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Co-trimoxazole (Trimethoprim-sulfamethoxazole)
An Updated Review of its Antibacterial Activity and Clinical Efficacy

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Summary

Synopsis: *Co-trimoxazole*[1] *(trimethoprim-sulfamethoxazole) is a 'broad spectrum' antimicrobial which is active* in vitro *against a wide variety of micro-organisms. Clinical experience with this agent now spans a decade or more in many countries. While it is clearly established as the agent of first choice only in* Pneumocystis carinii *infections, it is effective in many other infectious diseases. Thus, it has been shown to be effective in acute and persistent or recurrent urinary tract infections (treatment and prophylaxis), ear, nose and throat infections (including β-lactamase producing* H. influenzae*), acute exacerbations of chronic bronchitis, enteric fever, gonorrhoea, prophylaxis in neutropenic patients, and in several other less well established areas of possible usefulness. Recent availability of a parenteral preparation has further expanded the potential clinical application of the drug.*

Co-trimoxazole has made an important contribution to the treatment of infectious diseases, and will continue to do so for some time to come, as additional clinical experience and newer developments further clarify its optimum role in antimicrobial chemotherapy, with better definition of the role of the combination preparation versus its individual components.

Pharmacodynamic Properties: Co-trimoxazole is a 'broad spectrum' antimicrobial agent. *In vitro* it is active against a wide range of organisms including Gram-positive and -negative aerobic bacteria, chlamydia, Nocardia (actinomycetes), some mycobacteria and protozoa and many anaerobic bacteria. Organisms not susceptible to co-trimoxazole include *Mycobacterium tuberculosis, Treponema pallidum, Pseudomonas aeruginosa* and *Mycoplasma* species. Against most Gram-negative bacteria the activity of co-trimoxazole exceeds that of ampicillin and is comparable to that of chloramphenicol.

Synergy or a summation effect between the 2 components (trimethoprim and sulphamethoxazole in a 1 : 5 ratio) has been demonstrated both *in vitro* and in animals in most studies investigating this consideration, although whether or not synergy occurs under clinical conditions is less clear. For most organisms the optimum ratio for maximum potentiation is about 1 : 20 (trimethoprim : sulphamethoxazole), which is the approximate ratio present in plasma after administration of the standard formulation. However, some potentiation can be demonstrated *in vitro* over a wide range of ratios, analogous to the wide range found in various body fluids.

Co-trimoxazole exerts its antimicrobial effect by inhibiting synthesis of tetrahydrofolic acid, the metabolically active form of folic acid. Sulphamethoxazole acts primarily through inhibiting synthesis of dihydrofolic acid, while trimethoprim acts as a competitive inhibitor of dihydrofolate reductase, the final enzyme in the pathway to tetrahydrofolic acid. It appears that the major net effect of this action is inhibition of thymidine synthesis.

In vitro, resistance to trimethoprim alone can be produced by serial passage techniques. The clinical relevance of these findings is uncertain since the chromosomal resistance to trimethoprim seen in clinical strains is not usually due to the type of resistance selected *in vitro* by serial passage, but development of resistance in this manner by sulphonamide-sensitive organisms is delayed or prevented with the addition of a sulphonamide to trimethoprim. Bacterial clinical isolates may display either intrinsic or acquired resistance to co-trimoxazole, and acquired resistance may be chromosomally mediated or involve R-factor plasmids.

Effects on faecal flora have usually included a major reduction or elimination of Enterobacteriaceae, but little effect on anaerobic flora. During chronic therapy such changes persist, but without overgrowth of *Pseudomonas* species or resistant Enterobacteriaceae; however, overgrowth by yeasts may occur.

Pharmacokinetic Properties: Both trimethoprim and sulphamethoxazole are well absorbed after oral administration. Peak blood concentrations after a single standard adult dose (trimethoprim 160mg, sulphamethoxazole 800mg) are about 1 to 2 μg/ml for tri-

1 'Bactrim' (Roche); 'Septra' (Burroughs Wellcome Co.); 'Septrin' (Wellcome Foundation Ltd).

methoprim and 30 to 50 μg/ml for free sulphamethoxazole. Steady-state blood levels, achieved in adults in 2 to 3 days with a standard dose regimen, are about 50% higher. Trimethoprim is more widely distributed to body tissues than is sulphamethoxazole, producing a wide range of trimethoprim : sulphamethoxazole concentration ratios in various body tissues and fluids. The concentration of trimethoprim equals or exceeds the simultaneous plasma concentration in several tissues or fluids (saliva, intracellular fluid, breast milk, prostatic tissue, sputum, lung tissue, vaginal secretions and urine), while sulphamethoxazole tissue and fluid concentrations are considerably lower than plasma concentrations with the exception of urine concentrations which are higher. Both components of the drug are bound to plasma proteins to a similar extent (about 45 and 66% for trimethoprim and sulphamethoxazole respectively).

Trimethoprim is excreted in the urine primarily in unchanged form, while sulphamethoxazole is excreted primarily as inactive metabolites. The elimination half-life of trimethoprim is about 11 hours and that of sulphamethoxazole is about 9 hours. In the presence of severe renal failure sulphamethoxazole metabolites may accumulate, and dosage adjustments are required. In infants the elimination half-life of both drugs is longer than in the adult, but in children it may be shorter. There may be some reduction in clearance in the elderly, but important prolongation of half-life does not occur.

Therapeutic Use: Comparative studies have shown co-trimoxazole to be an effective treatment for both acute and persistent or recurrent urinary tract infections, even in patients with severe renal impairment. A single dose is often effective in uncomplicated bacterial cystitis. It is also effective in the prophylaxis of urinary tract infection. For these indications it is at least as effective as ampicillin, amoxycillin, cephalosporins or other commonly used agents such as nalidixic acid or nitrofurantoin. However, with the possible exception of chronic urinary tract infections, it appears that trimethoprim alone is as effective as the combination product in this area of use.

In ear, nose and throat infections co-trimoxazole is generally comparable in efficacy to ampicillin or amoxycillin, and importantly is highly effective against β-lactamase producing *Haemophilus influenzae.*

In the treatment or prevention of acute exacerbations of bronchitis co-trimoxazole is at least as effective as other frequently used drugs such as ampicillin, amoxycillin or various tetracyclines. It is also effective in Gram-negative pneumonias.

Co-trimoxazole is extremely effective in treating gonorrhoea when given for several days, but single dose or single day regimens may be unsatisfactory in the presence of relatively resistant strains of *Neisseria gonorrhoeae.* Variable results have been reported in non-gonococcal urethritis, and there are no studies comparing co-trimoxazole with tetracycline or erythromycin in this condition. The drug is not effective in treating syphilis.

Co-trimoxazole is effective in a number of enteric infections. It is a particularly useful alternative possibility (to chloramphenicol, parenteral ampicillin or oral amoxycillin) in *Salmonella typhi* infection, and a 5-day course is effective in acute shigellosis in adults or children.

In *Pneumocystis carinii* infections co-trimoxazole is the agent of first choice, with about two-thirds of patients responding. It also seems useful prophylactically in 'lower' doses in high risk patients to prevent *Pneumocystis carinii* infection.

In neutropenic patients co-trimoxazole (alone or in combination) may offer a useful alternative to non-absorbable oral antibiotics for prophylactic use in preventing or minimising infections. However, the possible effects of long term administration of co-trimoxazole (e.g. during bone marrow recovery following intensive cytotoxic therapy) needs further clarification.

Limited experience in some other areas of use, such as meningitis, nocardiosis, soft tissue or bone infections and acne have been encouraging, but such findings need further study before definitive statements of efficacy can be made.

Adverse Effects: The most common adverse reactions to co-trimoxazole are skin eruptions and mild gastrointestinal symptoms, each occurring in up to about 3% of patients. Haematological abnormalities, including thrombocytopenia, leucopenia or agranulocytosis, anaemia, eosinophilia or sulphaemoglobinaemia occur in less than 0.5% of adult patients. Haematological effects reported in children to date have not been clinically important. Patients with known folic acid or vitamin B_{12} deficiency are at increased risk of the antifolic acid effects of the drug. A predictable slight increase in serum creatinine and decrease in creatinine clearance occurs with co-trimoxazole administration, and rarely (usually in patients with underlying kidney disease) true renal dysfunction or renal failure may develop. Adverse hepatic effects (hepatitis, hepatic necrosis, intrahepatic cholestasis) have been reported in a few patients, as have serious cutaneous eruptions and other allergic reactions. As might be expected, trimethoprim used alone produces a lower overall incidence of side effects than co-trimoxazole.

Dosage and Administration: The usual recommended adult dosage is 2 standard tablets (trimethoprim 160mg, sulphamethoxazole 800mg) twice daily, but this can be increased in severe infections. In children the usual oral dose is trimethoprim 4 mg/kg, sulphamethoxazole 20 mg/kg given twice daily. The drug can also be given parenterally if necessary, by intramuscular injection (intramuscular preparation available in some countries) or intravenous infusion. In the presence of severe renal failure dosage should be reduced. (For detailed recommended dosage information on specific dosage forms the clinician should consult the product literature.)

1. Pharmacodynamic Properties

1.1 Spectrum of Activity

Co-trimoxazole (trimethoprim-sulphamethoxazole) is an antimicrobial agent composed of a fixed combination of a diaminopyrimidine and a sulphonamide. It was developed by the systematic investigation of a series of compounds known to be specific enzyme inhibitors of bacterial folate synthesis (Burchall, 1979; Hitchings and Bushby, 1961). *In vitro* the combination is decidedly more active than either agent is alone (Bushby, 1977). In 1968, under the generic name of 'co-trimoxazole', the combined agent was marketed for general use in the United Kingdom; 5 years later it was introduced into the United States but with the generic title of 'trimethoprim-sulfamethoxazole' (for an early review see Avery, 1971).

Accurate and reproducible antimicrobial sensitivity testing requires considerable care to ensure that inhibitors (e.g. para-aminobenzoic acid, thymine or thymidine) are not present in the media and that the inoculum size is standardised. Non-standardised media, such as Mueller-Hinton agar, which may be unreliable in respect to thymidine content are less suitable for *in vitro* testing than suitable standardised media. These factors are especially critical when attempting to demonstrate bactericidal activity and synergy and when working with particular organisms such as *Haemophilus influenzae* (Adeniyi-Jones et al., 1973; Bach et al., 1973; Brumfitt et al., 1973; Bushby, 1973a,b; Everett and Kishimoto, 1973; Jarvis and Scrimgeour, 1970; Leers, 1975; Marks and Weinmaster, 1975; Marks et al., 1973b; Moody and Young, 1975; Northrup et al., 1972; Ritzerfeld and Hasch, 1972;

Rudoy et al., 1974; Seligman, 1973; Yoshikawa et al., 1975; Yourassowsky et al., 1974).

Co-trimoxazole has a wide range of activity (table I) against both Gram-positive and Gram-negative aerobic bacteria, chlamydia, actinomycetes (*Nocardia*), mycobacteria (*Mycobacterium marinum*) and protozoa (*Pneumocystis carinii*; see also section 3.6.1, *Plasmodium* species, and limited activity against *Toxoplasma gondii*) [Bushby, 1973a; Overman, 1980; Winslow and Pankey, 1980]. Many anaerobic organisms, including *Bacteroides fragilis,* can be shown to be susceptible *in vitro* as well (Wüst and Wilkins, 1978).

Aerobic Gram-negative bacteria are the principal targets of co-trimoxazole in clinical usage. In table II, the activity of co-trimoxazole is compared with that of other broad spectrum antimicrobials against micro-organisms isolated by the clinical microbiology laboratory at the Bronx Veterans Administration Medical Center during 1979. As illustrated, the activity of co-trimoxazole exceeds that of ampicillin, cephalothin, and tetracycline,

Table I. In vitro antimicrobial spectrum of co-trimoxazole (after Bushby, 1973a and other sources)

Usually susceptible[1]	Possibly susceptible	Resistant
Escherichia coli[2]	*Proteus* species, indole-positive	*Mycobacterium tuberculosis*
Proteus mirabilis	*Serratia marcescens*	*Treponema pallidum*
Klebsiella pneumoniae	*Pseudomonas* species (non-aeruginosa)	*Pseudomonas aeruginosa*
Enterobacter species	*Providencia* species	*Mycoplasma* species
Citrobacter species	*Campylobacter fetus*	
Acinetobacter species	*Achromobacter* species	
Salmonella typhi	*Bacteroides* species	
Non-typhi Salmonella	*Streptococcus faecalis (?)*[3]	
Shigella species	*Toxoplasma gondii*	
Vibrio cholerae	*Plasmodium* species	
Yersinia enterocolitica	*Mycobacterium marinum*	
Brucella species	*Legionella* species	
Aeromonas hydrophilia		
Yersinia pestis		
Haemophilus influenzae		
Neisseria meningitidis		
Neisseria gonorrhoeae		
Streptococcus faecalis (?)[3]		
Streptococcus pneumoniae		
Streptococcus pyogenes		
Streptococcus agalactiae		
Streptococcus viridans		
Staphylococcus aureus		
Staphylococcus epidermidis		
Listeria monocytogenes		
Chlamydia trachomatis		
Nocardia species		
Pneumocystis carinii		

1 More than 75% of strains susceptible.

2 Including many strains of enterotoxigenic *Escherichia coli.*

3 Although *S. faecalis* is usually cited in the literature as being relatively non-susceptible, such findings may be a result of thymine or thymidine in the test medium.

equals that of chloramphenicol, and very narrowly falls short of that of both cefamandole and cefoxitin.

Most organisms are 20- to 100-fold more sensitive to trimethoprim alone than to sulphamethoxazole alone on a weight basis, but certain exceptions exist such as *Neisseria* species, *Nocardia* species, *Brucella* species, *Bacteroides fragilis,* and *Chlamydia trachomatis,* which are more susceptible to the sulphonamide (Austin and Holmes, 1975; Bennett and Jennings, 1978; Farrell and Robertson, 1980; Johannisson et al., 1979; Rein et al., 1980; Then and Angehrn, 1979).

In combination, these drugs potentiate one another against many organisms, although some studies describing potentiation may have involved sub-inhibitory concentrations of the two agents. Potentiation has been demonstrated by serial dilution techniques and disk sensitivity studies in antagonist free media *in vitro,* and by animal protection experiments *in vivo* (Böhni, 1969; Grünberg, 1973; Seydel et al., 1973). Although antagonism of the combination has also been reported (Anderson et al., 1974; Lewis et al., 1974), in most tests either synergy or a summation effect has been observed. Moderate resistance to a single member of the pair, particularly to sulphamethoxazole, does not necessarily preclude synergy when the 2 drugs are combined (Acar et al., 1973; Grey et al., 1979a; Grüneberg et al., 1975), although many clinical isolates show 'high level' resistance to sulphamethoxazole and in these strains synergy does not occur (Hamilton-Miller, 1979).

Sulphamethoxazole alone is bacteriostatic *in vitro,* but *in vitro* trimethoprim alone and the combination may be bactericidal (Then and Angehrn, 1974). For most organisms the ratio of the 2 drugs in combination that allows maximum potentiation is equal to the ratio of their individual minimum inhibitory concentrations (Bushby, 1973a). This optimal ratio is approximately 1 : 20, trimethoprim : sulphamethoxazole, which is the ratio present in plasma after administration of the standard 1 : 5 (trimethoprim : sulphamethoxazole) tablet. Although the 1 : 20 ratio of the combination produces a peak synergistic effect, significant potentiation is usually demonstrable *in vitro* over the wide range of ratios achieved in most body compartments other than plasma (see section 2.2) [Bushby and Bushby, 1975; Hansen, 1978].

1.2 Mechanism of Action

The 2 components of the drug are both inhibitors of bacterial synthesis of the metabolically active form of folic acid, tetrahydrofolic acid (fig. 1).

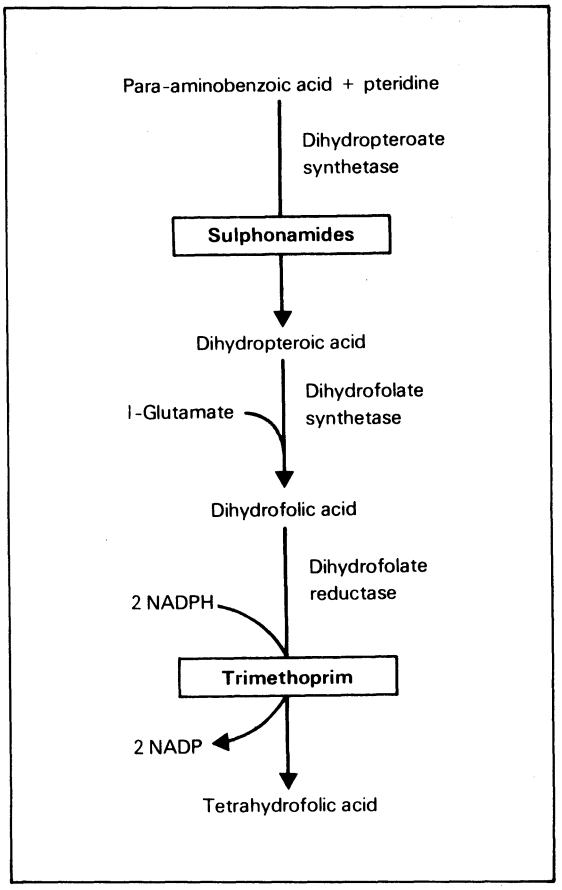

Fig. 1. Site of action of trimethoprim and the sulphonamides.

Sulphamethoxazole is a structural analogue of para-aminobenzoic acid (fig. 2), inhibiting synthesis of dihydrofolic acid. Trimethoprim (fig. 3) is a structural analogue of the pteridine portion of dihydrofolic acid, acting as a competitive inhibitor of dihydrofolate reductase, the final enzyme in the pathway to tetrahydrofolic acid (Burchall, 1973; Bushby, 1977). Enzyme inhibition by trimethoprim, however, increases the concentration of dihydrofolic acid, and it has been speculated this may drive the reaction to the right, partially reversing the metabolic block induced by the drug. This effect could be minimised by the sulphonamide component of the drug combination, which prevents synthesis and accumulation of new dihydrofolic acid (Hitchings, 1973). Whether sequential enzymatic blockade (Hitchings and Burchall, 1965), additional partial inhibition of dihydrofolate reductase by the sulphonamide (Golde et al., 1978; Poe, 1976), improved binding of trimethoprim to dihydrofolate reductase as a result of sulphonamide presence (Lacey, 1979), or a combination of such effects is primarily responsible for the enhanced activity of the combination remains uncertain.

The key chemotherapeutic effect of co-trimoxazole seems to be inhibition of thymidine synthesis, for extremely small concentrations of the nucleoside can reverse the antimicrobial action of the drug *in vitro* (Amyes and Smith, 1974; Then and Angehrn, 1973). Consistent with this concept, mutant bacteria incapable of synthesising thymidine are dependent on its presence for growth, and

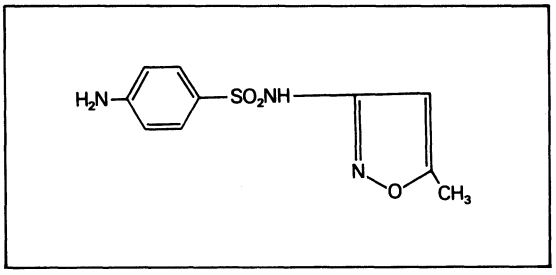

Fig. 2. Structural formula of sulphamethoxazole.

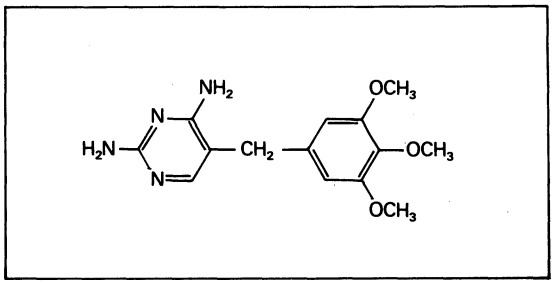

Fig. 3. Structural formula of trimethoprim.

these strains are appropriately indifferent to the action of the combination of agents (George and Healing, 1977; Maskell et al., 1978) [see section 1.3.3].

1.3 Development of Resistance

1.3.1 Chromosomally Mediated Resistance

In the laboratory, mutants resistant to trimethoprim can be produced by serial passage of heavy inocula of initially sensitive organisms in media containing increasing concentrations of trimethoprim. Development of resistance in this manner can be delayed or prevented by addition of a sulphonamide, provided the organism is sensitive to the sulphonamide (Darrell et al., 1968; Grünberg and Beskid, 1977).

The biochemical mechanism of resistance in most of these mutant organisms is unknown, but their clinical significance seems minimal as they appear grossly defective *in vitro* and have not been observed to arise *in vivo* after administration of trimethoprim alone (Knothe, 1979; Lacey et al., 1980b; Pancoast et al., 1980; Stamm et al., 1980; Toivanen et al., 1976). Nevertheless, concern over the ease with which trimethoprim resistance could be induced *in vitro* was at least partially responsible for the initial, and since revoked, decision not to release trimethoprim as a single agent.

Clinical isolates may have either intrinsic or acquired resistance to co-trimoxazole. Early studies

in Europe suggested that 90% of organisms with acquired resistance had chromosomally mediated resistance and the remaining 10% had R-factor plasmids (Amyes et al., 1978; Grey et al., 1979b), but more recent studies have shown a much higher proportion of resistant strains with R-factor plasmids (see below). Emergence of resistance during a course of therapy with co-trimoxazole or trimethoprim alone for an acute infection is an unusual event, although it has been described with enterococcal infections (Chattopadhyay, 1972). Evidence from Europe and the UK, where co-trimoxazole has been in use for more than a decade, indicates that the incidence of resistance among nosocomial isolates, particularly Klebsiella, *E. coli* and *Proteus mirabilis*, is slowly increasing with a disproportionate rise in the number possessing R-factors (Amyes et al., 1978; Hamilton-Miller et al., 1981; Towner et al., 1980).

It is still too soon to evaluate the long term effect of the use of trimethoprim alone (see Brogden et al., 1982) on the rate of development of resistance in a given area, but a recent report from Turku, Finland, where the single agent has been available for 5 years, showed a higher incidence of resistance than observed in Europe in general. The incidence of resistance to trimethoprim in Turku is also higher than reported for other regions in Finland, where trimethoprim has been less widely prescribed (Huovinen and Toivanen, 1980). However, the difficulties of making such comparisons, and findings of a recent survey, suggest it cannot be assumed from data presently available that there is a simple association between the use of trimethoprim alone and the development of resistance (Huovinen et al., 1982).

The biochemical basis of chromosomally mediated resistance in most strains of *Escherichia coli* and Klebsiella appears to be due to production of a dihydrofolate reductase enzyme with reduced susceptibility to trimethoprim. In some of these strains increased dihydrofolate reductase activity is also a contributing factor (Grey et al., 1979b). Resistance in other organisms, for example *Pseudomonas aeruginosa,* may be due to relative impermeability of the bacterial cell wall to trimethoprim (Hitchings, 1973).

1.3.2 Plasmid-mediated Resistance

A variety of plasmids, belonging to the I, P, or

Table II. Comparative susceptibility (per cent of isolates susceptible) of Gram-negative micro-organisms isolated at the Bronx Veterans Administration Medical Center in 1979

Drugs[1]	*Escherichia coli*	*Klebsiella* species	*Enterobacter* species	*Proteus*, indole-negative	*Proteus*, indole-positive	*Serratia marcescens*
Co-trimoxazole[2]	88	89	75	81	69	55
Ampicillin	77	4	14	72	21	2
Cephalothin	84	83	17	85	15	3
Cefamandole	96	92	74	95	81	20
Cefoxitin	98	95	31	95	81	63
Chloramphenicol	93	87	79	82	58	74
Tetracycline	75	78	78	3	23	8

1 Susceptibility testing performed by disk diffusion on Mueller-Hinton agar without the addition of lysed horse blood.
2 Only urinary isolates tested for susceptibility.

W compatibility groups, mediate resistance to trimethoprim, principally by coding for at least 3 different drug-resistant dihydrofolate reductase enzymes (Pattishall et al., 1977; Tennhammer-Ekman and Sköld, 1979; Towner, et al., 1979).

These enzymes are characterised by a molecular weight distinctly greater than that of the native enzyme. Among the different dihydrofolate enzymes coded for by the various plasmids, some are totally insensitive to trimethoprim while others show a substantially higher susceptibility. The latter, however, are synthesised in 10- to 20-fold greater amounts than the chromosomally determined enzyme (Amyes and Smith, 1978; Stone and Smith, 1979; Tennhammer-Ekman and Sköld, 1979). A rare type of R-factor has been described that contains a mutator gene modulating a chromosomally directed permeability barrier (Amyes and Smith, 1975).

Organisms with plasmid-conferred resistance are resistant to extremely high concentrations of trimethoprim, greater than 1000 μg/ml (Datta and Hedges, 1972). Generally, R-factors to trimethoprim usually code for concomitant sulphonamide resistance, and less frequently for a variety of other antibiotics as well (Towner et al., 1980). Growth in 1000 μg/ml of trimethoprim was initially regarded as a suitable screening test for detection of R-factor mediated resistance, but more recent data suggest that plasmid-mediated resistance is not demonstrable in 25% of such highly resistant strains (Towner et al., 1980; West and White, 1979).

Spread of R-factor resistant bacteria has been observed both in man and animals, but in view of the wide use of co-trimoxazole and the number of different R plasmids extant in the community, it is surprising how infrequently this occurrence has been documented (Grüneberg and Bendall, 1979; Richards et al., 1978). It is of particular concern that genes mediating trimethoprim resistance have now been identified on 2 transposons (tn 7 and tn 402), which increase the capacity of bacteria to alter their DNA content (Richards et al., 1978). Obviously there is a great need for continuing surveillance, as illustrated by a recent case report suggesting *in vivo*-acquired resistance of *Salmonella typhi* to both chloramphenicol and co-trimoxazole (Datta et al., 1981).

1.3.3 Thymidine Dependence

An infrequent but well defined type of trimethoprim resistance is known as thymidine-thymine dependence. Approximately 0.5 to 1.0% (less in some laboratories) of trimethoprim-resistant clinical isolates are mutant organisms which have lost the capacity to synthesise thymidine, and must depend on an exogenous source of this compound for growth (Grey et al., 1979b). Because trimethoprim interferes with thymidine synthesis, this action becomes irrelevant, and as a result the drug is not antibacterial. Such organisms are usually recovered from specimens from patients receiving chronic therapy with co-trimoxazole for treatment of urinary tract (frequently superimposed on renal calculi), bone or lung infections (George and Healing, 1977; Maskell et al., 1978). However, they appear to be increasing in incidence, especially among enterococci, and have been isolated even after short term therapy (Haltiner et al., 1980). It is important to point out that failure of these organisms to grow on agar plates used for co-trimoxazole susceptibility testing is due to the lack of thymidine in the media rather than an antimicrobial effect of the drug.

1.4 Effect on Faecal Flora

The administration of co-trimoxazole, even in dosages as low as 1 standard tablet (80mg trimethoprim and 400mg sulphamethoxazole) per week, may have demonstrable effects on the faecal flora. In most studies the enterobacteriaceae have been diminished significantly in number or eliminated, with no major alteration in the anaerobic flora and no consistent change in the enterococci. Of particular significance, these changes persisted with chronic therapy without overgrowth by

Pseudomonas species, staphylococci, or resistant Enterobacteriaceae (Cattell et al., 1976; Grüneberg et al., 1976; Knothe, 1973; Naff, 1971; Stamey et al., 1977). The latter phenomenon is attributed to 'colonisation resistance' provided by the undisturbed anaerobic flora (Van der Waaij et al., 1971, 1972). However, in a more recent diarrhoea prevention study conducted in Mexico, administration of trimethoprim alone or co-trimoxazole resulted in emergence of high level trimethoprim resistance in faecal *E. coli*, with no changes in the number of faecal Gram-negative bacteria in most patients (Murray et al., 1982). Overgrowth by yeasts may be a problem in some patients (Hughes et al., 1977). Trimethoprim alone, but not sulphamethoxazole, will produce a similar effect on the faecal ecology (Knothe, 1979; Stamm et al., 1980). The changes seen in most studies (see above) can be expected to revert back to normal within 1 month after co-trimoxazole is discontinued, but repopulation occurs with *Escherichia coli* of a new serotype (Knothe, 1979).

2. *Pharmacokinetic Properties*

Several pharmacokinetic considerations related to absorption, protein binding and elimination pattern led to the selection of sulphamethoxazole as the sulphonamide component in the fixed-dose combination, co-trimoxazole (for review, see Patel and Welling, 1980). However, important differences do exist between trimethoprim and sulphamethoxazole for certain pharmacokinetic properties, such as metabolic fate and volume of distribution, which may be of clinical relevance (see below).

2.1 Absorption and Plasma Concentrations

Both trimethoprim and sulphamethoxazole are well absorbed from the upper intestinal tract (Patel and Welling, 1980), even in the presence of acute gastroenteritis (Marks et al., 1973a), or concomitant administration of cimetidine (Rogers et al., 1980) or metoclopramide (unpublished data, on file Burroughs Wellcome). Peak blood levels after a single standard adult dose of 160mg trimethoprim and 800mg sulphamethoxazole are 1 to 2 μg/ml for trimethoprim, 40 to 60 μg/ml for total sulphamethoxazole and 30 to 50 μg/ml for free sulphamethoxazole (Kremers et al., 1974; Nolte and Büttner, 1974). Peak blood concentrations occur about 1 to 4 hours after ingestion.

When the usual dosage regimen of 160mg trimethoprim and 800mg sulphamethoxazole is given every 12 hours, a steady-state is achieved in adults after 2 to 3 days, and the blood levels of both drugs are approximately 50% greater than the peak levels after a single dose (Brumfitt et al., 1973; Dornbusch, 1976). The steady-state concentration of each component is directly proportional to the quantity administered (Dornbusch, 1976). With very high doses, such as 20 mg/kg trimethoprim and 100 mg/kg sulphamethoxazole as used in the treatment of pneumocystis infection, progressive drug accumulation may occur for 7 to 9 days (Hughes et al., 1978; Winston et al., 1980).

2.2 Distribution

As a consequence of lipophilic properties trimethoprim is more widely distributed throughout the body than is sulphamethoxazole (Hansen, 1978; Wilkinson and Reeves, 1979). This is reflected in the larger apparent volume of distribution for trimethoprim (about 100 to 120L) than for sulphamethoxazole (12 to 18L) [Patel and Welling, 1980]. The 1 : 5 weight ratio of trimethoprim to sulphamethoxazole in the standard tablet has been chosen to achieve an approximate 1 : 20 ratio of peak serum concentrations of the 2 drugs, which is optimum for synergistic antimicrobial activity for most organisms. Because of unequal distribution, however, a wide range of concentration ratios is actually achieved in other tissues and fluids (see table III).

The concentration of trimethoprim is equal to or exceeds the simultaneous plasma level in saliva (Eatman et al., 1977; Fowle, 1973; Jordan et al., 1975), intracellular fluid (Fowle, 1973), breast milk (Reeves, 1971), prostatic tissue (Dabhoiwala et al., 1976; Madsen et al., 1976; Oosterlinck et al., 1975; see also section 3.1.5 for more detailed discussion); sputum (Hansen et al., 1973a; Jordan et al., 1975), lung tissue (Hansen et al., 1973b), vaginal secretions (Stamey and Condy, 1975), bile (Rieder, 1973b), and urine (Bach et al., 1973). Lower, but potentially therapeutic concentrations have been documented for trimethoprim in aqueous humour (10 to 87% plasma level; Pohjanpelto et al., 1974; Salmon et al., 1975), cerebrospinal fluid (30 to 50% plasma level; Reeves, 1971; Svedhem and Iwarson, 1979); fetal (cord) blood (Reid et al., 1975), amniotic fluid (Ylikorhala et al., 1973), seminal fluid

Table III. Relative concentration of trimethoprim and sulphamethoxazole in various body tissues and fluids in humans following administration of co-trimoxazole. Data from various sources (see section 2.2)

Tissue or fluid	TMP[1] level in tissue/ TMP level in serum	SMX[2] level in tissue/ SMX level in serum	Approximate ratio TMP/SMX in tissue or fluid
Saliva	2.0	0.03	3 : 1
Middle ear fluid	0.75	0.2	1 : 6
Human breast milk	1.25	0.1	1 : 2
Prostatic tissue	2.0	0.35	1 : 3
Seminal fluid	0.5	0.3	1 : 10
Epididymis	2.0	0.51	1 : 5
Sputum	1.5	0.2	1 : 3
Lung parenchyma	3.5	0.3[3] (?)	1 : 2[3] (?)
Vaginal secretions	1.5	0.01	8 : 1
Fetal blood	0.6	0.8	1 : 30
Amniotic fluid	0.8	0.5	1 : 10
Aqueous humour	0.4	0.25	1 : 10
Cerebrospinal fluid	0.5	0.4	1 : 15
Bile	1.0	0.4	1 : 8
Bone			
Spongy	0.67	-	-
Compact	0.1	-	-
Synovial fluid	1.0	1.0	1 : 20

1 TMP = trimethoprim.
2 SMX = sulphamethoxazole.
3 Presumptive, based on animal data.

(Gnarpe and Friberg, 1976), abscess cavity (Greene et al., 1975), bone marrow and spongy bone (67% plasma level) [Hansen et al., 1975], and compact bone (10 to 20% plasma level) [Hansen et al., 1975].

In contrast, the concentration of active sulphamethoxazole in all tissues and fluids except urine is considerably lower than plasma levels. Nevertheless, fairly good penetration is documented for cerebrospinal fluid (Wilkinson and Reeves, 1979), bile (Rieder, 1973b), aqueous humour (Pohjanpelto et al., 1974; Salmon et al., 1975), and amniotic fluid (Ylikorhala et al., 1973) [see table III].

Trimethoprim is about 45% and sulphamethoxazole 66% bound to human plasma proteins (Patel and Welling, 1980).

2.3 Elimination

After absorption trimethoprim is metabolised to only a small extent (5 to 15%); most of the metabolites have limited antibacterial activity (Rieder, 1973a; Schwartz et al., 1970; Sigel et al., 1973). In contrast, sulphamethoxazole undergoes biotransformation to inactive compounds. Indeed, 20 to 25% of total plasma sulphamethoxazole consists of various transformation products, among which the N_4 acetyl derivative predominates (Rieder et al., 1974).

About one-half of a dose of trimethoprim is excreted in the urine over 24 hours, 80% of which appears in the unchanged form (Bach et al., 1973; Kremers et al., 1974; Sigel et al., 1973). Because trimethoprim is a weak base, renal clearance improves with increasing urine acidity (Bergan and Brodwall, 1976; Craig and Kunin, 1973a; Welling et al., 1973). In the presence of normal renal function, a single dose of 160mg trimethoprim has been shown to produce mean urinary concentrations in excess of 100 μg/ml during the first 4 hours, in excess of 50 μg/ml between 8 and 24 hours (Bach et al., 1973), and levels inhibitory for most urinary pathogens for 3 days.

A similar fraction (45 to 70%) of a single dose of sulphamethoxazole is excreted in urine over 24 hours, but only 20% is present in an active form (Kremers et al., 1974; Rieder, 1973a). Renal clearance of sulphamethoxazole (a weak acid) rises as the urinary pH becomes more alkaline (Craig and Kunin, 1973a; Welling et al., 1973). In most patients receiving co-trimoxazole the urinary concentration of active sulphamethoxazole approximately equals that of trimethoprim (Bergan and Brodwall, 1976; Craig and Kunin, 1973a).

Thus, the concentrations of trimethoprim and sulphamethoxazole normally observed in urine following administration of co-trimoxazole exceed the *in vitro* MIC values for most susceptible organisms (Bach et al., 1973; Rieder et al., 1974).

Both drugs have a similar elimination half-life. The average values which have been reported are about 11 hours and 9 hours for trimethoprim and sulphamethoxazole, respectively (Patel and Welling, 1980). Elimination half-lives may increase in the presence of severe renal failure (see section 2.4).

2.4 Effects of Renal or Hepatic Disease on Disposition

Renal insufficiency diminishes the clearance of trimethoprim, but the rate of decline is less than that of creatinine. Thus, the half-life of trimethoprim is still less than 3 times normal even when creatinine clearance is less than 10 ml/min (Rieder et al., 1974). Some investigators (Baethke et al., 1972; Rieder et al., 1974) have claimed no effect of abnormal renal function on the half-life of active sulphamethoxazole, but another group (Craig and Kunin, 1973a) found a 3-fold prolongation. All agree, however, that sulphamethoxazole metabolites accumulate when creatinine clearance falls below 30 ml/minute, and dosage adjustment is necessary in such patients. Importantly, effective concentrations of trimethoprim and possibly of sulphamethoxazole are achievable in the urine even in patients with severely depressed renal function (Craig and Kunin, 1973a; Rieder et al., 1974).

Trimethoprim and active sulphamethoxazole, but not its metabolites, are haemodialysable. Be-

Table IVa. Summary of therapeutic trials comparing co-trimoxazole (TMP, SMX) with sulphonamides or other sulphonamide combinations in treatment of acute urinary tract infection

Reference	Patient population	Number of evaluable patients	Treatment[1]	Results	
				cured (%)[2]	follow-up
Bailey and Pearson (1980)	Adult women	40	TMP 160mg, SMX 800mg, q12h × 5d	98	7 days
		40	TMP 90mg, SDZ 410mg, q12h × 5d	95	7 days
		40	SMZ 1000mg, q8h × 5d	90	7 days
Bergan and Skjerven (1979)	Adults	42	TMP 160mg, SMX 800mg, bid × 14d	97.6	5-14 days
		42	SMX 1000mg, bid × 14d	92.2	5-14 days
Buckwald et al. (1982)	Adult women	19	TMP 160mg, SMX 800mg, × 1 dose	95	28 days
		20	TMP 320mg, SMX 1600mg, × 1 dose	95	28 days
		20	SXZ 1g × 1 dose	85	28 days
		17	SXZ 2g × 1 dose	88	28 days
Feldman et al. (1975)	Children 4m to 18y (mean 6.25 years): 23 girls, 3 boys	13	TMP 40 or 80mg, SMX 200 or 400mg tid × 28d	100 54	⩽3 months ⩽12 months
		13	SMX 500 or 1000mg, tid × 28d	54 31	⩽3 months ⩽12 months
Howard and Howard (1978)	Children 6m to 10y	53	TMP 12 mg/kg/day, SMX 60 mg/kg/day in 3 doses × 10d	87	4 days
		46	SMX 50 or 65 mg/kg/day in 3 doses × 10d	87	4 days

Reeves et al. (1979)	Hospitalised adults	69	TMP 160mg, SMX 800mg, q12h × 7d	78 63 (42/66)	1 week 5 weeks
		76	Tetroxoprim 50 or 100mg, SDZ 250mg, q12h × 7d	71 60 (45/75)	1 week 5 weeks
Seppänen (1980)	Adults	40	TMP 160mg, SMX 800mg, bid × 7d	93	Immediate
		45	SDZ 250mg, TMP 160mg, bid × 7d	98	Immediate
Sietzen and Rugendorff (1981)	Adults	108	TMP 160mg, SMX 800mg, bid × 7d	96 87 (88/101)	Immediate 2-3 weeks
		99	TMP 180mg, SDZ 820mg, once daily × 7d	93 90 (84/93)	Immediate 2-3 weeks
Skjerven and Bergan (1979)	Adults	42	TMP 160mg, SMX 800mg, bid × 14d	97.6	5-14 days
		36	TMP 90mg, SDZ 410mg bid × 14d	97.2	5-14 days

1 TMP = trimethoprim; SMX = sulphamethoxazole; SDZ = sulphadiazine; SMZ = sulphamethizole; SXZ = sulfisoxazole (sulphafurazole); AMP = ampicillin; CXN = cephalexin; NFN = nitrofurantoin. All drugs were given orally.

2 Criteria for cure was sterile urine in most studies.

3 An ellipsis indicates not stated.

Table IVb. Summary of therapeutic trials comparing co-trimoxazole (TMP, SMX) with drugs other than sulphonamides (see table IVa) in treatment of acute urinary tract infection

Reference	Patient population	Number of evaluable patients	Treatment[1]	Results		
				cured (%)[2]	follow-up	relapse and reinfections
Comparisons with penicillins						
Böse et al. (1974)	Children	55	TMP 5 mg/kg/d, SMX 25 mg/kg/d, in 2 doses × 21d	95	4 days	3 reinfections
		40	AMP 100 mg/kg/d in 4 doses × 21d	73	4 days	5 reinfections, 6 relapses
Brumfitt and Pursell (1972)	Men and women; various population groups	83	TMP 160mg, SMX 800mg, q12h × 7d	83	4-6 weeks	Only relapses considered failures; number of reinfections not given
		84	TMP 200mg, q12h × 7d	83	4-6 weeks	
		88	AMP 1000mg, q12h × 7d	73	4-6 weeks	
		84	CXN 1000mg, q12h × 7d	69	4-6 weeks	
Harbord and Grüneberg (1981)	Adults (all women except for 1 man)	24	TMP 320mg, SMX 1600mg × 1 dose	88	7 days	. . .[4]
		20	AMOX 3g × 1 dose	90	7 days	
		20	TMP 400mg × 1 dose	95	7 days	
Ravn (1981)	Hospitalised adults, complicated infections	19	TMP 160mg, SMX 800mg, bid × 10d	42	2 weeks	3 relapses, 8 reinfections
		23	PIVMEC 200mg, PIVAMP 250mg, bid × 10d	35	2 weeks	5 relapses, 10 reinfections
Wren (1972)	Adult women	35	TMP 160mg, SMX 800mg, bid × 5-8d	91	2 days	. . .
		36	AMP 500mg q6h × 5-8d	66	2 days	
Comparisons with cephalosporins						
Brumfitt and Pursell (1972) (See above)						
Gower and Tasker (1976)	Adult women	46	TMP 160mg, SMX 800mg, bid × 7d	96 85 (33/39)	2 weeks 6 weeks	5 relapses, 1 reinfection
		47	CXN 1000mg bid × 7d	68 59 (24/41)	2 weeks 6 weeks	11 relapses, 6 reinfections
Rous (1981)	Adult women	26	TMP 160mg, SMX 800mg q12h × 10d	100	≤ 4-6 weeks	1 patient only (which treatment group not stated)
		30	CDN 250mg q12h × 10d	100	≤ 4-6 weeks	

Other comparative studies						
Cartwright et al. (1982)	Adults (4 men)	24	TMP 160mg, SMX 800mg, bid × 7d	92	7 days	1 relapse, 1 reinfection
		30	TMP 300mg once daily × 7d	93	7 days	2 reinfections
de Jersey and Wooller (1982)	Adults	14	TMP 160mg, SMX 800mg, q12h × 14d	100	≤ 4-6 weeks	...
		22	CIN 500mg q12h × 14d	81[3]	≤ 4-6 weeks	
Iravani et al. (1981)	Adult women	58	TMP 160mg, SMX 800mg, q12h × 10d	98	Immediate	2 relapses, 14 reinfections
				93	7 days	
				72	4 weeks	
		65	NA 1g q6h × 7d	99	Immediate	4 relapses, 12 reinfections
				90	7 days	
				74	4 weeks	
Lövestad et al. (1976)	...	27	TMP 160mg, SMX 800mg, bid × 10d	85	7 days	...
		18	NFN 50mg, qid × 10d	38	7 days	
Männistö (1976)	Adults	27	TMP 160mg, SMX 800mg, bid × 14d	74	5 days	4 relapses, 0 reinfections
		26	TMP 200mg bid × 14d	58	5 days	4 relapses, 2 reinfections
		29	OA 750mg bid × 14d	66	5 days	4 relapses
Schaeffer et al. (1981)	Adult women	20	TMP 160mg, SMX 800mg, bid × 10d	95	7 days	2 relapses
				75 (12/16)	30 days	2 reinfections
		20	CIN 500mg bid × 10d	100	7 days	1 relapse, 1 reinfection
				87 (13/15)	30 days	
Trimethoprim Study Group (1981)	Adult women	33	TMP 160mg, SMX 800mg, bid × 7d	100	7 days	Reinfections not distinguished from relapses
				93 (28/30)	5 weeks	
		40	TMP 50mg bid × 7d	98	7 days	
				100 (35/35)	5 weeks	
		41	TMP 100mg bid × 7d	98	7 days	
				97	5 weeks	
		30	TMP 200mg bid × 7d	100	7 days	
				100 (28/28)	5 weeks	

1 AMP = ampicillin; CNX = cephalexin; AMOX = amoxycillin; PIVMEC = pivmecillinam; PIVAMP = pivampicillin; CDN = cephradine; CIN = cinoxacin; NA = nalidixic acid; OA = oxolinic acid. For other abbreviations see table IVa.
2 Sterile urine was the criteria for cure in most studies.
3 More patients in the cinoxacin group had urinary tract abnormalities.
4 An ellipsis indicates not stated.

cause these metabolites accumulate in renal failure, with a possible danger of crystalluria, patients with impaired renal function receiving co-trimoxazole should be closely monitored (Baethke et al., 1972; Craig and Kunin, 1973a; Rieder et al., 1974). Indeed, some clinicians would recommend avoiding sulphonamides in patients with renal failure. In contrast, preliminary data on the efficacy of peritoneal dialysis suggest that this modality will eliminate only a small proportion of drug (Singlas et al., 1980).

Limited pharmacological studies in patients with liver disease indicate that serum levels of trimethoprim-sulphamethoxazole after repeated administration, and elimination half-lives, are comparable to normal controls; thus, dosage modification is not necessary in cirrhotic patients (Follath, 1979).

2.5 Disposition at the Extremes of Age

Both trimethoprim and sulphamethoxazole cross the placenta, reaching concentrations in fetal serum similar to those in maternal serum (see Patel and Welling, 1980).

In infants, during the first 10 days of life, the half-life of sulphamethoxazole is considerably longer than in the adult, but it falls rapidly to 9 hours at 3 weeks of age and 4 to 5 hours at 1 year (Brumfitt et al., 1973). By age 4 or so the half-life of sulphamethoxazole again increases to about 8.5 hours, which is comparable to the values found in adults (Ardati et al., 1979). The half-life of trimethoprim in newborn infants (about 19 hours, after intravenous administration) is also longer than in adults (Springer et al., 1982); however, in children (mean age 4.3 years) it is shorter than in the adult, averaging 5.25 hours after intravenous administration (Ardati et al., 1979).

While it has been suggested that the half-life of trimethoprim tends to be prolonged in elderly patients, in part reflecting the decreased glomerular filtration rates in this population even when blood urea nitrogen and serum creatinine are normal (Beck and Pechere, 1969), a recent study in geriatric patients (mean age 73 years) reported half-lives for both trimethoprim (10.4 hours) and sulphamethoxazole (11.8 hours) which are comparable to those in younger subjects (Naber et al., 1981). The only change in disposition seen in the elderly was a slight reduction in sulphonamide renal clearance.

2.6 Intravenous Administration

An intravenous preparation of co-trimoxazole is now available. The only significant problem with this form of the drug has been the relatively low aqueous solubility of trimethoprim base (trimethoprim lactate cannot be used since an alkaline solution is necessary to dissolve the sulphamethoxazole) which necessitates large infusion volumes with the possible consequence of fluid overload (Morgan, 1980; Winston et al., 1980). The mean plasma concentrations of trimethoprim-sulphamethoxazole following 1 hour intravenous infusion are about twice that following the same dose given orally (using historical controls) in both children and adults (Ardati et al., 1979; Grose et al., 1979). The elimination half-lives, however, fall into the range of values observed with oral use.

3. Clinical Use

3.1 Urinary Tract Infections

When evaluating any agent for use in urinary tract infection it is important to remember that a substantial proportion of those with acute uncomplicated infections may improve spontaneously, without chemotherapy. Co-trimoxazole has been widely used in the treatment of urinary tract infections.

3.1.1 Acute Infections in Adults

(tables IVa, IVb)

In the treatment of acute urinary tract infection in adults, controlled, comparative studies uni-

formly show co-trimoxazole to be at least as effective as ampicillin (Brumfitt and Pursell, 1972), pivampicillin plus pivmecillinam (Ravn, 1981), cephalexin (Brumfitt and Pursell, 1972; Gower and Tasker, 1976) or cefaclor (Rous, 1981), nitrofurantoin (Lövestad et al., 1976), cinoxacin (de Jersey and Wooller, 1982; Schaeffer et al., 1981) and nalidixic (Iravani et al., 1981) or oxolinic acid (Männistö, 1976). Of interest, co-trimoxazole was found to be superior to ampicillin (Wren, 1972) and to cephalexin (Gower and Tasker, 1976) in double-blind studies in which all of the organisms were sensitive to the antibiotics.

The sulphonamide is not critical to the efficacy of the combination in this clinical situation. Trimethoprim regimens including administration of drug ratios of 1 : 2 and 1 : 10 trimethoprim : sulphamethoxazole, or substitution of sulphadiazine for sulphamethoxazole, or even omission of the sulphonamide altogether, are all as efficacious as the standard formulation (Bailey and Pearson, 1980; Brumfitt and Hamilton-Miller, 1979a; Brumfitt and Pursell, 1972; Cartwright et al., 1982; Kasanen et al., 1978; Männistö, 1976; Reeves et al., 1969; Seneca et al., 1974; Seppänen, 1980; Skjerven and Bergan, 1979; Trimethoprim Study Group, 1981). These findings are not surprising when one considers that the concentration of trimethoprim achievable in urine of persons with normal renal function is inhibitory to most potential urinary tract pathogens susceptible to the combination with sulphamethoxazole. Additionally, there is considerable evidence that a significant synergistic drug effect does not occur in the normal urinary tract, probably for several reasons:

a) the 1 : 1 ratio of trimethoprim to sulphamethoxazole found in urine *in vivo* is far from the 1 : 20 ratio desired for *maximum* synergism;
b) experiments *in vitro* normally involve subinhibitory concentrations of each agent. When studied in models more closely simulating *in vivo* conditions, it has been demonstrated that the vastly higher sulphonamide concentrations may actually antagonise trimethoprim (Andersen et al., 1974; Greenwood and O'Grady, 1976); and
c) thymidine-like inhibitors can be found in urine (Stokes and Lacey, 1978).

As a sulphonamide alone is also as effective as the combination in therapy of acute uncomplicated urinary tract infection due to susceptible organisms (Bergan and Skjerven, 1979; Harding et al., 1975), there is no compelling reason in the non-allergic patient to choose either co-trimoxazole or plain trimethoprim (for a review of the use of plain trimethoprim in urinary tract infections see Brogden et al., 1982). Cost should therefore not be overlooked when making this choice. There is also no reason to recommend the newer trimethoprim-sulphonamide formulations such as co-trimazine (trimethoprim plus sulphadiazine), even though they may yield high concentrations of active sulphonamide in the urine (see section 7), unless newer combinations can be shown to have a lower incidence of adverse effects.

Increasing evidence suggests that only a single dose of an antimicrobial is necessary to cure uncomplicated bacterial cystitis. Several trials have shown this to be true with a single dose of co-trimoxazole (usually 4 to 6 tablets) or trimethoprim or a sulphonamide used alone (Bailey and Abbott, 1978; Buckwald et al., 1982; Cattell et al., 1968; Harbord and Grüneberg, 1981; Pitt et al., 1982; Russ et al., 1980), although in a study of geriatric patients a single dose of trimethoprim 200mg was less effective than the same dose given twice daily for 5 days (Lacey et al., 1981).

Co-trimoxazole is also effective in treatment of bacteriuria of pregnancy (Brumfitt and Pursell, 1972; Williams et al., 1969).

Enterococcal Urinary Tract Infection: Most enterococci are resistant to sulphonamides and some to co-trimoxazole *in vitro* (Bushby, 1973a; Wormser, 1978). Co-trimoxazole treatment of patients with urinary tract infections due to susceptible strains fails to cure infection in one-third of cases, due to the rapid emergence of resistance (Chatto-

Table V. Summary of therapeutic trials comparing co-trimoxazole with other antibacterial agents in chronic urinary tract infections

Reference	Patient population	Number of patients	Treatment[1]	Results		
				cure (%)	follow-up	relapse and reinfections
Comparisons with sulphonamides alone or trimethoprim alone						
Gleckman (1973)	Adults	161	TMP 160mg, SMX 800mg, bid × 10d	84	Immediate	. . .[2]
				64	10 days	
				63	20 days	
				51	45 days	
		152	SMX 1000mg, bid × 10d	53	Immediate	
				35	10 days	
				33	20 days	
				31	45 days	
		146	TMP 200mg, bid × 10d	66	Immediate	
				47	10 days	
				44	20 days	
				38	45 days	
Harding et al. (1975)	Adults	42	TMP 80mg, SMX 400mg, qid × 15d or TMP 160mg, SMX 800mg, bid × 15d	72	2-6 weeks	9 relapses, no reinfections (?)
		48	SMX 500mg, qid × 15d or SMX 1000mg, bid × 15d	54	2-6 weeks	10 relapses, no reinfections (?)
Seneca et al. (1974)	Adults	12	TMP 160mg, SMX 800mg, bid × 10d	50	2 weeks	. . .
				17	4 weeks	
				8	6 weeks	
		13	TMP 200mg, bid × 10d	85	2 weeks	
				39 (*sic*)	4 weeks	
				54 (*sic*)	6 weeks	
		11	SMX 1000mg, bid × 10d	55	2 weeks	
				46	4 weeks	
				36	6 weeks	

Comparison with ampicillin						
Gleckman (1975)	Adults	77	TMP 320mg, SMX 1600mg, daily × 10d	82 61	4 days 25 days	At least 8 reinfections
		86	AMP 200mg, daily × 10d	66 46	4 days 25 days	At least 9 reinfections
Comparisons with cephalosporins						
Cooper et al. (1980)	Adults	41	TMP 160mg, SMX 800mg, bid × 7d	85 72.5 (29/40)	1 week 5 weeks	Only relapses considered failures; 11 relapses, 6 reinfections
		43	CDN 500mg, q6h × 7d	70 56 (23/41)	1 week 5 weeks	18 relapses 5 reinfections
Thomas and Hopkins (1972)	Children with spina bifida cystica	24	TMP 20-40mg, SMX 100-200mg, bid × 14d	38 25 13	1 week 1 month 3 months	...
		23	CXN, 60 mg/kg/d in 3 doses, × 14d	39 17 9	1 week 1 month 3 months	

1 AMP = ampicillin; CDN = cephradine; for other abbreviations see table IVa,b. All drugs were given orally.
2 Indicates not stated.

padhyay, 1972). Thymidine dependency, rather than production of an insensitive dihydrofolate reductase, may be the most common mechanism of emerging resistance (Haltiner et al., 1980). Ampicillin or amoxycillin are still the drugs of choice in urinary tract infection due to *S. faecalis*.

3.1.2 Persistent or Recurrent Infections in Adults (table V)

Co-trimoxazole is highly effective in the treatment of persistent or recurrent urinary tract infection (Cooper et al., 1980; Gleckman, 1975; Gleckman et al., 1979), even in patients with severe renal impairment (Bennett and Craven, 1976). In a double-blind study, co-trimoxazole was found to be superior to ampicillin in the treatment of chronic *Escherichia coli* urinary tract infections, in which all isolates were susceptible to ampicillin (Gleckman, 1975). Co-trimoxazole also appears to be more effective than sulphamethoxazole alone, even when all organisms are sulphonamide sensitive (Gleckman, 1973). The same author found the combination to be more effective than trimethoprim alone for patients with gross structural abnormalities of the urinary tract, but his study is difficult to interpret because no information was provided about the susceptibility of the organisms to trimethoprim alone (Wormser and Keusch, 1979). A number of other studies have also generally shown trimethoprim alone to be less effective than co-trimoxazole in chronic or recurrent urinary infections, although some conflicting results have been reported (for further review see Brogden et al., 1982).

3.1.3 Urinary Tract Infections in Children (tables IV and V)

Clinical trials in children have confirmed the efficacy of co-trimoxazole, both in the treatment of urinary tract infection and in the prevention of recurrences (Feldman et al., 1975; Forbes and Drummond, 1973; Sher, 1975; Smellie, 1976). Co-trimoxazole is equally effective, or superior, to ampicillin (Böse et al., 1974) or cephalexin (Thomas and Hopkins, 1972) in therapy of these infections. For sulphonamide-sensitive organisms co-trimoxazole is not better than sulphamethoxazole alone (Howard and Howard, 1978). Comparative studies with plain trimethoprim have not been reported, although one group of investigators have claimed that their results with plain trimethoprim when used for prophylaxis of urinary tract infections in children were comparable to those with co-trimoxazole in earlier studies (Smellie and Grüneberg, 1980). Since some studies have suggested an unusual propensity for paediatric patients to develop haematological changes from co-trimoxazole, it seems prudent to follow blood counts closely when longer term therapy with co-trimoxazole is undertaken in this population (Böse et al., 1974) [see section 4].

3.1.4 Prophylaxis of Urinary Tract Infections (table VI)

Desirable features of co-trimoxazole that contribute to its efficacy in prophylaxis of recurrent urinary tract infection are the prolonged excretion of active drug into urine (which permits infrequent dosing) the marked and persistent reduction in numbers of Enterobacteriaceae in the colon, vagina, distal urethra, and prostate (the usual reservoirs of new infecting strains) without selection of resistant flora, and the low incidence of side effects (Harding et al., 1979; O'Grady et al., 1969; Pearson et al., 1979; Stamey et al., 1977). Clinical trials show that co-trimoxazole is superior to either placebo (Stamm et al., 1980), sulphamethoxazole alone or methenamine (Harding and Ronald, 1974; Kalowski et al., 1975; Ronald et al., 1975), as effective or superior to nitrofurantoin (Little et al., 1974; Stamey et al., 1977; Stamm, 1980), and equally effective as ampicillin or amoxycillin in catheterised males (Little et al., 1974). Co-trimoxazole is also efficacious in prevention of bacteriuria after prostatectomy (Hills et al., 1976), prostatic needle biopsy per rectum (Ruebush et al., 1979), and vaginal hysterectomy (Mathews et al., 1979). Low dose therapy (40mg trimethoprim, 200mg sulphameth-

Table VI. Summary of some therapeutic trials comparing co-trimoxazole with other antibacterial agents in prophylaxis of urinary tract infections

Reference	Patient population	Number of patients	Treatment[1]	Results: infections per patient year (% of patients infected)
Harding and Ronald (1974)	Women and female children	40 pts received sequentially 3-month courses of treatment	TMP 40mg, SMX 200mg, daily[2] × 3m	0.1
			SMX 500mg, daily[2] × 3m	2.5
			MM 2000mg with AA 2000mg, daily[2] × 3m	1.6
			No treatment × 3m	3.6
Kalowski et al. (1975)	Adult men and women	16	TMP 80mg, SMX 400mg, daily × 10.6m	1.4[3] (25)
		13	MH 1000mg, daily × 10m	2.7 (69)
Kasanen et al. (1974)	Adult men and women	62	TMP 80mg, SMX 400mg, daily × 4m (ave)	0.28[3] (9.7)
		66	TMP 100mg, daily × 4m	0.18 (6.1)
		61	NFN 50mg, daily × 4m	0.46 (16.4)
		58	MH 1000mg, daily × 4m	0.56 (19.5)
Kasanen et al. (1978)	Adult men and women	14	TMP 100mg, po, daily × 3-14m	1.40
		14	TMP 100mg, po, bid × 3-14m	1.53
		14	Nitrofurantoin 100mg, po, bid × 3-14m	1.27
		54	TMP 100mg, po, daily × 3-5m	0.71
		55	Nitrofurantoin 100mg, po, daily × 3-5m	0.79
Männistö (1976)	Adult men and women	15	TMP 80mg, SMX 400mg, daily × 11w (ave)	2.7[3] (46.7)
		12	TMP 100mg, daily × 11w	1.5 (33.3)
		12	OA 375mg, daily × 11w	1.46 (41.7)
Ronald et al. (1975)	Women and female children	28 pts received 47 courses of therapy	TMP 40mg, SMX 200mg, bi-weekly[4] × 6-12m	0.4
			TMP 80mg, SMX 400mg, once weekly[4] × 6-12m	1.3
			NFN 50mg, daily[4] × 6-12m	1.0
Stamey et al. (1977)	Adult women	28 pts received initial regimen and then 10 crossed over	TMP 40mg, SMX 200mg, daily × 6m	0.0[3]
			NFN 100mg, daily × 6m	0.74 (20)
Stamm et al. (1980)	Adult women	13	TMP 40mg, SMX 200mg, daily × 6m	0.15 (7.7)
		14	TMP 100mg, daily × 6m	0.0
		13	NFN 100mg, daily × 6m	0.14 (7.7)
		13	Placebo × 6m	2.8 (7.7)

1 MM = methenamine (hexamine) mandelate; MH = methenamine hippurate; AA = ascorbic acid; OA = oxolinic acid. For other abbreviations see table IVa. All drugs were given orally.
2 Children received one-half the adult dose.
3 Original results recalculated in terms of patient years.
4 Pre-adolescent girls received one half the adult dose.

Table VII. Summary of therapeutic trials comparing co-trimoxazole with other antibiotics in ear, nose and throat infections

Reference	Patient population	Number of patients	Treatment[1]	Results	Side effects (no. of pts)
Cameron et al. (1975)	Children with otitis media	74 ears	TMP 40-52mg, SMX 132-200mg, q8h × 1w	59% cured	GI upset (1)
		77 ears	AMP 250-334mg, q8h × 1w	57% cured	GI upset (2)
Cooper et al. (1976)	Children with otitis media	30 patients	TMP 40-160mg, SMX 200-800mg, bid × 7d	97% cured	Nausea (3) Diarrhoea (1) Tiredness (1)
		31 patients	AMOX × 125-250mg, tid × 7d	97% cured	Nausea (1) Vomiting (1) Diarrhoea (2) Rash (1)
Federspil and Bamberg (1981)	Maxillary sinusitis (acute or exacerbations of chronic condition)	20 patients	TMP 160mg, SMX 800mg, bid × 10d	80% 'good' or 'improved' at 6-8d follow-up and 95% at 12-16d	'Acne' (1) Gastric pain (1)
		17 patients	TMP 180mg, SDZ 820mg, once daily × 10d	94% 'good' or 'improved' at 6-8d and 95% at 12-16d	Exanthema (1)
Harbison et al. (1980)	Children with otitis media	16 patients	TMP 8 mg/kg/d, SMX 40 mg/kg/d × 10d	100% cured	
		16 patients	Cefaclor 40 mg/kg/d in 2 doses × 10d	100% cured	
		16 patients	Cefaclor 40 mg/kg/d in 3 doses × 10d	100% cured	
Japan study group (1973)	Children and adults with otitis media	19 ears	TMP 160mg, SMX 800mg, bid × 6d	73% cured	
		20 ears	SMX 1000mg, bid × 6d	50% cured	

Meijer (1973)	Adults and children with pharyngitis due to *Streptococcus pyogenes*	28 patients	TMP 160mg, SMX 800mg, q12h × 10d in adults Co-tri 2.5-10ml suspension, q12h × 10d in children	85% clinical response 50% bacteriological response	Skin rash (6)
		27 patients	PEN G × 10 days[2]	100% effective clinically and bacteriologically	Nausea and diarrhoea (1)
Shurin et al. (1980)	Children with otitis media	77 patients	TMP 10 mg/kg/d, SMX 50 mg/kg/d, in 2 doses × 10d	91% cured	Thrombocytopenia (1)
		55 patients	AMP 70 mg/kg/d, in 4 doses × 10d	93% cured	Diarrhoea (2) Urticaria (1) Thrombocytopenia (1)
Trickett et al. (1973)	Adults with *Streptococcus pyogenes* pharyngitis	44 patients	TMP 160mg, SMX 800mg, bid × 10d	70% bacteriologically cured	GI upset (1) Rash (2) Leucopenia (3) Increased SGOT (1) Increased creatinine (1)
		43 patients	PEN G 250mg, qid × 10d	88% bacteriologically cured	GI upset (3) Rash (1) Leucopenia (1) Increased SGOT (1)
Willner et al. (1978)	Children with otitis media	249 patients	TMP 8 mg/kg/d, SMX 40 mg/kg/d × 10d[3]	93% cured	Skin rash (1)
			AMP 62 mg/kg/d × 10d[3]	98% cured	Diarrhoea (2)

1 Co-tri = co-trimoxazole; PEN G = penicillin G (benzylpenicillin). For other abbreviations see tables IVa,b.
2 Dose not stated.
3 Approximate mean doses.

oxazole) given 3 times weekly has been effective in prophylaxis of recurrent urinary tract infection in women (Harding et al., 1979).

It appears that there is no reason to recommend co-trimoxazole over plain trimethoprim, as several trials have found these agents to be equivalent (Iwarson and Lidin-Jonson, 1979; Kasanen et al., 1974; Männistö, 1976; Stamm et al., 1980).

3.1.5 Prostatitis

Trimethoprim levels in uninfected human prostatic tissue may exceed twice the serum concentration (Dabhoiwala et al., 1976; Madsen et al., 1976; Oosterlinck et al., 1975). It had been assumed that this therapeutically favourable tissue concentration followed largely from trimethoprim's basic pKa (7.3), which theoretically should favour trapping of the drug in the acid milieu of the prostate gland. In fact, comparable or higher tissue levels can be found in lung, liver, pancreas, adrenal and other organs in which a pH gradient would not be predicted to exist (Craig and Kunin, 1973b; Hansen et al., 1973b). Additionally, the pH of normal human expressed prostatic secretions, which averages 7.28, is higher than may have been anticipated from experiments using dog prostatic secretions which have a pH of 6.4 (Fair et al., 1979). Moreover, the pH gradient in patients with *prostatic infection* may actually work against trimethoprim. Fair and colleagues (1979) measured the pH of 41 samples of expressed prostatic secretion from 14 patients with documented chronic bacterial prostatitis and found an average value of 8.32. They predicted, therefore, that the level of trimethoprim in infected prostatic secretions should be approximately 50% of the simultaneously measured plasma level. Experimental proof of their conjecture is lacking, but the 60% failure rate seen in clinical trials with co-trimoxazole in the treatment of chronic bacterial prostatitis is consistent with their predictions (Dow, 1975; McQuire and Lytton, 1976; Meares, 1975). Alternatively, such findings may reflect that the bacteria thought to be causing prostatitis are in fact secondary 'invaders'.

Treatment of this infection using twice the usual dose deserves evaluation (see Meares, 1981). Unfortunately, chronic or relapsing prostatitis is a notoriously difficult clinical problem, and agents other than co-trimoxazole do not offer any better chance of cure.

3.2 Ear, Nose and Throat Infections (table VII)

In both adults and children, the principal aetiological agents in acute otitis media are *Streptococcus pneumoniae* and *Haemophilus influenzae,* organisms readily inhibited by co-trimoxazole or trimethoprim alone *in vitro.* Actual measurements in middle ear fluid demonstrate levels of trimethoprim and sulphamethoxazole 0.75 and 0.2 times respective serum levels, with a concentration ratio of trimethoprim to sulphamethoxazole of 1 : 6 (Klimek et al., 1980). Comparative clinical trials in children have demonstrated co-trimoxazole to be equal in efficacy to ampicillin (Cameron et al., 1975; Shurin et al., 1980), amoxycillin (Cooper et al., 1976), or cefaclor (Harbison et al., 1980) and more effective than sulphamethoxazole alone (Japan Cooperative Clinical Study Group for Co-trimoxazole, 1973). Whether trimethoprim alone would be equally effective in this clinical situation has not been determined.

In contrast to ampicillin and amoxycillin however, co-trimoxazole is highly effective therapy for infection with β-lactamase-producing *Haemophilus influenzae,* an increasing clinical problem (Schwartz et al., 1979), despite an increase in resistance of *Haemophilus influenzae* to trimethoprim in recent years (Philpott-Howard and Williams, 1982). Another practical advantage of co-trimoxazole is the convenient bid schedule.

Co-trimoxazole has been used successfully in prophylaxis against recurrent infection in children with residual middle ear effusion following a bout of acute otitis, but the drug did not influence the rate of resolution of the effusion (Schwartz and Rodriguez, 1980).

Favourable anecdotal results have been reported with co-trimoxazole in uncontrolled trials in otitis externa (a condition not generally requiring a systemic antimicrobial) [Pomahac, 1975], and in sinusitis (Fedespil and Bamberg, 1981; Whitehead, 1975). Co-trimoxazole is inferior to penicillin in the treatment of *Streptococcus pyogenes* pharyngitis and should not be used in this condition. Cure rates are lower and recurrences are more frequent (Trickett et al., 1973); in 1 study there was a 50% bacteriological failure rate using co-trimoxazole (Meijer, 1973).

3.3 Bronchitis and Pneumonia (table VIII)

Trimethoprim penetrates into pulmonary tissues including tracheobronchial secretions, as well as lung parenchyma, to give levels exceeding the simultaneous plasma concentration. On the other hand, levels of active sulphamethoxazole are usually less than plasma concentration; as a result the ratio of trimethoprim to sulphamethoxazole in sputum is about 1 : 3 to 1 : 5 (Hansen et al., 1973a,b; Jordan et al., 1975) [see table III]. Nearly all of the published clinical studies using co-trimoxazole in the treatment and prevention of acute exacerbations of chronic bronchitis have been conducted outside the United States. In these studies the drug was equal or superior to either ampicillin (Chodosh et al., 1973; Hughes, 1973), amoxycillin (Carroll et al., 1977; Medici et al., 1981; Pines et al., 1977), cephalosporins (Anderson et al., 1981; Cooper and McGillion, 1978), or various tetracyclines (Abengowe, 1979; Al-Bahrini, 1974; Lal and Bhalla, 1969; Pandy, 1979; Pines, 1973; Renmarker, 1976) in the acute illness, when clinical evaluation of the patient, volume and purulence of the sputum, and eradication of presumed sputum pathogens (usually *Streptococcus pneumoniae* and both encapsulated and non-encapsulated *Haemophilus influenzae*) were considered. In one study, however, comparing co-trimoxazole with amoxycillin, there were significantly more relapses after completion of therapy in the patients receiving the combined agent (Pines et al., 1977). As predicted (Wormser and Keusch, 1979), a recent double-blind trial has found trimethoprim alone to be equally effective as the combination in the treatment of pneumococcal and Haemophilus chest infections (Lacey et al., 1980b).

The value of antimicrobials, if not in the treatment, then certainly in the prevention of the acute exacerbation of bronchitis is rather controversial. Nevertheless, it has been shown that co-trimoxazole is significantly more effective than placebo (Pines, 1973), and of comparable efficacy to amoxycillin (Cooper et al., 1975) and clomocycline (Lennox-Smith et al., 1972) in preventing exacerbations in a high risk population.

The optimum dosage of co-trimoxazole for both treatment and prophylaxis of bronchitis has not been established. Pines (1973) claims better results with the use of 6 (total of 480mg trimethoprim/2400mg sulphamethoxazole) *versus* 4 standard tablets (320mg trimethoprim/1600mg sulphamethoxazole) per day in the treatment of acute exacerbations, and with 4 *versus* 2 tablets (160mg trimethoprim/800mg sulphamethoxazole) per day for prophylaxis. More controlled trials are needed to substantiate the efficacy of co-trimoxazole and to establish the dose and duration of optimal treatment.

Co-trimoxazole has also been used successfully in the therapy of lobar pneumonia, infected bronchiectasis, and lung abscess due to *Staphylococcus aureus* (Abengowe, 1979; Hughes, 1973; Sallam and Sallam, 1975). It is unlikely that the drug would ever be preferentially chosen for *Staphylococcus aureus* infection, but it is definitely a valuable drug for difficult to treat Gram-negative pneumonias; this agent may be effective even in neutropenic oncology patients who have already failed to respond to carbenicillin plus an aminoglycoside (Grose and Bodey, 1980; Grose et al., 1977).

Legionella species may be susceptible as well to co-trimoxazole, and this drug appears to have been

Table VIII. Summary of therapeutic trials comparing co-trimoxazole with other antibacterial agents in the treatment of pneumonia and bronchitis

Reference	Population	Number of patients	Treatment[1]	Results (% clinical response)
Comparisons with tetracyclines				
Abengowe (1979)	Lower respiratory tract infection	63	TMP 480mg, SMX 2400mg, daily in 2 doses[2]	68.2
		63	TET 500mg q6h[2]	36.5
Al-Bahrini (1974)	Lower respiratory tract infections	34	TMP 160mg, SMX 800mg, bid × 10d	97
		32	TET 250mg q6h × 10d	88
Lal and Bhalla (1969)	Acute exacerbation of chronic bronchitis	24	TMP 320mg, SMX 200mg, daily × 1w	. . .[3]
		22	TET 1000mg, daily × 1w	
Pandy (1979)	Acute exacerbation of chronic bronchitis	27	TMP 160mg, SMX 800mg, bid × 5d	74
		29	DOX 100mg, daily × 5d	79
Pines (1973)	Elderly males with acute exacerbation of chronic bronchitis	98	TMP 480mg, SMX 2400mg, daily × 2w	76
		96	TET 2000mg, daily × 2w	58
Renmarker (1976)	Acute exacerbation of chronic bronchitis	37	TMP 160mg, SMX 800mg, bid × 1w	86
		36	DOX 100mg, daily × 1w	83
Comparisons with ampicillin or amoxycillin				
Carroll et al. (1977)	Acute bronchitis	52	TMP 160mg, SMX 800mg, bid × 5d	85
		52	AMOX 250mg, tid × 5d	83
Chodosh et al. (1973)	10 patients with chronic bronchitis treated in double-blind crossover trial during two exacerbations	10	TMP 320mg, SMX 1600mg, daily × 14d	. . .[4]
		10	AMP 2000mg, daily × 14d	
Hughes (1973)	Acute exacerbation of chronic bronchitis	25	TMP 160mg, SMX 800mg, bid × 7d	96
		25	AMP 500mg, qid × 7d	76
Medici et al. (1981)	Acute exacerbation of chronic bronchitis	20	TMP 480mg, SMX 2400mg, daily × 14d	75
		19	AMOX 2250mg, daily × 14d	68

Table VIII. (continued)

Reference	Population	Number of patients	Treatment[1]	Results (% clinical response)
Pines et al. (1977)	Acute exacerbation of chronic bronchitis	50	TMP 320-480mg, SMX 1600-2400mg, daily × 10d	70 22/34 relapsed within 2-4 weeks
		50	AMOX 500mg, tid × 10d	78 9/37 relapsed within 2-4 weeks
Other comparative studies				
Anderson et al. (1981)	Acute exacerbation of chronic bronchitis	19	TMP 160mg, SMX 400mg, bid × 7d	85[5]
		20	CFR 500mg, tid × 7d	65[5]
Cooper and McGillion (1978)	Acute exacerbation of chronic bronchitis	30	TMP 160mg, SMX 800mg, bid × 7d	90
		27	CXN 1000mg, bid × 7d	82
Lacey et al. (1980b)	Lower respiratory tract infections	109	TMP 100mg, SMX 500mg, q12h × 5d	82
		107	TMP 100mg, q12h × 5d	79

1 TET = tetracycline; DOX = doxycycline; AMOX = amoxycillin; CFR = cefaclor; CXN = cephalexin. For other abbreviations see table IVa,b.

2 Duration of treatment not stated.

3 TMP-SMX treated patients had a larger reduction in sputum volume and purulence.

4 TMP-SMX had more statistically significant favourable changes for frequency of cough, pulse rate, rales and rhonchi, volume of sputum, sputum neutrophil count, and bronchial epithelial cells (in sputum). Ampicillin was favoured for severity of cough and prolongation of expiration.

5 Percentage of patients achieving mucoid sputum.

effective in treatment of 2 patients with Legionnaires' disease. More data are needed, however, to establish the efficacy of the combination in this potentially important area (Kirby et al., 1980; McDonald et al., 1980; Myerowitz et al., 1979).

3.4 Venereal Diseases

3.4.1 Gonorrhoea (table IX)

Most *Neisseria gonorrhoeae* are susceptible to a 1 : 20 ratio of trimethoprim : sulphamethoxazole *in vitro*, but this ratio is never optimal for synergy and for some strains it actually may be antagonistic (Rein et al., 1980). In contrast to most other organisms 1 : 1 concentrations sulphamethoxazole and trimethoprim are maximally and universally synergistic (Rein et al., 1980). The combined action is important clinically, as either agent administered alone is unsatisfactory therapy for gonorrhoea (Austin and Holmes, 1975; Csonka, 1969). Most studies have found co-trimoxazole to be extremely effective in the treatment of gonococcal urethritis, cervicitis, pharyngitis, and the asymptomatic cervical, pharyngeal, and anal carrier states (Austin et al., 1973; Brathwaite, 1975; Bro-Jørgensen and Jensen, 1973; Carroll and Nicol, 1970; Csonka, 1969; Danielsson and Wikstrom, 1975; Duncan et al., 1975; Kristensen and From, 1975; Lawrence et al., 1973; Mahony et al., 1973; Nelson et al., 1975; Rahim, 1975; Schofield, 1971; Schofield et al., 1969; Waugh, 1971).

However, 1 recent report from the Center for Disease Control showed a 19 to 23% failure rate

Table IX. Summary of studies of co-trimoxazole in the treatment of gonorrhoea

Author	Site of infection	Patients		Treatment[1]	Cure rate (%)
		sex	number		
Austin et al. (1973)	Urethritis	Men	80	Co-tri 6 tabs, once daily × 3d	92.5
			85	Co-tri 3 tabs, bid × 3d	80
Bro-Jørgensen and Jensen (1973)	Pharynx	Men and women	29	Co-tri 2 tabs, tid × 1w	97
Carroll and Nicol (1970)	Urethritis Proctitis	Men	111	Co-tri 4 tabs in a single dose daily × 5d	95.5
	Cervix	Women	42		93
Csonka (1969)	Urethritis	Men	20	TMP 250-300mg, SMX 2.5-3g, × 2d	76.7
			30	TMP 400mg, SMX 4g, × 1d	81.8
			11	Co-tri 8-12 tabs ⩽ 3d	85.9
			64	Co-tri 2 tabs, bid × 4d	93.3
			15	Co-tri 3 tabs, bid × 3d	95.6
			46	Co-tri 3 tabs, bid × 4d	
Csonka (1969)	Cervix	Women	18	Co-tri 10-18 tabs ⩽ 3d	77.8
			17	Co-tri 2 tabs, bid × 4d	76.5
			24	Co-tri 3 tabs, bid × 4d	83.4
Danielsson and Wikström (1975)	Urethritis	Men	73	TMP 400mg, SMX 2000mg, × 2 doses, with 5h interval between doses	98.5
Duncan et al. (1975)	Urethritis	Men	54	Co-tri 6 tabs in single dose daily × 3d	93
			25	Co-tri 12 tabs in single dose	88
	Cervix	Women	20	Co-tri 6 tabs, bid × 1d	90
			20	Co-tri 6 tabs in single dose, daily × 3d	90
Elliott et al. (1977)	Urethritis	Men	86	Co-tri 9 tabs as single dose	77
			94	Co-tri 6 tabs, then 6 more in 6h	81
Kristensen and From (1975)	Urethritis Cervix Pharynx Rectum	Men Women	235 184	TMP 400mg, SMX 2000mg, 1 dose and then again in 8h	98
Lawrence et al. (1973)	Urethritis Rectum	Men and women	102	Co-tri 4 tabs, once daily × 5d	96.6
			103	Co-tri 1 tab, qid × 5d	82.5
			1103	Co-tri 4 tabs, bid × 2d	97.7
			779	Co-tri 5 tabs, bid × 1d then 5 tabs × 1d	96.7
			214	Co-tri 8 tabs once daily	92
Mahoney et al. (1973)	Urethritis Cervix	Men Women	118 48	Co-tri 6 tabs day 1 then 2 tabs bid × 4.5d (24 tabs total)	96 98
Nelson et al. (1975)	Cervicitis Proctitis	Women	82 86	Co-tri 6 tabs, once daily × 3d Co-tri 6 tabs, then 6 more in 6h	85.4 93.4
Sattler and Ruskin (1978)	Urethritis	Men	43	Co-tri 4 tabs, bid × 2d	95
Schofield (1969)	Cervix	Women	58	Co-tri 2 tabs, bid × 5d	98
Schofield et al. (1971)	Cervix	Women	103	Co-tri 2 tabs, bid × 5d	98
Waugh (1971)	Rectum	Men	66	Co-tri 2 tabs, bid × 7d	88

1 Co-tri = co-trimoxazole standard tablet (trimethoprim 80mg, sulphamethoxazole 400mg); for other abbreviations see table IVa,b.

using a single day (1 or 2 dose) treatment protocol (Elliott et al., 1977). Success correlated with sensitivity of the *Neisseria gonorrhoeae* isolates to sulphamethoxazole or to the combination. These results suggest that a single or double dose treatment schedule, which would be highly desirable for patient tolerance and compliance, will be unsatisfactory when relatively resistant strains are present in the community. Conceivably, better results with single dose therapy might be achieved by altering the proportion of trimethoprim and sulphamethoxazole in the formulation to allow for a more synergistic ratio in serum or tissue. Although the optimal treatment schedule has not been defined, the most effective regimen is probably a relatively large unit dose given once or twice daily for several days.

The New York City Department of Health has specifically recommended a regimen of 9 standard tablets daily for 5 days, while recommendations in the UK are for 5 tablets every 12 hours for 2 days or an initial dose of 5 tablets followed 8 hours later by another dose of 5 tablets.

It is important to have patients return 5 to 7 days after treatment with co-trimoxazole, as with other antibiotics, for 'test of cure' (repeat) cultures. Also, co-trimoxazole is not effective therapy for either incubating or active syphilis, and this infection must be ruled out by serological study in any patient who is treated for gonorrhoea (Csonka, 1969; Lawrence et al., 1973).

Efficacy has been demonstrated for co-trimoxazole in the treatment of gonorrhoea when it involved the oropharynx (Bro-Jørgensen and Jensen, 1973) or when the organism produces penicillinase (Lao et al., 1980). It thus seems reasonable to suggest that co-trimoxazole might prove valuable for treatment of patients with pharyngeal involvement by penicillin-resistant strains. This potential use is rendered even more important by evidence of associated resistance to tetracycline of penicillinase-producing *Neisseria gonorrhoeae,* and the unreliability of spectinomycin in oral infection (Sattler and Ruskin, 1978).

3.4.2 Non-gonococcal Urethritis

There are no studies available comparing co-trimoxazole with tetracycline or erythromycin, the presently accepted standard treatments, in non-gonococcal urethritis. Co-trimoxazole is active against one agent of nongonococcal urethritis, *Chlamydia trachomatis,* but not against another proposed agent, *Ureaplasma urealyticum* (formerly called T-strain mycoplasma) [Gnarpe, 1975; Gnarpe and Friberg, 1976; Johannisson et al., 1979; Karney et al., 1977]. Genital strains of Chlamydia are susceptible to sulphonamides and highly resistant to trimethoprim alone, and experiments *in vitro* have demonstrated either an additive or at best a slightly synergistic behaviour of the combination (Hammerschlag, 1982; Johannisson et al., 1979). A clinical study documented a lowered incidence of non-gonococcal urethritis after co-trimoxazole therapy for acute gonorrhoea compared with the incidence in patients treated with penicillin (Mahony et al., 1973). Consistent with these findings, preliminary results from another study have shown that treatment with co-trimoxazole is significantly more effective than ampicillin in eradication of Chlamydia from patients with simultaneous Neisseria and Chlamydia genital infection (Brunham et al., 1980).

Treatment of non-gonococcal urethritis with co-trimoxazole was successful in 68% of one series of 78 male patients with an additional 17% showing partial responses when 2 standard tablets were given twice daily for 10 days (Danielsson and Wikström, 1975). However, with shorter course regimens (2 or 3 tablets twice daily for 4 days) less than 50% of patients responded (Carroll and Nicol, 1970; Csonka, 1969). Clinical response depends on the organism involved and its sensitivity to the drug. Johannisson and co-workers (1979) compared co-trimoxazole with a sulphonamide alone in therapy of both Chlamydia-positive and -negative non-gonococcal urethritis. Although the regimens were about equally successful in eradicating genital Chlamydia (20 of 20 in the sulphonamide group and 18 of 20 in the co-trimoxazole group) the

symptoms of urethritis responded more frequently to the combination in both the Chlamydia-positive (14 of 20 receiving the sulphonamide *versus* 18 of 20 receiving the combination; p = 0.11) and the Chlamydia-negative groups (19 of 38 receiving the sulphonamide *versus* 30 of 47 receiving co-trimoxazole; p = 0.25). However, whether these results reflect an *in vivo* synergistic effect of the combination is not clear, as it is impossible to tell if the patient groups were strictly comparable.

3.4.3 Miscellaneous Venereal Diseases

Small numbers of patients with chancroid (Fitzpatrick et al., 1981; Rajan and Pang, 1979), granuloma inguinale (Garg et al., 1978), and lymphogranuloma venereum (Csonka, 1969; Lal and Garg, 1980), diseases already known to respond to sulphonamides, have also been successfully treated with co-trimoxazole. At this time there is no clear evidence to support use of the combination over a plain sulphonamide or another antimicrobial in these conditions, although preliminary evidence does suggest that it may be as effective as intramuscular streptomycin and more effective than oral sulfisoxazole alone or combined with tetracycline in treating chancroid (Fitzpatrick et al., 1981).

Despite anecdotal claims to the contrary, there is no logical reason to expect co-trimoxazole to be effective against *Herpes simplex* (Gosling, 1975; Laird and Roy, 1975).

3.5 Enteric Infections

3.5.1 Typhoid Fever

The current standard drugs for treatment of typhoid fever are chloramphenicol for the severely ill patient and parenteral ampicillin or oral amoxycillin for milder disease or for infection due to chloramphenicol-resistant strains. Co-trimoxazole is an effective agent for *Salmonella typhi* infection and is particularly useful for patients unable to take a penicillin derivative or chloramphenicol because of toxicity, or for strains of the organism resistant to one or both of the above agents (Butler and Rumans, 1981; Butler et al., 1977; Gilman et al., 1975; Uwaydah et al., 1975). There is no clear explanation for the occasional failure of co-trimoxazole despite adequate blood levels and an organism which appears sensitive *in vitro* (Portnoy and Seah, 1979). Some data indicate that co-trimoxazole alone, or with rifampicin (rifampin) is curative of the established carrier state, and this treatment may be tried in long term carriers allergic to, or who fail to respond to, ampicillin or amoxycillin (Freerksen et al., 1977; Pichler et al., 1973).

3.5.2 Salmonella Gastroenteritis

Antibiotics do not shorten the course of acute salmonella gastroenteritis, and they may significantly prolong the carrier state. Neither does treatment with co-trimoxazole improve the symptomatic response, but there is no evidence that the duration of faecal carriage is prolonged, at least for patients of more than 2 years of age (Clementi, 1975; Kazemi et al., 1973). Indeed, it has been demonstrated that a 2-week course of co-trimoxazole may actually hasten the eradication of *Salmonella enteriditis* from stool in older children and adults, but this observation needs confirmation (Clementi, 1975). These findings may be reassuring to the clinician faced with the dilemma of initiating or withholding empiric antimicrobial therapy for an acutely ill patient, who on clinical grounds could have either salmonellosis or shigellosis.

3.5.3 Shigellosis

Good evidence supports the efficacy of a 5-day course of co-trimoxazole in treatment of acute shigellosis in both children and adults (Barada and Guerrant, 1980; Nelson et al., 1976a,b; Orenstein et al., 1981), although many patients with shigella infections may not require antibiotics. In geographical locations where ampicillin and tetracycline resistance is prevalent among Shigella isolates, or for patients unable to take these medications, co-trimoxazole is the antimicrobial of choice.

3.5.4 Cholera

Isolates of *Vibrio cholerae* are highly sensitive to co-trimoxazole, and clinical trials with this agent in the treatment of cholera have shown efficacy comparable to that of tetracycline (Cash et al., 1973; Gharagozloo et al., 1970; Pastori et al., 1977) and chloramphenicol (Gharagozloo et al., 1970; Pastori et al., 1977). Drug therapy in this disease is, however, of lesser importance than fluid replacement and acid/base balance in determining the outcome.

3.5.5 Enterotoxigenic Escherichia coli

Strains of enterotoxigenic *Escherichia coli* are known to be common causes of diarrhoea in individuals travelling to or young children living in the developing world, as well as an occasional cause of nursery outbreaks of diarrhoea in developed countries (Sack, 1980).

Doxycycline (100 mg/day) has been shown to be highly effective as prophylaxis for traveller's diarrhoea (Sack et al., 1978). Protection was correlated with failure to acquire enterotoxigenic *Escherichia coli* in the faeces. Co-trimoxazole might be particularly suitable as a prophylactic agent in this setting since:

a) almost all strains of enterotoxigenic *Escherichia coli* are susceptible *in vitro* (DuPont et al., 1978; Sack et al., 1977)
b) the drug persistently and completely eradicates susceptible strains of *Escherichia coli* from stool (see section 1.4)
c) co-trimoxazole is highly active against another potential enteric pathogen, Shigella
d) the drug preserves the anaerobic flora, which may be an important factor in maintaining natural 'colonisation resistance' (Van der Waaij et al., 1971, 1972)
e) its long half-life would allow a convenient dosage schedule; and
f) the drug is known to be well tolerated with chronic administration.

Indeed, in a study conducted among students travelling in Mexico co-trimoxazole was more effective than a placebo in preventing diarrhoea (incidence of diarrhoea of 16% *versus* 55%; DuPont et al., 1982). Nevertheless, the possibility of promoting the emergence of resistant organisms should preclude the widespread use of *any* antimicrobial prophylaxis at this time; clearly more information is needed to assess adequately the risk and benefits of prophylactic therapy in this situation in general, and of co-trimoxazole in particular.

The role of antibiotics in treatment of patients with symptomatic illness due to toxin-producing strains of *Escherichia coli* is not defined. Thorén and colleagues (1980) randomised children with endemic infantile diarrhoea due to enteropathogenic *Escherichia coli* (mainly serotype 0111 : B4) to receive either mecillinam, co-trimoxazole or no antibiotic. Compared with controls, the patients who were given either antimicrobial had a significantly better clinical and bacteriological response rate.

3.5.6 Yersinia enterocolitica *and* Campylobacter fetus ss jejuni

Yersinia enterocolitica has been shown to be sensitive *in vitro* to co-trimoxazole (Gutman et al., 1973; Hammerberg et al., 1977); however, there are no clinical data to substantiate whether acute yersinial enteritis, or mesenteric adenitis, will respond to this, or any other, antimicrobial agent (Wormser and Keusch, 1981).

Most strains of *Campylobacter fetus ss jejuni* are resistant to co-trimoxazole (Vanhoof, 1980). Tetracycline or erythromycin may be useful in serious infections due to this organism.

3.6 Protozoal Infections

3.6.1 Pneumocystis carinii

Sufficient experimental and clinical data are available to conclude that co-trimoxazole given in adequate dosage (3 to 4 times the usual daily dose) is the treatment of first choice for infection due to *Pneumocystis carinii.* Neither the age of the patient nor the route of administration (oral or intraven-

ous) alter the response to co-trimoxazole, provided adequate serum levels are achieved (about 5 μg/ml trimethoprim, 100 μg/ml active sulphamethoxazole) [Hughes et al., 1978; Lau and Young, 1976; Winston et al., 1980; Sattler and Remington, 1981]. The overall cure rate derived from reported cases is about 68% with co-trimoxazole (compared with 43% with pentamidine; Winston et al., 1980).

In 1 study, the median time for clinical response to co-trimoxazole was about 5 days, which was usually manifested by normalisation of temperature and stabilisation or improvement in arterial blood gas levels (Winston et al., 1980). As initial serum drug levels are significantly lower than later ones in patients receiving high dosage co-trimoxazole (see section 2.1), it is conceivable that a more rapid clinical response might be achieved by use of a higher first dose (loading dose). The 30% failure rate with co-trimoxazole suggests the possibility that some Pneumocystis organisms may be intrinsically resistant to this compound. About 10% of patients who fail to respond to co-trimoxazole can be cured with pentamidine (Winston et al., 1980), but combination therapy with co-trimoxazole and pentamidine offers no advantage over either agent alone according to an experimental animal model (Kluge et al., 1978). Plain trimethoprim is also ineffective in an animal model (Hughes et al., 1978; Kluge et al., 1978).

Daily administration of lower dose co-trimoxazole (5 mg/kg trimethoprim, 25 mg/kg sulphamethoxazole) is highly effective in prevention of *Pneumocystis carinii* infection in high risk patient populations (Harris et al., 1980; Hughes et al., 1977; Wilbur et al., 1980). The period of protection is limited to the time the drug is being administered (Wolff and Baehner, 1978). Additional bone marrow depression in patients already receiving cytotoxic therapy must be considered when co-trimoxazole is used for this indication (see section 4).

Several lines of evidence can be advanced that the action of co-trimoxazole against the *Pneumocystis carinii* organism is not lethal. The most convincing are the results of an animal experiment by Hughes (1979) in which control or treated rats given co-trimoxazole for up to 6 weeks, were placed in individual isolator cages and immunosuppressed with corticosteroids. 12 weeks later at time of sacrifice, Pneumocystis organisms could be found in the lungs of more than 90% of both co-trimoxazole-treated and -untreated animals. Some anecdotal evidence in humans is consistent with these observations. *Pneumocystis carinii* have occasionally been found in the lungs at postmortem examination of patients who were clinically successfully treated with co-trimoxazole, but succumbed to unrelated complications (Hughes et al., 1978; Kluge et al., 1978). Also, recurrent active Pneumocystis pneumonia after apparent cure is described in patients treated with co-trimoxazole but of course the interpretation of this phenomenon is open to question because reinfection cannot be distinguished from relapse (Grose and Bodey, 1980; Tebbi, 1979).

3.6.2 Toxoplasmosis

Although trimethoprim alone is not particularly active against *Toxoplasma gondii,* in combination with sulphamethoxazole irreversible inhibition of the organism occurs in an infected cell culture system *in vitro* (Grossman and Remington, 1979). Experimental studies of murine infections with toxoplasmosis have given contradictory results on the activity of co-trimoxazole, but serum levels of the drugs were not controlled (Feldman, 1973b; Remington, 1976; Seah, 1975; Thiermann et al., 1978). The mouse may be a particularly unfortunate model as the half-life of trimethoprim in this animal is only 24 minutes (Grossman and Remington, 1979). Clinical experience in human infection is limited to uncontrolled trials and anecdotal accounts, and although the results have been encouraging, randomised, controlled trials are needed (Norrby et al., 1975; Williams and Savage, 1978). An important question is whether or not sulphadiazine might be preferable to sulphamethoxazole for combination with trimethoprim in

treatment of this infection. It is also important to remember that toxoplasmosis in adults seldom requires treatment.

3.6.3 Malaria

In vitro studies have demonstrated trimethoprim to be active against the dihydrofolate reductase enzymes of certain species of plasmodia (Rollo, 1975). Clinical studies with trimethoprim alone or trimethoprim plus a sulphonamide in the treatment of chloroquine-sensitive and -resistant forms of malaria have shown inconsistent results (Canfield et al., 1971; Clyde, 1969; Clyde et al., 1971; Martin and Arnold, 1967, 1968), although the drug may modify or cure falciparum malaria and may confuse the diagnosis of malaria (Williams et al., 1982).

3.6.4 Coccidiosis

There are few data available on the treatment of chronic, symptomatic *Isospora belli* infection in humans. A case report, however, suggests that co-trimoxazole may well be the treatment of choice in this rare infection (Westerman and Christensen, 1979).

3.7 Prevention and Treatment of Serious Systemic Infections

In experience to date with co-trimoxazole in patients with serious systemic infections, they often had underlying life-threatening illnesses, were infected with organisms resistant *in vitro* to many antimicrobial agents, and received multiple drugs simultaneously, thus complicating the task of evaluating the efficacy of the trimethoprim-sulphamethoxazole combination. An overall impression is that the drug may well be particularly valuable for treatment of *Serratia marcescens, Klebsiella* and *Enterobacter* species, particularly when the organisms are resistant to the usually employed antibiotics or the patients are not responding to the drugs being used (e.g. Grose and Bodey, 1980; Nair et al., 1978; Stratford et al., 1978; Thomas et al., 1976).

The availability of the parenteral preparation undoubtedly will permit a greater number of critically ill patients to receive co-trimoxazole and will encourage further studies to define the utility of this agent in serious systemic infections. Data are also needed on the efficacy of trimethoprim alone and trimethoprim combined with aminoglycosides, a combination often synergistic *in vitro* against Enterobacteriaceae (Paisley and Washington, 1978; Zinner et al., 1980).

3.7.1 Use in Neutropenic Patients

Treatment of established infections: Grose and Bodey (1980) recently reported that about 50% of infected (and often neutropenic) cancer patients, who fail to improve on antibiotic regimens that include an aminoglycoside, will respond to co-trimoxazole. Stuart and colleagues (1980) randomised granulocytopenic patients in a double-blind manner to receive carbenicillin plus either co-trimoxazole or gentamicin as empiric therapy for infection. A favourable outcome was observed significantly more frequently in the carbenicillin/co-trimoxazole group.

Prophylactic use: Reduction in acquisition of new organisms and suppression of potential pathogens already colonising the patient are considered important elements in the prevention of infection in the highly susceptible granulocytopenic patient population. Total reverse isolation using laminar air flow rooms and intestinal microbial suppression using oral non-absorbable antibiotics have reduced infection by 75% in patients with profound, prolonged granulocytopenia (Schimpff, 1980).

Early, uncontrolled reports suggested that co-trimoxazole might prevent infection in this population (Burge et al., 1975; Grünberg et al., 1970). Recently, a controlled trial has shown a significant reduction in bacteraemias and febrile days in granulocytopenic leukaemia patients receiving co-trimoxazole compared with controls not receiving an antimicrobial (Gurwith et al., 1979). Other studies found a similar incidence of infection in granulocytopenic leukaemic patients randomised to re-

ceive co-trimoxazole plus nystatin compared with more conventional prophylaxis with oral gentamicin plus nystatin (Schimpff, 1980; Wade et al., 1981), or in patients receiving co-trimoxazole alone compared with co-trimoxazole plus framycetin and colistin (Starke et al., 1982). When co-trimoxazole alone was compared with a non-absorbable regimen of neomycin plus colistin, fewer infections occurred with co-trimoxazole (Watson et al., 1982).

Enthusiastic interest in co-trimoxazole has been in large part related to several negative features associated with many of the non-absorbable oral antimicrobial regimens such as high cost, bad taste, gastrointestinal intolerance, and risk of emergence of aminoglycoside-resistant Gram-negative bacilli (Schimpff, 1980). The mechanism by which co-trimoxazole protects against infection may be more complex than simply an effect on gut flora. One study using a population base similar to the above found a significantly greater reduction in the number of infections in a group of patients randomised to receive both co-trimoxazole and oral non-absorbable antibiotics compared with a group receiving only non-absorbable drugs (Enno et al., 1978).

When co-trimoxazole is administered for this purpose, it seems reasonable to suggest that nystatin be given concomitantly to prevent overgrowth of Candida (Hughes et al., 1977). However, before widespread use of these agents can be recommended, more data are needed to assess the haematological effects of co-trimoxazole in such specialised settings as during bone marrow recovery following intensive cytotoxic therapy or during the engraftment period of bone marrow transplantation.

3.7.2 Endocarditis

Since non-aeruginosa pseudomonads, such as *P. cepacia* and *P. maltophilia*, are usually resistant to other antimicrobials except the bacteriostatic agent chloramphenicol and possibly some newer cephalosporins, co-trimoxazole alone or combined with a polymyxin may be a useful choice for the rare patient with endocarditis due to these organisms (Fischer, 1973; Hamilton et al., 1973; Neu et al., 1973; Rahal et al., 1973). Even this triple antimicrobial regimen, however, may fail and cardiac valve replacement is often required in these patients. Results of co-trimoxazole therapy in the few other reported cases of endocarditis have been variable (Fowle and Zorab, 1970; Noble et al., 1981; Seligman et al., 1973); and it seems unlikely that co-trimoxazole will be considered even an alternate form of therapy for the vast majority of patients with this infection, although combined with other antibiotics it may be a potential alternative when 'conventional' therapy has failed (Noble et al., 1981).

3.7.3 Meningitis

Because both trimethoprim and sulphamethoxazole penetrate inflamed or uninflamed meninges to achieve therapeutic concentrations in the cerebrospinal fluid, a few patients with bacterial meningitis due to organisms otherwise difficult to treat, as well as a few patients with meningococcal or pneumococcal disease, have received co-trimoxazole (Barling and Selkon, 1978; Farid et al., 1976; LaFaix et al., 1972; Sabel, 1976). Results have been favourable, but experience is too limited to permit general conclusions. The author's personal experience is that systemic administration of co-trimoxazole (at 10 mg/kg trimethoprim and 50 mg/kg sulphamethoxazole) may be a valuable adjunct to intrathecal (intralumbar) plus systemic aminoglycoside therapy in adult patients with Gram-negative meningitis complicated by ventriculitis (Wormser and Strashun, 1980). The availability of the intravenous preparation of co-trimoxazole will probably encourage further, more definitive studies in this area.

At present, the data certainly do not warrant any change in the usual listing of alternate agents for treatment of acute meningitis. Specifically, whether co-trimoxazole is as effective a choice as chloramphenicol for treatment of ampicillin-resistant β-lactamase-producing *Haemophilus influenzae* is still not known. Preliminary data from

a rabbit model of meningitis due to this organism do however, support efficacy of co-trimoxazole and should stimulate a controlled clinical trial (Mylotte et al., 1980).

Concern over the prevention of morbidity due to *Neisseria meningitidis* and *Haemophilus influenzae* has been the impetus for evaluating the efficacy of co-trimoxazole in eradicating asymptomatic nasopharyngeal carriage of these organisms. A similar combination was not satisfactory prophylaxis for the meningococcal carrier state (i.e. trimethoprim plus sulphisoxazole; Feldman, 1973a), but co-trimoxazole will eradicate *Haemophilus influenzae* provided the agent demonstrates bactericidal activity against this organism *in vitro*, an event that occurred with only 31% of isolates in one recent study (Kirven and Thornsberry, 1978). It is unclear why trimethoprim plus sulphamethoxazole would fail to eradicate *Neisseria meningitidis* from the nasopharynx (although this may also occur with other antibiotics) when co-trimoxazole has been so successful in similar circumstances with *Neisseria gonorrhoeae* (Bro-Jørgensen and Jensen, 1973). Consideration should be given to performing studies directed at eradicating the meningococcus using dosage schedules similar to those employed for pharyngeal gonorrhoea.

3.7.4 Nocardiosis

Nocardia species are generally susceptible to sulphamethoxazole but resistant to trimethoprim. Synergism between trimethoprim and sulphamethoxazole is usually demonstrable *in vitro* after prolonged incubation using relatively low ratios of sulphamethoxazole : trimethoprim (from about 0.1 : 1 to 2.5 : 1) [Bennett and Jennings, 1978]. Thus, the current drug formulation does not provide an optimal serum concentration ratio, but tissue levels may be more favourable (see table III). Limited clinical experience with the combined agent has been encouraging (Baikie et al., 1970; Bayley et al., 1981; Geiseler et al., 1979; Maderazo and Quintiliani, 1974, Wallace et al., 1982), but despite a few anecdotal accounts to the contrary (Baikie et al., 1970; Maderazo and Quintiliani, 1974) there is no convincing evidence that co-trimoxazole is superior to a sulphonamide alone. Perhaps the most compelling observation that can be made from an analysis of reported cases treated with co-trimoxazole is that most responded to less than 2.5g of sulphamethoxazole per day, whereas the usually recommended dose of sulphonamide is from 4 to 9 g/day (Krick et al., 1975). Whether a given patient would benefit from increasing the total daily dose of both agents, or just the trimethoprim component, may ultimately depend on *in vitro* study with each individual Nocardia isolate.

3.7.5 Other Serious Systemic Infections

Several life-threatening infections including brucellosis (Daikos et al., 1973; Farrell and Robertson, 1980; Kontoyannis et al., 1975), plague (*Yersinia pestis*) [Ai et al., 1973], and melioidosis (*Pseudomonas pseudomallei*) [Morrison et al., 1979; Fuller et al., 1978], for which other effective therapy is established, have also been found to be responsive to co-trimoxazole in a few patients. Unless special circumstances prevail, this drug should be reserved for treatment of otherwise resistant strains or when toxicity or allergy preclude use of the standard treatment. In a small number of infants with biliary atresia co-trimoxazole has been used successfully to treat and prevent ascending cholangitis following hepatic portoenterostomy (Chaudhary and Turner, 1981).

3.8 Other Uses

3.8.1 Anaerobic Infections

Co-trimoxazole is active against many anaerobic organisms *in vitro*, including *Bacteroides fragilis*, provided small inocula and other appropriate conditions are established (Wüst and Wilkins, 1978). Most strains of *Bacteroides fragilis* are, however, resistant to trimethoprim alone, because of an insensitive dihydrofolate reductase enzyme (Then and Angehrn, 1979). Maximum synergy for

the combination occurs at a drug ratio of 1 : 1 (Then and Angehrn, 1979; Wüst and Wilkins, 1978). Too few patients with anaerobic infections have been treated to allow a meaningful assessment of clinical efficacy, but data from several divergent sources suggest that co-trimoxazole as currently formulated, may be unsatisfactory for Bacteroides infections for a number of reasons. Firstly, co-trimoxazole treatment does not consistently disturb the anaerobic faecal flora *in vivo* (Knothe, 1973; Naff, 1971). Secondly, compared with placebo, prophylactic treatment with co-trimoxazole did not reduce the 40% incidence of *Bacteroides fragilis* bacteraemia following transrectal prostatic biopsy (the duration of anaerobic bacteraemia was shortened, however, compared with the placebo-treated group) [Ruebush et al., 1979]. Thirdly, in a faecal-peritonitis model in rats, Bartlett and Onderdonk (1979) observed no significant effect of co-trimoxazole in the prevention of abscess formation. *Bacteroides fragilis* was the major isolate recovered from culture of the abscess cavities.

3.8.2 Soft Tissue and Bone Infections

Various soft-tissue infections (e.g. cellulitis) will respond to co-trimoxazole, even in immunosuppressed patients (Grose and Bodey, 1980). The few patients with acute and chronic osteomyelitis due to susceptible organisms, who were treated with co-trimoxazole, responded favourably provided a foreign body was not present (Craven et al., 1970; McAllister, 1974; Millard, 1973). It is surprising, therefore, that no controlled trials have been published comparing conventional parenteral therapy with oral co-trimoxazole.

Mycetoma (Madura foot or maduramycosis) due to *Actinomadura madurae, Actinomadura pelletieri, Nocardia brasiliensis, Nocardia asteroides,* and *Streptomyces somaliensis* seems to respond favourably to prolonged administration of co-trimoxazole (Mahgoub, 1972; Nitidandhaprabhas and Sittapairochana, 1975). Fungal agents, notably *Petriellidium boydii* in the United States, are more likely causes of the problem, however, and would not respond to the antibacterial combination. A few patients with cutaneous infection due to *Mycobacterium marinum* have also been successfully treated with the drug (Black and Eykyn, 1977; Kelly, 1976), but many of these organisms appear resistant *in vitro* and because this infection may heal spontaneously, interpreting these results is difficult (Cunningham et al., 1978; Sanders and Wolinsky, 1980; Wolinsky, 1979).

3.8.3 Acne

The beneficial effects of systemic antibiotics in the treatment of acne vulgaris are thought to be related to an antibacterial effect on the skin organism, *Proprionibacterium acnes.* This organism is responsible for the liberation from sebum of free fatty acids and/or other irritants which lead to the development of the characteristic cutaneous lesion (Melski and Arndt, 1980). The dihydrofolate reductase enzyme of *Proprionibacterium acnes* is susceptible to trimethoprim and the organism is readily inhibited by co-trimoxazole *in vitro* (Then and Angehrn, 1979).

Although administration of trimethoprim or a sulphonamide alone does not alter the free fatty acid content of human sebum (using titratable acidity as a measure of free fatty acids), use of the combination does decrease their concentration (Cotterill et al., 1971a; Strauss and Pochi, 1970). Clinical trials have shown co-trimoxazole to be superior to placebo (Hersle, 1972), and comparable to tetracycline (Cotterill et al., 1971b). The combined agent may be effective in tetracycline-resistant cases (Nordin et al., 1978). Thus, co-trimoxazole deserves consideration in any patient not responding to or unable to take a tetracycline. Caution should be exercised in its use, however, in young female patients who are 'at risk' for pregnancy.

3.8.4 Miscellaneous Uses

Far too few data are available to clarify the possible role of co-trimoxazole in histoplasmosis (due to *Histoplasma capsulatum* and *duboisii*) [Egere et al., 1978], South American blastomycosis (Ferreira

Lopez and Armond, 1968), Whipple's disease (Elsborg et al., 1975; Tauris and Moesner, 1978); Q-fever (Freeman and Hodson, 1972), and ulcerative colitis (Savidge, 1969), although favourable reports have appeared for each of these conditions.

Perhaps the most novel use of co-trimoxazole has been in the treatment of lice. This infestation, *Pediculosis capitis,* was eradicated in 10 of 12 adults receiving a 3-day course of the drug (Shashindran et al., 1978). A similar trial in the treatment of scabies showed that co-trimoxazole was completely without effect (Shashindran et al., 1979).

4. Adverse Effects

As might be expected, in studies comparing trimethoprim alone with co-trimoxazole the overall frequency of side effects has been lower with the single agent (see Brogden et al., 1982). However, despite the risk of possible toxicities of 2 different medications, co-trimoxazole is generally well tolerated by adults (Havas et al., 1973; Jick, 1982; Lawson and Paice, 1982), even with chronic administration. In part this is due to a marked difference in susceptibility to trimethoprim of bacterial, compared with mammalian, dihydrofolate reductase. For example, the concentration of trimethoprim necessary to inhibit *Escherichia coli* dihydrofolate reductase by 50% is some 50,000 times less than that required for the same degree of inhibition of the mammalian enzyme (Brumfitt et al., 1973).

The most common adverse reactions are mild gastrointestinal symptoms and skin eruptions, both occurring in up to 3 to 4% of patients receiving the drug (Bernstein, 1975; Frisch, 1973; Havas et al., 1973; Lawson and Paice, 1982). Nausea and vomiting are the principal gastrointestinal complaints, but some patients develop abdominal pain, diarrhoea, anorexia, constipation, pseudomembranous colitis, glossitis or stomatitis (Bernstein, 1975; Cameron and Thomas, 1977; Frisch, 1973; Havas et al., 1973; Scott, 1982).

4.1 Haematological Effects

Less than 0.5% of adult patients develop haematological abnormalities (Havas et al., 1973), due in most cases to an unknown (idiosyncratic) mechanism and not an alteration in human folate metabolism. These abnormalities include thrombocytopenia, leucopenia or agranulocytosis, anaemia (including haemolytic or aplastic), eosinophilia, and sulphaemoglobinaemia (Anonymous, 1979; Bernstein, 1975; Girdwood, 1976). Indeed, all haematological toxicities associated with sulphonamides are possible with co-trimoxazole. Only rarely does haemolysis occur in patients with glucose-6-phosphate dehydrogenase deficiency, possibly because the blood levels of sulphamethoxazole in patients receiving the combination are low (Chan and McFadzean, 1974; Lexomboon and Unkurapiana, 1978; Salter, 1973).

In some patients, thrombocytopenia appears to result from enhanced peripheral destruction due to co-trimoxazole specific antiplatelet antibodies. These immunoglobulins may be directed at either component of the drug combination (Barr and Whineray, 1980; Claas et al., 1979).

Trimethoprim-sulphamethoxazole individually or in combination can impair haematopoiesis in cultures of mammalian bone marrow cells *in vitro.* This effect is enhanced by using folate-deficient marrow and reversed by the addition of folinic acid (Bradley et al., 1980; Golde et al., 1978; Waxman, 1971). With chronic use, evidence of an antifolate effect may be found occasionally in patients as well. Less important changes include increased neutrophil lobe counts and elevated formimino glutamate excretion, while more significant alterations have consisted of pancytopenia with frankly megaloblastic bone marrow (Blackwell et al., 1978; Kahn et al., 1968). Patients with known folic acid or vitamin B_{12} deficiency are at increased risk of the antifolic effects of the combination, and patients with questionably adequate folic acid stores such as pregnant women (use of the drug not recommended), the elderly, patients with malabsorption

or malnutrition, alcoholics, patients receiving phenytoin or folic acid antimetabolites, or those with chronic haemolysis (such as sickle cell disease) should be carefully observed (Bradley et al., 1980; Chanarin and England, 1972; El-Tamtamy, 1974; Hill and Kerr, 1973). Concomitant administration of folinic acid will reverse these effects without interference in antimicrobial or antiprotozoal activity *in vitro* or *in vivo,* except in *Streptococcus faecalis* infections in which antimicrobial activity may be reduced (Bushby, 1973a; Grünberg et al., 1970).

Effects in children: Evidence from some individual studies suggests that children may be more susceptible to the haematological toxicity of co-trimoxazole than adults, but one large survey failed to identify any increased incidence of such toxicity in children (Reusser, 1977). Why certain trials have noted this adverse reaction and others did not is unclear, although the positive studies tended to treat with higher dose and/or for longer duration in association with careful follow-up of haematological parameters. Neutropenia developed in 16% (Forbes and Drummond, 1973), 26% (Scragg and Rubidge, 1971), 33% (Asmar et al., 1981), and 50% (Ardati et al., 1979) of paediatric patients in 4 different studies, respectively, and thrombocytopenia has been recorded in up to 18% of such patients (Böse et al., 1974). Significantly more haematological abnormalities have been observed in children receiving co-trimoxazole compared with controls receiving ampicillin (Böse et al., 1974), amoxycillin (Asmar et al., 1981) or chloramphenicol (Scragg and Rubidge, 1971), but a similar incidence of toxicity was found in one study in which controls were given sulphamethoxazole alone (Howard and Howard, 1978).

In a number of cases, the neutropenia reverted despite continuation of the drug combination; in some instances this was attributed to a concomitant 'viral infection' (Forbes and Drummond, 1973). Böse et al. (1974) found, however, that the thrombocytopenia progressed until the drug was discontinued. To date, the haematological changes found have not been clinically important. Yet pending more data, it would seem prudent to monitor closely the complete haematological profile of paediatric patients in whom longer term therapy with co-trimoxazole is undertaken.

4.2 Renal Effects

Administration of co-trimoxazole predictably results in mild increases in serum creatinine and decreased creatinine clearance, without alteration in glomerular filtration rate, apparently via competitive inhibition by trimethoprim of tubular creatinine secretion through the base secreting pathway (Berglund et al., 1975; Dijkmans et al., 1981; Rainer and Rosenberg, 1981). A small number of patients, principally those with underlying kidney disease, may develop genuine renal dysfunction or even complete renal failure which, although usually reversible when the medication is discontinued, may be irreversible (Bailey and Little, 1976; Kalowski et al., 1973; Osama and Krishnamurti, 1979; Richmond et al., 1979; Trollfors et al., 1980), and some workers have recommended that the drug be avoided in patients with a significant degree of renal impairment (Bailey and Little, 1976; Kalowski et al., 1973). In some patients, recovery of renal function has followed a course of corticosteroids (Kalowski et al., 1973). Histological findings show interstitial nephritis or tubular necrosis, changes previously associated with sulphonamides (Kalowski et al., 1973; Smith et al., 1980). Additionally, since sulphamethoxazole is excreted into urine chiefly as the relatively insoluble acetylated metabolite, adequate fluid intake must be maintained to prevent crystalluria (Buchanan, 1978; Siegel, 1977).

Co-trimoxazole may lead to mild natriuresis or more rarely profound diuresis with volume depletion, possibly related to a chemical similarity between sulphonamides and the thiazide or acetazolamide diuretics (Kaufman et al., 1980; Shouval et al., 1978).

4.3 Miscellaneous Reactions

Hepatitis, hepatic necrosis, intrahepatic cholestasis or pancreatitis have been reported rarely (Brøckner and Boisen, 1978; Coto et al., 1981; Nair et al., 1980). Cutaneous eruptions of any type may occur; erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and exfoliative dermatitis, although rare, may be serious or fatal complications (Bernstein, 1975; Frisch, 1973).

Miscellaneous central nervous system effects (headache, confusion, depression, hallucinations), peripheral neuritis, drug fever, and chills are described. Allergic or hypersensitivity phenomena, including anaphylaxis and vasculitis with periarteritis nodosa or lupus erythematosus have also been seen (Girdwood, 1976; Wahlin and Rosman, 1976).

Although dysmorphogenicity has been found in rats (principally cleft palate), no effects were noted in limited experience during human pregnancy (Brumfitt and Pursell, 1972; Williams et al., 1969). It is of interest that the fetal malformations produced in rats by the administration of co-trimoxazole during days 8 to 16 of pregnancy could be prevented by the co-administration of folinic acid (Salter, 1973; Udall, 1969).

Rats receiving sulphamethoxazole or co-trimoxazole, but not trimethoprim alone, continuously for a year have developed metastasising thyroid carcinoma (Salter, 1973), but there is no evidence for any such effect in man. Although small changes in thyroid function have been demonstrated during therapy with co-trimoxazole or with trimethoprim alone, the changes seen were not clinically significant (Cohen et al., 1980, 1981).

Trimethoprim in concentrations usually found in human plasma can prolong survival of skin allografts in mice (Ghilchik et al., 1970), and combined with sulphamethoxazole can suppress thymidine uptake by human lymphocytes *in vitro* (Gaylarde and Sarkany, 1972). These concentrations, however, are not associated with either inhibition of human lymphocyte transformation or with interference with polymorphonuclear leukocyte function *in vitro*, nor is there convincing evidence for an immunosuppressive action clinically (Anderson et al., 1980; Gaylarde and Sarkany, 1972).

5. Drug Interactions

Co-trimoxazole potentiates the anticoagulant effect of warfarin by selective inhibition of the metabolic clearance of its levorotatory (S) enantiomorph (O'Reilly, 1980). Similarly, by inhibition of metabolic clearance, co-trimoxazole may prolong the elimination half-life of phenytoin (Hansen et al., 1975). Like other sulphonamide-containing compounds it may potentiate the effects of oral sulphonylurea hypoglycaemic therapy (Mihic et al., 1975), although in practical terms this has not been shown to be a problem in clinical use.

Co-trimoxazole can also affect the assessment of certain laboratory values. A tiny overestimation of plasma creatinine may occur when the 'Technicon' autoanalyser is employed (Bye, 1976). Unless a resistant strain is used, the *Lactobacillus casei* method for determination of serum folate levels should not be used during co-trimoxazole therapy because therapeutic concentrations of the medication in serum may inhibit growth of the test bacteria (Hjortshøj et al., 1978).

6. Dosage and Administration

The standard tablet of co-trimoxazole consists of trimethoprim 80mg and sulphamethoxazole 400mg. In some countries a double strength formulation is also marketed, as well as a flavoured suspension for paediatric use, which contains the equivalent of trimethoprim 40mg and sulphamethoxazole 200mg per 5ml, and a paediatric tablet (trimethoprim 20mg and sulphamethoxazole 100mg). In general terms, the usual recommended adult dose is 2 standard tablets (or equivalent) twice daily, but

Table X. Oral dosage of co-trimoxazole in children. All doses shown are to be given twice daily. Use in children under 6 weeks (UK) or 2 months (USA) of age is not recommended

UK			USA[1]			
age	dose of suspension[2]	dose of tablets[3]	weight (lb)	weight (kg)	dose of suspension[2]	dose of tablets[4]
6w-6m	2.5ml		22	10	5ml	½
6m-6y	5ml		44	20	10ml	1
2y-6y		2	66	30	15ml	1½
6y-12y	10ml	4	88	40	20ml	2

1 In the USA the recommended dose in *Pneumocystis carinii* infections is 20 mg/kg trimethoprim and 100 mg/kg sulphamethoxazole per day given in 4 divided doses for 14 days.

2 The commercially available paediatric suspension, containing 40mg trimethoprim and 200mg sulphamethoxazole per 5 ml.

3 *Paediatric* tablets, containing 20mg trimethoprim and 100mg sulphamethoxazole.

4 *Standard* tablets, containing 80mg trimethoprim and 400mg sulphamethoxazole.

this can be increased in severe infections. The drug is not recommended for infants younger than 6 weeks to 2 months of age, because of the danger of kernicterus from the competitive effects of sulphamethoxazole on bile metabolism. The dosage for treatment of infections in children is shown in table X.

Co-trimoxazole can also be given parenterally if oral administration is not feasible. Intramuscular or intravenous infusion preparations may be given to adults in a dose of trimethoprim 160mg and sulphamethoxazole 800mg twice daily. In children or in severe infections these doses may need adjustment; for detailed recommended dosage information the clinician should consult the product literature.

In patients with reduced renal function, no modification of dose is necessary if creatinine clearance exceeds 25 to 30 ml/minute. For patients with creatinine clearance of 15 to 25 or 30 ml/min the dose should be reduced by half, with some recommending administration of the standard dosage for at least 3 days before instituting this dosage reduction. The drug is not recommended for patients with creatinine clearance less than 15 ml/min. However, if clinical need necessitates the use of this agent in severe renal failure (creatinine clearance less than 15 ml/minute) it has been suggested that one-half to 1 standard dose be given every 24 hours (Patel and Welling, 1980). In moderate to severe renal failure total sulphamethoxazole should be measured in plasma 12 hours after every third treatment day, and should not exceed 150 μg/ml (see Patel and Welling, 1980). It has also been suggested that in severe renal failure it may be preferable to use trimethoprim plus sulphadiazine, and give each unit dose every 30 to 40 hours (Bergan et al., 1977) [see section 7].

A list of presently 'approved indications' for co-trimoxazole is shown in table XI.

7. Recent Developments: Newer Trimethoprim Combinations and Trimethoprim Analogues

Antimicrobial synergism can be demonstrated between trimethoprim and the general class of sulphonamides (Kuipers, 1979; Seppänen, 1980). Reappraisal of the appropriateness of sulphameth-

Table XI. 'Approved' indications for co-trimoxazole in the USA and the UK

USA	UK
Genitourinary tract infections	
Urinary tract infection due to *E. coli, Klebsiella* or *Enterobacter,* and *Proteus mirabilis, vulgaris* or *morganii*	Urethritis, cystitis, pyelitis, pyelonephritis, and prostatitis. Male and female gonorrhoea
Respiratory tract and ear infections	
Acute exacerbations of chronic bronchitis in adults. *Pneumocystis carinii* pneumonitis. Childhood otitis media	Acute and chronic bronchitis, bronchiectasis, lobar and bronchopneumonia. *Pneumocystis carinii* pneumonitis, otitis media and sinusitis
Gastrointestinal tract infections	
Shigellosis	Typhoid and paratyphoid fevers, chronic carriage of Salmonella typhi and paratyphi, cholera and shigellosis
Skin infections	
None	Pyoderma, abscesses and wound infections
Other bacterial infections	
None	Acute and chronic osteomyelitis, acute brucellosis, septicaemias and other infections caused by sensitive organisms

oxazole as the partner to trimethoprim based on sound pharmacokinetic principles, as well as commercial considerations, have led to the release of numerous trimethoprim-sulphonamide preparations in many different countries (Bernstein, 1982). One of the newer combinations is trimethoprim plus sulphadiazine (co-trimazine). Compared with sulphamethoxazole, sulphadiazine has several desirable properties, including greater urinary excretion of active drug, wider tissue distribution with better penetration into the cerebrospinal fluid, and a similar alteration in elimination half-life of both active and metabolised drug in renal impairment (Acar et al., 1979; Barling and Selkon, 1978; Bergan et al., 1977, 1979; Örtengren et al., 1979; Reeves and Wilkinson, 1979). However, higher urinary levels may well be irrelevant, as the sulphonamide contributes little if at all to the efficacy of trimethoprim alone in the majority of patients with urinary tract infection (Lacey et al., 1980a). The other pharmacokinetic features, particularly its disposition in patients with renal failure, may be more significant clinically, but further data are needed to evaluate the elimination characteristics in this setting in slow *versus* fast acetylator populations. Another combination claimed to offer some potential advantages is trimethoprim plus sulphamoxole (co-trifamole), which is now available in some countries (Knothe, 1980).

Much attention has been focused on the combination of trimethoprim plus rifampicin (e.g. Alvarez et al., 1982; Arioli and Berti, 1979; Brumfitt and Hamilton-Miller, 1978, 1979b, 1981; Goldstein et al., 1979; Grüneberg and Emmerson, 1980; Harvey, 1978; Norden and Keleti, 1980; Steward and Eble, 1979). This combination is usually not synergistic in antibacterial activity, but by some definitions is interpreted to be so because trimethoprim effectively prevents emergence of rifampicin-resistant mutants. This combination has been demonstrated to be effective in the treatment of urinary tract infection (Adachi and Ribeiro de Almeido, 1979; Brumfitt and Hamilton-Miller, 1981; Palminteri and Sassella, 1979) as well as in the eradication of the chronic *Salmonella typhi* carrier state in a few patients (Freerksen et al., 1977). However, other effective agents are available for most urinary infections.

There is considerable interest in finding other diaminobenzylpyrimidines that may be intrinsically more active than trimethoprim or that may still be useful for organisms that have acquired resistance to trimethoprim (Burchall, 1979; Seydel and Wempe, 1980). Tetroxoprim, a close analogue of trimethoprim, has been investigated. Unfortu-

nately, this agent is less active than trimethoprim and does not appear to offer any special advantage (Bywater et al., 1979; Reeves et al., 1979; Wiedemann, 1979).

8. The Place of Co-trimoxazole in Therapy

Since its release in the late 1960s co-trimoxazole has been used in the treatment or prevention of an ever-expanding array of infectious disorders. The antimicrobial activity of the combination *in vitro* frequently exceeds that of either agent alone. Whether or not synergy occurs under clinical conditions has been less clearly established (see below). Co-trimoxazole is effective for therapy and prevention of *Pneumocystis carinii* and urinary tract infection, and for treatment of acute otitis media, shigellosis, acute exacerbations of chronic bronchitis, gonorrhoea, nocardiosis, typhoid fever, soft tissue or bone infections and acne. It also appears to be a promising agent for prophylaxis against infection in neutropenic leukaemic patients. When used parenterally (e.g. Ardati et al., 1979; Grose and Bodey, 1980; Mylotte et al., 1980; Schmidt et al., 1982; Stratford et al., 1978; Stuart et al., 1980; for review see Gleckman et al., 1981) it may be effective in the treatment of pneumonia, sepsis, meningitis and other life-threatening disorders, although more data are needed to define its role in these areas. The drug is not suitable for treatment of syphilis, tuberculosis, *Pseudomonas aeruginosa* infections or pharyngitis due to *Streptococcus pyogenes,* and its effectiveness in anaerobic infection appears doubtful. Co-trimoxazole is generally well tolerated, even with long term administration, but its potential for haematological effects and nephrotoxicity must be monitored, especially in paediatric patients or those with underlying renal damage, respectively.

There remain a number of unanswered questions about co-trimoxazole. Firstly, for which clinical situations would trimethoprim alone be as effective as the combination (e.g. Brumfitt and Pursell, 1972; Lacey et al., 1980b; Männistö, 1976; Seneca et al., 1974; for review see Brogden et al., 1982)? Although clinical superiority of the combined drug over its components has been strongly suspected for *Pneumocystis carinii* infection, such an advantage has been demonstrated in humans only in the treatment of gonorrhoea. Indeed, in the treatment of urinary tract infection in patients without gross structural abnormalities, either trimethoprim or a sulphonamide alone is equally as effective as the combined agent.

Secondly, will the use of plain trimethoprim lead to a more rapid emergence of resistance than would have occurred with restriction of its use to the combination? The data available suggest that this worry has been exaggerated in the past, although some data suggest that careful monitoring of patterns of trimethoprim resistance should continue (see Brogden et al., 1982). Certainly, the risk of emergence of resistance to trimethoprim as a single agent cannot be considered analogous to that of rifampicin.

Thirdly, is sulphamethoxazole the sulphonamide best pharmacologically matched for combination with trimethoprim? Aside from the preferable elimination kinetics of sulphadiazine in patients with renal failure, and possibly advantageous distribution kinetics in some situations there appears to be no practical advantage of other sulphonamide preparations over sulphamethoxazole.

Lastly, can a diaminopyrimidine be synthesised which will be active against micro-organisms that have acquired resistance to trimethoprim?

The results of studies designed to answer these questions will be eagerly awaited.

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