PRICE'S TEXTBOOK OF THE PRACTICE OF MEDICINE

TWELFTH EDITION

Sir Ronald Bodley Scott

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Preface to the Twelfth Edition

In the preface to the first edition of this textbook Dr. Frederick Price declared its purpose and scope to be the presentation of a comprehensive survey of modern medicine. Its aim remains unchanged and this edition will be found to reflect once again contemporary practice in the United Kingdom and to provide practitioners and students of medicine with a useful work of reference. Considerable changes in the book's arrangement were made in the last edition and in this the new design has been completed. The entire text has now been rewritten with the single exception of the chapter on psychological medicine. This article by the late Sir Aubrey Lewis stands as a model of such lucid and elegant exposition that Professor Shepherd decided to make only minor changes.

Medicine has expanded so rapidly that few physicians now feel competent to write with unassailable authority on all aspects of any one specialty. Thus more contributors have been enlisted for this edition than for any of its predecessors; indeed the number has risen from 34 to 77. Examples in which many authors share the task are the sections on renal and cardiovascular diseases to each of which there are now nine contributors. The section on diseases of the skin has been replaced by one entitled 'Dermatology in relation to general medicine' and that on environmental medicine has been greatly expanded. Additions which it is hoped readers will find useful are appendices giving the normal ranges of laboratory tests on the various body fluids, the average and ideal body weights for age and height, and a glossary of the many abbreviations and acronyms which appear in the book and are in common medical usage.

Of our contributors Dr. Bomford, Dr. Brigden, Dr. Lloyd Davies, Professor Maegraith, Dr. Brian Russell, Professor Smart, Dr. Denis Williams, and Professor Clifford Wilson have retired. It is a privilege to be able to thank them and to pay tribute to their contributions which have brought the book such renown. Our new contributors number 51 and their names are set out in the prefatory pages. They will be familiar to all working in the same fields not only for their repute, but also for the comparative youth of many. I take this opportunity of recording my gratitude to them for their patient co-operation, for devoting many leisure hours to writing, and, above all, for the distinction of their contributions to this edition. My thanks are due to the Medical Director General of the Royal Navy for allowing the outstanding team of medical officers from the Institute of Naval Medicine to contribute to the section on environmental disease.

It is with great sadness that I record the death of two contributors. Dr. Michael Mason who wrote the section on diseases of joints died suddenly in September 1977. His death is a serious loss to rheumatology. Professor Gordon Hamilton Fairley died from a senseless bomb outrage in October 1975. He had scarcely started his articles on lymphoma and leukaemia and, because it was too late to recruit another author, I was forced to break my own rule and write these sections myself. He and I had worked together for many years and shared the same professional interests. I believe that my chapters reflect the views he held and I hope they will be taken as a tribute to this gifted pioneer of medical oncology.

Finally it is with sincerity and pleasure that I express my thanks to the publishers and record my appreciation of the courtesy and forbearance shown by its staff, qualities for which the Oxford University Press is justly renowned.

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Section 1

Infection and antibacterial agents

INFECTION
ANTIBACTERIAL AGENTS

Section 1

Infection and antibacterial agents

INFECTION
ANTIBACTERIAL AGENTS

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. R. A. Shooter

Diseases caused by bacteria and viruses are common and, despite chemotherapy, still kill many patients. They may be naturally serious, or serious because untreated or mistreated, or because they occur in patients who for one reason or another are more susceptible than other people. Until now it has been possible to prevent only a minority by immunization. Some can be prevented by controlling the spread of organisms from patient to patient, but for many diseases this is not yet practicable. It is the intention in this section to review the sources of infection, the routes by which micro-organisms spread, and to note some of the effects of chemotherapy.

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Sources of infection and and out a bandurado airo a this by muoma

Sources of infection occur in other people, in animals, or in objects such as soil. Other people may be a source of infection because they are suffering from the disease. Alternatively in some diseases the patient may be infectious during the incubation period, and before the diagnosis is known; or, the infection may be so trivial that no notice is taken of it, although the patient may be as capable of infecting others as those with a florid form of the disease. A patient with this type of infection is referred to as 'a missed case', and is frequently responsible for the introduction or continuation of outbreaks of infection in institutions. The most difficult source to identify and control is the healthy carrier. Carriers may harbour pathogenic bacteria as a late result of suffering from a disease such as typhoid fever or diphtheria, or, as for the staphylococcus, they may carry the organism without a history of disease due to it. In either case they are only likely to be identified by bacteriological

Animals of many kinds are possible sources of infection. In this country in the past milk from tuberculous cows was responsible for an untold number of human cases of tuberculosis. Unpasteurized milk may still contain the causative agent of undulant fever, Brucella abortus, or organisms contributed by the milker, such as Streptococcus pyogenes. Members of the salmonellae are widespread in the animal kingdom, and are regularly responsible for outbreaks of food poisoning as a result of eating food which has not been satisfactorily preserved, or has been contaminated after preservation or cooking. One of the commoner forms of food poisoning is that caused by animal-derived heat-resistant strains of Clostridium welchii. Animal products such as catgut and horse hair may contain organisms originally carried by the animal, and have in the past been responsible for tetanus and anthrax. In other parts of the world, animals may be the reservoir for viral diseases, such as rabies or yellow fever, or for protozoal diseases such as trypanosomiasis.

Pathogenic bacteria found in soil, dust, and water have nearly always come from people or animals. Organisms such as the typhoid bacillus readily survive in water. Spore-forming organisms, notably the clostridia and Bacillus anthracis, can survive for long periods in soil or in dust. Non-spore-forming bacteria such as Strep. pyogenes and Staphylococcus aureus can remain alive for weeks or months in dust. Recent work, however, suggests that some dried organisms may be less able to initiate infection than those which have been recently shed by their human host.

Spread of bacteria and viruses delibered and vilame

People may become infected because they inhale or swallow

organisms, or because organisms enter the body through the skin or mucous membranes. Infection with some bacteria and viruses can occur before birth by passage through the placenta.

from escaybere in the body. When more is known about

With such an apparently simple background it has been easy to postulate and to teach general principles of bacterial spread applicable to pathogenic bacteria. Epidemiological studies, greatly aided in recent years by the ability to type organisms within a species, have, however, shown that it may be rash to predict how individual pathogens spread from general principles alone. For some time it will probably be better for the doctor to accept that much more needs to be found out about most viruses and many bacteria before the way in which they spread from patient to patient is known in full detail.

Among the factors that are important before infection occurs are the dose of the organism, the route by which it infects, and the resistance of the individual [a subject discussed in Section 2]. For many infections information on some of these heads is missing. Sepsis caused by Staph, aureus provides an example. Although the dose needed to start an infection is uncertain, in many patients superficial skin sepsis and wound infections are both autogenous, being derived from the patient's own carrier sites. Of these the nose is the most common, some 30-40 per cent of normal people being carriers. Transfer of staphylococci from one normal person to another must occur in several different ways, of which one is direct contact. It is also likely that colonization of the nose results from breathing in staphylococci in the air. With the exception, however, of sneezing, respiratory activities do not disseminate staphylococci from the normal respiratory tract, and the sometimes large numbers of staphylococci found in the air are probably dislodged from the skin either by themselves, or more usually, carried on shed skin

Patients with infections of the lung may cough out bacteria. These emerge carried on a spray of particles of different sizes ranging from those large enough to be visible, down to those of only a few micrometres in diameter. Larger particles fall to the ground within a few feet of the patient. The moisture content of the smaller particles may evaporate and the residual material, perhaps containing micro-organisms, may stay airborne and travel considerable distances. Such particles are known as droplet nuclei.

It has been customary to ascribe the spread of many respiratory infections and some specific fevers to droplet spread. For infections in the lungs this is probably true as the air velocity in the lung at the peak of a cough may approach 300 m/s at which point large numbers of small particles will be formed. The generalization should not, though, be applied without proof to all infections of the respiratory tract. Although haemolytic streptococci multiply freely in the throat, they are rarely expelled in the sneezes of patients with streptococcal sore throat. As has already been noted, few staphylococci are shed during respiratory activities.

The spread of intestinal organisms has been studied for years, and a great deal is known about it. For some organisms, of which the typhoid bacillus is one, typing methods have more recently provided epidemiologists and public health authorities with the means of tracing routes of spread to a high degree of

Advances to come may include the realization that other intestinal organisms as well as the recognized pathogens may pass from

person to person. It now appears that organisms in the bowel do not necessarily form a static community. Strains may be changing continually, those being lost being replaced by new strains swallowed in the food. This is probably true, at any rate in hospital patients, for Escherichia coli and Pseudomonas aeruginosa (pyocyanea), organisms that, although innocuous in the bowel, can cause infections elsewhere in the body. When more is known about this subject, the treatment of patients with infections of the urinary tract

and elsewhere with these organisms may have to include attention to the bacterial content of the bowel, and its origin.

Fortunately intact mucous membrane and skin constitute impassable barriers for most organisms, but lacerations and abrasions are common and organisms may be introduced through insect and animal bites. Deliberate breaks of the skin, by surgical incision or in the course of giving an injection, carry the possibility of introducing infection.

ANTIBACTERIAL AGENTS

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THE SULPHONAMIDES AND THE ANTIBIOTICS

mucous membranes, infection with some bacteria and viruses

Over the last thirty years chemotherapy has entirely altered the picture of infectious disease. Provided that the patient has no complicating condition there are few bacterial diseases which will not respond to proper treatment. So far the only viral infections which can be treated with success are those due to a few of the largest viruses, but for some others, for example influenza, antibiotics have very sharply reduced the mortality by dealing with secon-

Pare import

darily invading bacteria.

Although so successful in treatment, antibiotics have met with only modified success in the prevention of infection. On the credit side they can be used for some forms of mass prophylaxis, as in the suppression of dysentery in an institution; or for individual prophylaxis, as in the prevention of recurrences of rheumatic fever by the regular administration of penicillin to prevent haemolytic streptococcal throat infections. Antibiotics have, obviously, also contributed to the prevention of disease by reducing the period of infection, as, for instance in tuberculosis and syphilis. In hospitals they have, however, been responsible for the evolution of strains of bacteria, particularly of Staph. aureus and some Gram-negative bacilli, which are not only antibiotic resistant, but which appear to be more virulent than their antecedents. Hospital studies, usually based on typing methods, have shown that cross-infection, defined as the acquisition by a patient of another patient's organisms, occurs far more often than was once thought. Transfer of this sort provides newly evolved bacterial strains with a good chance to survive and spread. It is for this reason that chemotherapy can no longer be considered alone. For good results attention must be paid to the way in which bacteria spread, as well as to how they can be killed in the individual patient.

Unless applied directly to a lesion, antibiotics are not likely to act solely on the organisms causing infection; any other bacteria susceptible to their action will be attacked. This interference with the normal bacterial flora of the patient may produce undesirable results, and even a virtually new disease. Thus the administration of drugs which alter the flora of the alimentary tract may be followed by an overgrowth of yeasts or of staphylococci. In some cases there is erosion of the bowel wall with the production of staphylococcal

enterocolitis.

eign of small particles will be beimed. The photos shaded proof to Necessity for treatment as an element digment A construction

The majority of infections will resolve in time without specific treatment, but chemotherapy will sometimes save life and can often shorten the illness, prevent complications, and save the patient the discomfort incidental to the disease. It is obvious that serious infections should be treated. There is some argument as to whether relatively minor infections should be treated, or whether they should be left to recover unaided. There is, at any rate in theory, complete agreement that in the absence of a clear indication, antibiotics should not be used.

There are several reasons for the reluctance to use antibiotics unless necessary. Treatment may stop development of natural

immunity to the infecting organism, although by the time the diagnosis has been made and treatment begun, the immune processes are often under way. Every course of treatment, too, carries with it some risk, either because of the development of hypersensitivity, or because of a toxic effect of the drug itself. Probably the most valid reason for using antibiotics only when necessary is that the proportion of resistant bacteria in a community is directly related to the amount of antibiotic consumed. The mechanism and the rate of development of resistance may be different, but for all antibiotics, the greater the usage, the greater the number of resistant bacterial strains, if resistance is going to develop at all. Once resistance to a drug is acquired, it is usually a permanent property of the organism and the larger the pool of resistant organisms becomes, the less is the value of the antibiotic.

Choice of drug

Sensitivity tests, correctly performed, and with their limitations understood, are the proper basis for chemotherapy. As normally done they show if an antibiotic can inhibit bacterial growth at a concentration likely to be achieved in the body. Inhibition is all that is needed in the treatment of most infections, as once this is achieved the body's natural defences will remove the cause. Thus a report stating that an organism is sensitive to an antibiotic should normally imply that an infection due to that organism will respond to the antibiotic. There are certain recognized exceptions, which

In a few diseases, notably typhoid fever, demonstration of sen-

come under three rather separate headings.

sitivity in the laboratory is not a guide to the outcome of treatment. Typhoid bacilli are inhibited by a number of antibiotics, but of those in common use, only chloramphenicol is likely to cure the patient. The reasons for this are not known. Sensitivity tests may also mislead if it is assumed that antibiotics will be effective whatever the condition of the patient. Chronic urinary infections provide a good example. In the presence of obstruction of urinary flow, the chances of curing the infection by chemotherapy are slight, even if the infecting organism is at first sensitive to the drug used. Thirdly, for a very few diseases treatment will only succeed if the antibiotic kills all, or nearly all the bacteria; inhibition of bacterial growth alone is not sufficient. Not all antibiotics are bactericidal. Many are bacteriostatic, and those that are bactericidal will not always kill all organisms exposed to them. Thus in subacute bacterial endocarditis a conventional sensitivity report stating that the streptococcus is sensitive to one or other antibiotic may mislead, if all that has been tested is the ability of the antibiotic to prevent growth. In this disease it is essential to kill bacteria and further tests should be done to choose an antibiotic which will do this. It may be that no single drug can be found that is bactericidal. When this occurs, tests should be done with two, or rarely, more, antibiotics in combination, as together antibiotics may be bactericidal, although not so when used singly. This potentiation of effect is known as synergism.

Occasionally the combination of two antibiotics may result in

antagonism. In this condition one drug, usually a bacteriostatic one,

hampers the action of its bactericidal partner, and the effect is less than that of either drug alone. Antagonism can easily be demonstrated in the laboratory, although the conditions have to be chosen with care. The evidence that it occurs in the treatment of patients is less clear. It has been claimed to occur in the treatment of pneumococcal meningitis, in which the simultaneous administration of penicillin and tetracycline has been said to lead to a higher death-rate than if penicillin alone is given, presumably because the tetracycline interferes with the action of penicillin. Antagonism has not been convincingly demonstrated in the treatment of other infections, although this statement would be denied by some authorities, who claim to have seen it, particularly in the treatment of bacterial endocarditis.

It is often necessary to start treatment without laboratory help. The condition may be one which is known to respond regularly to one of the antibiotics; it may be difficult to send specimens to the laboratory, or the patient's condition may be such that treatment has to be started as a matter of urgency before a sensitivity report is available. For many infections this course is not likely to lead to difficulty so long as its empirical nature is recognized and the patient's chemotherapy re-assessed in the light of his clinical progress. It should be avoided if possible in diseases such as endocarditis

Table 1.1

Recommended drugs for treatment

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Actinomycosis	al a pag	210	0 <u>10</u>	<u>ud</u> :	2	<u>w</u>	4	uio	20	d_j	<u>H</u> V
Anthrax build the area 1911 buth	11-11-02	-	107-10	4	2		4		-	-	-
Brucellosis		_	_	+1	+1	3	4	100	3		1
Diphtheria Dysentery—bacillary	2 -	_	-	2	2	1-	1	_	1	2	
—infantile		901	1115	15	Qt.	18.7	317	MO:	i Cita	2	000
Gas gangrene	en en el el el	350	dia.		2	100	4				-
Gonorrhoea	1 4	_	_	2	2	_	4	_	-	_	-
Leptospirosis	1 -	_	_	_	2	_	_	_	_	77 . 5 .	4.0
Meningitis H. influenzae		2	_	_	_	_	. 1	<u>.</u>	3	_	-
meningococcal	2 -	2	110	_	250	300	-	1000	1-5	5 —	1301
pneumococcal	1 4	2	3.24	3	-		_	-	3	1	3
Paratyphoid fever	131 21 46	. 3	-	-	-	-	. 1	1	S ir .	-	100
Pneumonia H. influenzae	3–5 –	2	77	4	1	3-5	4	100	UTO:	-	5
Kl. pneumoniae	3–5 –	-	_	4	1	3-5	4	_	-	-	-
pneumococcal	o brudata	1990	2	T	2 2	2	1	(11)	3	die	3
staphylococcal	1 2	0.00	2	4	2	2	4	7	1	W.	3
Strep. pyogenes Psittacosis		J. K	_		1	_	Ξ	_			_
Staphylococcal infection	1 2	-	2	4	2	2	4	-			3
Strep. pyogenes infections	1 4		2	_	2	2	7	10101	-	-	3
Strep. viridans infections	1 -	350.	2	4	_	-	_	-	_	0_1	UO.
Syphilis 1919 to Date 34 bl	uedajav <u>a</u>	1190	100	5	2	3	4	177	-	للتباج	qi.
Typhoid		3	_	_	_	-	1	_	7	-	_
Urinary infections			:81		SB			191	100	1	HQ.
Ps. aeruginosa infection	s 5 —	100	5	3	3	5	5	5	5	1	15
Proteus infections	1-5 -	2	1-5	2	3	5	4	2	3	3	-
Esch. coli infections	3-3 -	2	1-5	1	2	3	4	1	1	2	1
Strep. faecalis infections Staph. infections	1 2	2	5	3	1 2	9	4	2	3	5	-
Klebsiella infections	5 _			1	2	5		3	3	. 170	10000

Key to table

1=drug of choice if infecting strain sensitive.

2=alternative drug if organisms resistant to first choice, or if patient hypersensitive.

3=alternative drug usually of lesser activity.

4=effective drug, but toxicity limits use.

5=organism resistant to drug, or infection will not respond.

in which the rational, and possibly life-saving, choice of drug for treatment rests on laboratory findings.

In such infections as meningitis and pneumonia valuable help may be obtained from the laboratory within a few hours from the microscopical examination of a stained film of cerebospinal fluid and sputum.

When the results of treatment conflict with the guidance given by the laboratory, there may be several possible explanations. In time most patients will recover without treatment and the apparently successful treatment of an infection due to an organism said to be resistant to the drug prescribed, does not necessarily mean that the antibiotic has been responsible for the recovery. Discrepancies between the results of sensitivity tests and the outcome of treatment probably occur most often in respiratory infections. As for other infections, the reason may be that the tests have not been feel done, but an alternative reason may be that the laboratory has been sent poor material with which to work. The importance of the proper collection of specimens when laboratory guidance in chemotherapy is desired, cannot be over-emphasized.

In deciding which drug to use, the merits of administration by mouth will have to be compared with the advantages of injections. For seriously ill patients and for patients who may fail to take oral preparations there is a certainty about an injection which may recommend it, particularly in the early stages of treatment. Finally the cost should be considered. Many doctors are unaware of the considerable differences in price between the various preparations available.

Duration of treatment

As a result of experience, supported in many cases by extensive clinical trials, there is general agreement about the length of treatment for many diseases. Tuberculosis, for example, may require months, subacute bacterial endocarditis and actinomycosis weeks, and haemolytic streptococcal infections only days. Difficulties arise when after a reasonable period of treatment the patient has failed to respond and his condition deteriorates. When this occurs the original diagnosis should be carefully reviewed. In some cases, although the original clinical and laboratory decisions were correct, the organisms may be found to have become resistant to the drug used during the course of treatment. Alternatively the original sensitive organism may have been replaced by another and resistant organism which was present only in small numbers at the start of treatment, or the patient may have become infected by entirely new bacteria, derived from himself or by cross-infection from other patients or the staff. For many infections, failure of treatment should be evident within a few days; when it is seen there is usually no benefit to be obtained from persevering with the same drug.

Resistance

Resistant bacteria increase in numbers primarily because antibiotics are used, and the greater the use, the more numerous the resistant strains. There are three main reasons why bacteria are resistant to antibiotics. Resistance may be a natural property in that the organisms are insusceptible to the action of the antibiotic, or, as in the case of staphylococci and benzyl-penicillin, because they produce an enzyme that destroys the antibiotic. They may acquire resistance to an antibiotic during the course of exposure to it, either in the test tube or in the patient during the course of treatment. Thirdly, they may become resistant through the phenomenon of infectious or transferred drug resistance. This recently discovered form by which genetic material conferring resistance can pass from resistant organisms to sensitive ones is of great theoretical and important practical interest. It has been shown to occur in the intestines of animals and man and may occur in the respiratory tract and elsewhere in the body. A disturbing possibility is that resistant non-pathogenic bacteria may be able to transfer resistance to pathogenic bacteria, previously sensitive to antibiotics.

The great frequency of antibiotic-resistant bacteria is, however, the result of their spread from patient to patient, usually in the hospital. In the general population spread occurs less readily. Where it has been studied, for staphylococci, it has been shown that members of the public with resistant strains frequently have had

contact with hospitals.

Plainly, in attempting to prevent resistance, antibiotics should be prescribed only when necessary. Hospitals are, however, for the treatment of the sick and the legitimate use of antibiotics in them will almost certainly result in an increasing number of resistant bacteria. Theoretically it should be possible to delay the appearance of resistance by prescribing two antibiotics together. This has been notably successful in the treatment of tuberculosis, but as yet is a policy of only doubtful value for most other infections. The necessity of preventing the emergence and accumulation of resistant bacteria in order that antibiotics may remain effective agents has stimulated research into the routes of hospital cross-infection. This work is beginning to yield valuable results, particularly for staphylococcal infections and infections of the urinary tract, and it is to be hoped that it will also prove of value in other diseases.

THE SULPHONAMIDES all less at gurb dalidw gnibide at

Modern chemotherapy began in 1935 with the description by Domagk of the effectiveness of the first sulphonamide in the treatment of experimental streptococcal infections. There are now many sulphonamides, all of which have the same general structure. Changes in composition are responsible for the varying physical,

pharmacological, and antibacterial properties.

Sulphonamides are bacteriostatic and owe this action to their ability to compete with para-aminobenzoic acid and so block the enzyme system in the bacterial cells which utilizes para-aminobenzoic acid as a precursor of folic acid. Folic acid is essential for both human and bacterial cells, but they differ in that human cells absorb the vitamin preformed from the diet while bacterial cells are unable to absorb it preformed, and have to make it themselves from para-aminobenzoic acid. The details of this synthesis have become of more importance with the discovery of compounds such as pyrimethamine and trimethoprim that block a later stage of folic acid synthesis in the bacterial cell and that will act synergistically with sulphonamides.

Distribution and excretion and Alternation and excretion a

Although there are individual differences between the sulphonamides, the absorbable compounds are taken up from the bowel and diffuse freely throughout the body, reaching the cerebrospinal fluid in good concentration [Table 1.3, p. 7]. An appreciable amount of the dose is usually excreted in the urine in an active form. Non-absorbable sulphonamides are designed to exert their effect within the lumen of the bowel and relatively little is absorbed.

Toxicity and hypersensitivity that he appeared partial and heristed.

A wide range of toxic reactions may be seen with the sulphonamides, the different compounds varying in the frequency and kind of toxic effects they produce. Gastro-intestinal disturbances and cerebral effects such as depression and confusion are not uncommon. Serious damage has been caused by the precipitation of sulphonamides in the kidney. This hazard may be avoided by keeping the urine alkaline and the patient's water intake adequate. Other toxic reactions include agranulocytosis, aplastic anaemia, thrombocytopenia, and hepatitis.

Hypersensitivity to sulphonamides is easily acquired. Hypersensitive patients on re-treatment may show drug reactions and contact dermatitis. Sulphonamides have, rarely, been held responsible for the onset of polyarteritis nodosa. Another rare complication has been the Stevens-Johnson syndrome [see Section 14], particularly following the use of long-acting sulphonamides. Acute haemolytic anaemia is liable to occur when sulphonamides are given to individuals whose red blood cells are deficient in glucose 6-phosphate

dehydrogenase [see Section 13].

Preparations

A considerable number of sulphonamides is available, and new preparations are regularly being added to the list. The various preparations may differ in regard to speed of absorption, activity in the body, and rate of excretion, but in the final outcome the practical differences between compounds may not be great, as advantages in one direction may be counterbalanced by disadvantages in another. The prescriber's final choice may well depend on experience and local practice. There are three main types. Absorbable sulphonamides are taken up from the bowel and spread rapidly through the tissues. Poorly absorbed sulphonamides are designed to act within the bowel, and relatively little of the drug is absorbed. Lastly there are the long-acting sulphonamides which are absorbed when given by mouth, but which are retained for prolonged periods in the body.

Absorbable sulphonamides application of the sulphonamides application of the sulphonamides application of the sulphonamides applications of th

The choice of absorbable sulphonamides is a wide one. The following are amongst the most used. He among the most used and among the most used.

Sulphadimidine. This compound is rapidly absorbed. It is one of the most soluble of the sulphonamides and least likely to lead to deposition of crystals in the urine. Since it is not as active as some it should not be used for the treatment of gravely ill patients.

Sulphafurazole. A compound with similar properties to sulphadimidine.

Sulphadiazine. This is one of the more active sulphonamides. It diffuses freely through the tissues, and in particular reaches satisfactory concentrations in the cerebrospinal fluid. Special care must be taken to prevent the deposition of crystals in the urinary tract because it is only sparingly soluble in the urine.

Trisulphonamide tablets. These tablets are a mixture of sulphathiazole, sulphadiazine, and sulphamerazine. The chief virtue of this compound is the lesser risk of crystalluria, due to the fact that the presence of one sulphonamide in the urine does not interfere with the solubility of the others and a lesser amount of each drug can be administered. It can be recommended for use in urinary and other infections.

Poorly absorbed sulphonamides

The choice of poorly absorbed sulphonamides is smaller. Among them are:

Succinylsulphathiazole. Since the drug is poorly absorbed, only about 5 per cent of the dose is available for excretion in the urine, and crystalluria is not a hazard. Sulphathiazole is the active principle, being released by hydrolysis in the bowel.

Phthalylsulphathiazole. This compound differs from the preceding one chiefly in having greater bacteriostatic action in the bowel. The dose is consequently smaller. Poorly absorbed sulphonamides were used originally for the treatment of bacillary dysentery. Results as good or better can be obtained in this disease with absorbable sulphonamides, which many believe should be used in preference.

Long-acting sulphonamides

New forms of long-acting sulphonamides are still being produced. Time will show which is most useful. Sulphadimethoxine, sulphamethoxypyridazine, and sulphormethoxine are among the best known.

Dosage

This is shown in Table 1.2. When using absorbable sulphonamides in the treatment of acute infections it is advisable to give an initial loading dose to procure the necessary blood concentrations as soon as possible. For patients who are unable to take the drug by mouth,

treatment should begin with the intravenous injection of a 5 per cent solution of the sodium salt of the sulphonamide. The injection should be given slowly and care should be taken to avoid extravasation into the tissues. The sodium salt may be given intramuscularly, but the injections are likely to cause pain; they should be spaced out at least three inches apart, and be limited in number. Nerves must be avoided as cases of foot and wrist drop have been reported. Sulphonamides should never be injected intrathecally. This is fortunately not necessary as they diffuse into the cerebrospinal fluid.

To avoid deposition of crystals in the urinary tract the urine should be made alkaline, and the patient's fluid intake should not be below 3 l in the day.

Table 1.2
Dosage of sulphonamides

		-	
A	ы	 140	

Oral	Loading dose	Maintenance dose	Interval
- Spould not be	gm 61	590 Jag	gm (ti
Sulphadimidine		Theb	
Sulphafurazole			7.50 mg
Sulphadiazine	2-3 g	1-1·5 g	4-6 hourly
Trisulphonamide (not intravenously)	(1.5 g-2 g i.v.)		
Succinylsulphathiazole	_	2 g	5 doses in day
Phthalysulphathiazole	Neves	1800	3 doses in day
Sulphadimethoxine	1 g	0.5 g	Daily
Sulphamethoxypyridazine	1 g	0.5 g	Daily
Sulphormethoxine	-	1-2 g	Weekly

Lower doses recommended for urinary infections [Table 1.6].

Children

Loadir	ng dose	Mainten	ance dose	- Interval	
0–3 yr	3–10 yr	0–3 yr	3–10 yr		
330				- yird a	
9/915.					
0.5 g	0.75 g	0.5 g	0.75 g	4-6 hourly	
(0·5 g i.v.)	(1 g i.v.)			(bedroad	
		0.5 g	1 g	5 doses in day	
171-0 -	gu <u>z</u> (t) −6	0.5 g	0-75.g	3 doses in day	
	0–3 yr	0.5 g 0.75 g	0-3 yr 3-10 yr 0-3 yr 0-5 g 0.75 g 0.5 g (0.5 g i.v.) (1 g i.v.) - 0.5 g	0-3 yr 3-10 yr 0-3 yr 3-10 yr 0-5 g 0.75 g 0.75 g 0.75 g (0.5 g i.v.) (1 g i.v.) - 0.5 g 1 g	

Antibacterial activity

Sulphonamides exert a bacteriostatic effect on a considerable number of Gram-positive and Gram-negative organisms. For some species, however, resistant strains are common, and an organism resistant to one sulphonamide can be regarded as resistant to all.

Indications

For most infections sulphonamides have been replaced by more effective and possibly less toxic antibiotics. In a few diseases, for example gonorrhoea, they have in the past been rendered valueless by the predominance of sulphonamide-resistant strains.

Sulphonamides have been the drug of choice for meningitis caused by Neisseria meningitidis, but their position is now threatened by the appearance of resistant strains. They are widely used for urinary infections due to the Gram-negative organisms, Escherichia coli, Klebsiella, and Proteus, particularly as the drug with which to start treatment before the results of sensitivity tests are known, and for the treatment of the bacillary dysenteries. For both forms of infection, resistant strains are now so common that the value of sulphonamides is less than it was in the past. Sulphonamides may be given together with streptomycin or chloramphenicol for the treatment of pneumococcal meningitis [Table 1.1]. Although the sulphonamides have been superseded for the treatment of gonorrhoea, they are suitable in chancroid and lymphogranuloma venereum. Dermatitis herpetiformis responds well to

sulphapyridine. This action appears to be of a different nature from the usual antibacterial activity of a sulphonamide, as many other sulphonamides are without effect.

In surgery the poorly absorbed sulphonamides are used before abdominal operations to reduce the number of bacteria in the bowel.

The long-acting forms of sulphonamides have advantages for the treatment of patients in countries with inadequate medical services and where patients can only be seen at considerable intervals. In countries in which patients can be seen with regularity the short-acting soluble preparations remain the most useful for diseases suggested in this section. The long-acting preparations appear to have no substantial therapeutic advantages.

Sulphonamides should not be used as topical applications because of the significant risk of contact dermatitis.

TRIMETHOPRIM

Sulphonamides act by blocking the enzyme system in the bacterial cell that uses para-aminobenzoic acid as the first stage in the synthesis of folic acid. Other substances have been found that block the next step. Trimethoprim is one of these, first synthesized in the U.S.A., and when used with a sulphonamide the combined effect on a sensitive organism is usually greater than would be produced by either of the drugs acting alone.

Distribution and excretion

When given by mouth, trimethoprim is well absorbed [see TABLE 1.3], most of the drug being excreted in the urine.

Table 1.3
Distribution of antibacterial drugs in body

	14-47 ta B	Route	Urine	CSF	Serous cavities	Bile	Placenta
Drug		administered Proportion of dose		Pro	oportion o	of blood l	evel
Sulphona	mides	oral	most	high	׳	low	׳
Trimetho	prim	oral	70%	×	_	×7	NOTE 1
Penicillin	G	intramuscular	60%	low	X1 (×5	X
Phenoxyn (Penici	nethylpenicillin llin V)	oral	25%	low	low	low	low
Phenoxye	thyl and			\			
phenox	ypropyl penicillin	oral	60%	_	9. 16 10.	luz -s iro	165-45
Methicilli	n	intramuscular	60%	low	present	present	low .
Cloxacilli	n	oral	35%	low	present	· -	-
Ampicilli	n	oral	30%	low	high	high	present
Cephalos	porins .	intramuscular	most	low	low	low	high
Tetracycli	ines	oral	10-30%	low	×1	×10	×
Chloramp		oral	90% 80% inactive	×1 .	×1	׳	×1
Erythrom	vcin	oral	3%	0	low	×8-64	low
Streptom		intramuscular	80%	low	׳	×	׳
Neomycir		intramuscular	арргох. 25%	present		_	
Kanamyc		intramuscular	80%	low	low	low	low
Gentamy		intramuscular	most	low	14 (40)	low	low
Polymyxi		intramuscular	low	0	0	0	0
Vancomy		intravenous	most	present	present	present	
Lincomyc		oral	5%	low	high	×2-4	low
Cycloseri		oral	60%	ת		present	
Isoniazid		oral	most		freely in I		
PAS	The second second second	oral	most	poor	0	0	0
Viomycin		intramuscular	65-100%	×ŧ	low	750	THE IN
Fucidin O			1%	0		conc.	low

Toxicity and hypersensitivity

As trimethoprim is nearly always given with a sulphonamide, it is not easy to decide to which drug to attribute a reaction. Sensitivity reactions, mainly skin rashes, and nausea and vomiting make up nearly three-quarters of reported reactions. Adverse effects on the blood have been seen but the theoretical risk of the induction of folate deficiency seems to be slight.

Preparations and dosage

It is given by mouth, usually in a preparation containing five times as much sulphamethoxazole as trimethoprim [Table 1.4].

Table 1.4 Suggested doses for adults

Drug	Intramuscular	Intravenous	Oral	Intrapleural	Intrathecal	Ointment	Miscellaneous
Sulphonamides	n conducts with a	terent of patient	See Table 1.2	Resultedally J	เ bstobiju.ad a	अंग्रह्म अंग्रह वर्षण	alphonamors
Trimethoprim	'can only <u>he seen at</u>	where nations	80-160 mg	perida <u>ca</u> rabina	olumssmup Ar	erssa <u>r</u> v as th	negatety not bec
with regulately than hort-	patients can be seen	itries in which	12 hrly			a to months	To avoid dep
Penicillin G	1-5 million	Varies	ritui ton bluodi	20 000 units	20 000 units	alkaline, an	2000 units/ml
ed sub-union in broad to comment of on	units in 24 hr						eye drops
Procaine penicillin	600 000-1 200 000	lating the same		-	_	· <u>-</u>	
rocanic penienim	units in 24 hr	mante seame var	5 (34)				
Phenoxymethylpenicillin	[2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2] 1 [2]	r sammene and a	125-250 mg	_	2. 1 SHOW 1		, · · · · · ·
(Penicillin V)	ilicant risk of Conuc	EST OF THE OWN	6 hrly				
Phenoxyethyl and			125-250 mg		_		_
Phenoxyethyl and		METHOPPIM	4–6 hrly		200.00		
phenoxypropyl penicillin	own with antidantic ways	transport and the second	4-0 IIIIy	0.5.1.	10-40 mg		
Methicillin	Tig and Tig	1 g	Horareal coll	0·5–1 g		Lond	lenC -
-time is our or ober's were one	4-6 hrly			500	daily		
Cloxacillin	250 mg		500 mg	500 mg	10 mg	_	Should not be
ether enthesped in the	4-6 hrly		6 hrly	daily	daily		used in eye
Ampicillin and modern ship	THE CONTRACTOR SERVICES	150 mg/kg daily		—	10-40 mg	-	1% eye drops
	6 hrly		8 hrly		daily		ulpendiarans .
Carbenicillin	1 g 4 hrly	1 g 4 hrly	vitio -	_		(3-1) — {	rantoler amide
Cephaloridine	250 mg-1·5 g			- ·	_		(Aprilmantantan)
	6 hrly		Barrier and Company				
Tetracyclines	1 g in 24 hr	1 g in 24 hr	0.25-0.5 g	0-25 g	Never	0.5-3%	нокантановику и чеп
anski best bedroada llew	ath brimethoprim is	rom zo taviajn:					
Chloramphenicol	2 g in 24 hr	2 g in 24 hr	0.25 g	4 March 19 c		1%	0.5% as eye
			6 hrly				drops
Erythromycin	Not used	1-4 g in 24 hr	0.25 g	2-5 mg/ml	Not used	1%	
Lincomycin	300-600 mg	600 mg	500 mg	or a tracing many		ipiliomini ser	9300 1 NWO.1
ybod ni agrib,	12 hrly	12 hrly	6–8 hrly				
Streptomycin	1 g	1 g in 24 hr	(not absorbed)	1 g	25-100 mg		
(Not Tb)	8–12 hrly	1 g III 2 7 III	1-2 g daily	1 B	daily		
Neomycin	2–3 g in 24 hr		(not absorbed)	0.25%	Never	0.5%	Lotion 0.5%
Neomycin	2-3 g iii 24 iii	_	1 g 4 hrly	0.23%	INEVEL	0.3%	Lotton 0.3%
ve a boost begin to waters that	activities of	0.5-		THE THE	100	F	
Kanamycin	0.5 g	0.5 g	(not well absorbed)	_	100 mg	5 mg/g	_
_ kan a pala tera a sala te	12 hrly	12 hrly	1 g 6 hrly				a population
Framycetin	rine . — has a	- ythregoti	(not absorbed)		_	5 mg/g	Nasal spray
(Soframycin)			1-1.5 g daily				1.25%
Paromomycin		ANADA TERRITORIA	(not absorbed)	_	<u> </u>		s demonstration of the least
			1-6 g daily				de reint retail huse
Polymyxin sulphate	25 mg	0-1 g in 24 hr	(not absorbed)	5-10 mg	5-10 mg	0.1%	alona - Trapa I
y a Market Telecolog	6 hrly		0-1 g 4 hrly		daily		
Polymyxin methane	120 mg		0·1 g	5-10 mg	5-10 mg	_	·
sulphonate	8 hrly		4 hrly	daily	daily		The Company of the
Vancomycin	1 (3) 101 halo	2 g daily	vars _			-700	A NO MOLEGISTICAL
Fucidin	minds and The Property of	_logunadanii	250-500 mg	CONTRACTOR DA	ffs) shi— has	ned to its	estraten agr
with the delivery wear	more and the			working one ov	Daw midi		unber of Cirem
The second secon	20 A C C C C C C C C C C C C C C C C C C						

Antibacterial activity

The range of activity of trimethoprim closely resembles that of the sulphonamides, and trimethoprim/sulphonamide mixtures are active against the pyogenic cocci, enterobacteria (Esch. coli, Proteus, Klebsiella, Salmonella, Shigella) gonococci, and Haemophilus influenzae. Tubercle bacilli, Treponema pallidum, and Ps. aeruginosa are resistant. Resistant strains can develop to sulphonamides and to trimethoprim.

Indications

A wide variety of infections have been treated with trimethoprim, including brucellosis and typhoid fever, but its principal value lies in the treatment of urinary tract infections and infections of the respiratory tract due to susceptible organisms.

PENICILLIN

Penicillin was described by Fleming in England in 1929, and was made available for the treatment of patients in 1940–1. Although the first of a long series of antibiotics it remains in many respects the most useful. Penicillin is the product of the moulds *Penicillium notatum* and *P. chrysogenum* and its chemical composition is now

known. Early preparations contained several penicillins. The form which, until recently, has been the only one used extensively in medicine is benzylpenicillin—penicillin G. It will be described first.

Penicillin G (benzylpenicillin)

Pure benzylpenicillin will retain its potency at room temperature for some years in a dry state. In solution it is much less stable. Solutions at 4°C deteriorate slowly; at room temperature there is a variable but considerable loss after one day. The activity of other antibiotics is defined in terms of weight, but for penicillin G the unit is still used although the *British Pharmacopoeia 1974* now gives doses in milligrams. One unit is the equivalent of $0.6~\mu g$ of the International Penicillin Standard, and 150 mg is approximately equivalent to 250 000 units of penicillin.

Penicillin is a bactericidal antibiotic, killing bacteria as well as preventing growth. It will, however, act only on bacteria that are growing, and it will not always kill all the organisms in a population exposed to it. This is rarely of clinical significance, but is important in the treatment of a few diseases of which subacute bacterial endocarditis is the outstanding example. Its action is relatively

unaffected by minor changes in pH.