinson & Csonka, 1976). However, its effect against N. gonorrhoeae is related to the sensitivity of the strain to tetracycline. Against most strains minocycline has an MIC of <0.5 mg/l, and although four times more active than tetracycline against sensitive strains, it is not more active against resistant strains (Percival & Hart, 1977; Waterworth et al., 1979). A significantly lower incidence of post gonococcal urethritis after minocycline than ampicillin has been reported by some (Waterworth et al., 1979), but not by others (Waugh et al., 1979).

Rosaramicin is a new macrolide antibiotic with in vitro activity against Chlam. trachomatis (MIC 0.015 mg/l, Ridgway & Oriel, 1979) and is more active than penicillin, tetracycline or erythromycin against N. gonorrhoeae (Dutton, Duck & Eidus, 1978). Reports of clinical studies presented at the 11th International Congress of Chemotherapy at Boston show it to be more effective than ampicillin in the treatment of gonococcal and chlamydial infections in females and more effective than tetracycline in the treatment of non-chlamydia NSU in males. Also recently a β-lactamase plasmid has appeared in Haemophilus ducreyi (Brunton et al., 1979). In vitro, the macrolides were highly active against such strains (Feltham, Ronald & Albritton, 1979).

Tetracycline in vitro has bactericidal activity against gonococci and is synergistic with benzyl penicillin against β-lactamase producing tetracycline insensitive strains (Percival & Hart, 1979). Therefore, combination treatment beginning with the appropriate single dose of penicillin together with tetracycline which is then continued might prove effective against both chlamydial and gonococcal infection. If so, this would be particularly valuable in areas of high prevalence of β-lactamase producing and multiply resistant gonococci where cost is a significant factor affecting choice of therapy.

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References


Leading articles


**Building better β-lactams**

Since the discovery of the first penicillin by Fleming just over 50 years ago, organic chemists have composed literally thousands of variations on the original molecular theme. Only a minuscule proportion of all these penicillins and cephalosporins have proved to be useful to the clinician in the treatment of infectious diseases. But two recent developments promise an acceleration in the rate at which clinically useful new β-lactam antibiotics can be devised. One is a significant improvement in our understanding of the mechanisms of antibiotic action of these agents, and the other is an increasing appreciation of the potential scope of variations in the molecular structure of these antibiotics.

Fleming (1929) himself determined many important features of the antibacterial action of penicillin, but he was unable to elucidate its precise mode of action. Soon after the 'rediscovery' of penicillin by Florey and Chain and their colleagues around 1940, studies along several quite distinct lines yielded findings which eventually led to a coherent and temporarily satisfactory model: (1) bacterial cells exposed to penicillin lost their characteristic regular morphology and assumed bizarre forms (Gardner, 1940; Duguid, 1946); (2) radiolabelled penicillin bound to components of the bacterial cell membrane (Cooper, 1956); (3) precursors of cell wall mucopeptide accumulated in bacteria exposed to penicillin (Park & Johnson, 1949); and (4) several enzymes involved in synthesis of mucopeptide were inhibited by penicillin (Strominger, 1970).

By the late 1960s the following theory had been formulated to explain the antibacterial action of penicillin (Strominger & Tiper, 1965; Tipper & Strominger, 1965). Penicillin is structurally similar to the terminal D-alanyl-D-alanine dipeptide involved in the final cross-linking step in the assembly of the mucopeptide polymer of the bacterial cell wall. Because of this structural similarity, penicillin is capable of inhibiting the enzymes which catalyze this cross-linking transpeptidation reaction. Inhibition of cross-linking results in a cell lacking a rigid cell wall, one which will undergo lysis in a hypotonic environment. Integrity of the β-lactam ring is necessary for maintenance of the penicillin molecule in the configuration required for inhibition of the transpeptidase. All penicillins and cephalosporins were assumed to have this same mechanism of action.

A clearer view of the complexity of the actions of β-lactam antibiotics was revealed through investigation of the penicillin-binding proteins of the bacterial cell membrane (Blumberg & Strominger, 1974; Spratt & Pardee, 1975; Spratt, 1977; Spratt, 1980). Preparations of bacterial cell membranes exposed to radiolabelled penicillin, the membrane proteins separated by polyacrylamide gel electrophoresis, and binding of penicillin to specific proteins examined by radioautography. Eventually seven different proteins (designated 1A, 1B, 2, 3, 4, 5 and 6) to which penicillin G binds were identified. Binding of other penicillins and cephalosporins to specific proteins could also be measured by determining the degree to which these unlabelled compounds inhibit the binding of radiolabelled penicillin G (Spratt, 1975; Curtis et al., 1979). These studies yielded the unexpected result that whereas penicillin G bound to seven different proteins, most other β-lactam agents bound to only one or two of these proteins. The morphological effects of different β-lactam antibiotics were found to be determined by the protein to which the agent was bound. Drugs binding to proteins 1A and 1B (peni-