PROGRESS
IN
CLINICAL
MEDICINE

EDITED
BY
DALEY
AND
MILLER

FOURTH
EDITION

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CLINICAL MEDICINE

BY VARIOUS AUTHORS

EDITED BY

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PREFACE TO THE FOURTH EDITION

THE purpose and method of this book remain unchanged since its first appearance in 1948. It aims to describe the main developments of the past few years in general medicine, and its orientation is essentially clinical.

A feature of the present edition is its extended treatment of the topical problems of arterial disease; the clinical manifestations of lesions of the coronary, cerebral and renal arteries are discussed at length. As in the case of previous editions the work has been entirely re-written, and, amongst subjects treated for the first time, aldosteronism, psychopharmacology, auto-immunity, hypophysectomy and space medicine justify special mention.

We are grateful to the Air Ministry for permission to include the chapter on Space Medicine by Wing Commander Peter Whittingham.

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TREATMENT AND PREVENTION OF INFECTIONS

by

T. B. BINNS

Chemotherapy: Sulphonamides. Penicillin. New antibiotic preparations. Antibiotic combinations. The problem of the staphylococcus. Antifungal antibiotics.
Immunisation: Poliomyelitis. Diphtheria. Whooping cough. Tetanus. Combined prophylactics. Recommended schedules. Gamma-globulin. Immunisation for International Travel.

CHEMOTHERAPY

In the therapeutic revolution of the past twenty-five years, antibacterial drugs are clearly of first importance both historically and clinically. It is difficult for the imagination to grasp the scale on which they are now used. World production of both penicillin and broad spectrum antibiotics exceeds 500 tons annually—each sufficient for 100 million courses of treatment, though by no means all is used in human medicine.

It is surprising, but perhaps significant, that the most valuable of these drugs were discovered comparatively early in the period. During the past ten years numerous modifications of the first antibiotics have been introduced to improve efficiency and meet special requirements; several hundred new ones have been discovered and a few have found, temporarily at least, a useful, even if restricted, place. On the other hand many new problems have arisen, the chief of them being staphylococcal resistance.

Antibiotic medicine has developed into an enormous subject and is still growing rapidly. This review is necessarily restricted to a few aspects of current interest.

Sulphonamides

A reviving interest in sulphonamides has been encouraged by the development of new compounds, especially those with a prolonged

action. Oral sulphamethoxypyridazine* (Lederkyn, Midicel) is well absorbed but is excreted by the kidney extremely slowly. This may be related in some way to protein-binding but the full explanation is still uncertain. Thanks to its high solubility in urine, crystalluria is unlikely. The desirable plasma level is 5–10 mg. per cent of the free sulphonamide; though considerable variation occurs, this is usually achieved by a single daily dose of 0.5 g. for an adult or 25 mg./kg. for a child. A loading dose of double this amount should be given at the outset (Jackson, 1958).

Side-effects seem to occur no less often than with other sulphonamides; most commonly headache, fever, alimentary symptoms and skin rashes which may last unusually long (Bell *et al.*, 1958; Perry and Winklemann, 1959). Owing to the slow rate of excretion, over-dosage readily leads to cumulation and toxic reactions, particularly in patients with impaired renal function.

Other new compounds with similar properties are sulphadimethoxine† (Madribon) and sulphaphenazole‡ (Orisulf). These may have a lower incidence of side-effects but it is too early to compare their merits.

Infrequent dosage is a convenience and sometimes an advantage; for example, in one small trial Lepper *et al.* (1957) found a single weekly dose of sulphamethoxypyridazine 30 mg./kg. satisfactory for the prophylaxis of rheumatic fever. However, all three drugs diffuse poorly into the cerebro-spinal fluid, probably because of the high proportion bound to the plasma proteins (Boger, 1959; Ross *et al.*, 1959). Other sulphonamides such as sulphadiazine are, therefore, to be preferred for the treatment of meningitis. In other respects these compounds appear to give satisfactory results (Jackson, 1958; Susset, 1958; Ross *et al.*, 1959) but not to increase the scope or reduce the cost of sulphonamide therapy. They have not clearly established their superiority over old favourites like sulphadimidine, which has remained deservedly popular for many years. The use of sulphamerazine is no longer justified in view of the high incidence of crystalluria and hæmaturia which it causes, especially in children (Arneil, 1958).

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* 3-sulphanilamido-6-methoxypyridazine. † 2, 4-dimethoxy-6-sulphanilamido-1, 3-diazine.
‡ 1-phenyl-5-sulphanilamidopyrazole.

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Penicillin

Penicillin remains the antibiotic of choice unless the patient has become sensitised or his infecting organism is insensitive to it. Surprisingly, after all these years the gonococcus not infrequently now shows some degree of resistance (King, 1958).

For serious infections there is no doubt that massive injections of sodium penicillin are best and they can safely be given intravenously if necessary. In milder cases success can be achieved with the minimum of inconvenience to the patient either by giving injections only once or twice a day, by using repository preparations or by oral treatment. The natural variation among infections makes it notoriously difficult to compare dosage régimes and no doubt this accounts for the remarkable differences that still exist. In the past few years the use of procaine penicillin alone has been partly superseded by combined preparations containing also the sodium and benethamine or benzathine salts. A single injection of these immediately gives a high bactericidal blood level for a few hours, falling to more modest levels that persists for three days or more. These combined preparations give excellent clinical results, make the least demands on either doctor or patient and are the most economical form of penicillin for routine use.

Oral Penicillin. The use of oral penicillin, especially for children, has increased steadily for several years, so that it probably represents about half the total quantity used. The trend has undoubtedly gained impetus from the introduction of penicillin V or phenoxymethyl penicillin. This is made by adding N-(2-hydroxyethyl)-phenoxy-acetamide as a precursor to the broth during fermentation, and differs from benzyl penicillin only by the inclusion of one alcohol (OH) group in the side-chain. This, however, confers upon it distinct biological properties.

To judge by the total urinary excretion, approximately twice as much penicillin V is absorbed as (benzyl) penicillin G. Though of similar duration, the blood levels are decidedly higher, especially when the more soluble potassium salt is used rather than the free acid. Its absorption is also less influenced by the presence of food in the stomach (Jones and Finland, 1955; Welch, 1956; Wright and Welch, 1958). The better absorption of penicillin V cannot be due, as is often stated, entirely to its superior acid-stability, for it was estimated long ago that destruction of benzyl penicillin by gastric acid accounts for only 10–15 per cent of an oral dose (Bunn, 1956).

There are other differences; penicillin V is bound by plasma proteins to a somewhat greater extent, it is inactivated more rapidly by the liver and it has a slightly different antibacterial spectrum. None of these, however, appears of much practical importance. Penicillin V has been reported to be clinically effective in a wide variety of infections due to sensitive organisms (Macleod, 1957; Reeves *et al.*, 1959), but it is extremely difficult to show a definite superiority over penicillin G and several attempts to demonstrate this have failed (Schalet *et al.*, 1958; Breese and Disney, 1958; Weiss *et al.*, 1959). Therefore it does not greatly increase the scope of oral therapy, and it is not justifiable to give it in smaller doses (Bunn, 1956). In equivalent doses (60 mg. V = 100,000 units G), it may reasonably be expected to have some advantage in improving the reliability of oral penicillin, although it adds considerably to the cost. The usual dose for an adult is 250 mg. q.i.d. in tablets or capsules, preferably of the potassium salt; for a child 125 mg. and for an infant 60 mg. q.i.d., both as liquid suspension.

Newer penicillins. The isolation in Britain of the penicillin nucleus, 6-aminopenicillanic acid, by Batchelor, Doyle, Naylor and Rolinson (1959) made possible the chemical manipulation of the side-chain to produce numerous penicillin analogues that could be screened for desirable therapeutic properties. The first practical outcome was the development of α-phenoxyethyl penicillin or phenethicillin (Broxil), which has a side-chain similar to that of penicillin V but containing an additional methyl group. It is soluble, acid-stable and well absorbed from the small intestine.

The technical difficulties of making a valid comparison of different penicillins are increased by the variation in responsiveness that occurs not only between but within bacterial species. Laboratory results depend upon the conditions of the test. Some organisms are slightly less sensitive to phenethicillin than to penicillins G or V, but it is claimed that in equivalent doses phenethicillin gives serum levels up to twice as high as those derived from penicillin V orally and at least as high as those obtained with penicillin G intramuscularly. When McCarthy and Finland (1960) measured the number of times the serum or urine could be diluted without losing activity against three different organisms, they found that by far the greatest activity in serum and urine in all their tests, and the greatest proportion of drug recovered in the urine occurred after the intramuscular injection of penicillin G, which provided much better sustained serum concentrations. In the same doses, penicillin V produced greater activity than phenethicillin against the streptococcus and pneumococcus and at least equivalent activity against the staphylococcus chosen. From present evidence one may conclude that phenethicillin is approximately as effective as penicillin V and should be given in the same dosage (q.v.).

Of greater importance was the later development of sodium 6-(2,6-dimethoxybenzamido) penicillanate monohydrate (Celbenin), the first available penicillin analogue to be unaffected by penicillinase. This enzyme is responsible for the only clinically important type of staphylococcal resistance to penicillin, though not, of course, to other antibiotics.

The compound is highly soluble but unstable in acid solution. It is uninfluenced by serum and is bactericidal at little more than the minimum inhibitory concentrations. It is no more toxic than penicillin G, but is much less active against organisms sensitive to both, so that it is necessary to give injections of 1 g. at intervals of four to six hours (*British Medical Journal*, 1960). This is obviously a valuable new drug but, with past experience in mind, it should be reserved for cases that really need it.

Reactions. Guthe, Idsöe and Willcox (1958) have made a remarkably comprehensive review, which confirms that in practice the pharmacological toxicity of penicillin is negligible. The human LD50 of a single dose of sodium penicillin has been estimated to be 150 million units. They lay emphasis on allergic reactions which may be of several types. On prolonged exposure about five per cent of patients will develop contact dermatitis and in 1953 the Ministry of Health issued a memorandum on the precautions to be taken by handlers. Other antibiotics, such as bacitracin and neomycin, are better for topical use. Systemic penicillin sometimes causes eczematous eruptions in the groins or interdigital spaces or pompholyx of the palms and soles. These may possibly be due to cross-sensitisation from a previous fungal infection. In a few patients a serum-sickness-like syndrome occurs at any time between thirty minutes and several weeks after penicillin administration. Urticaria is characteristic and may be accompanied by anorexia, malaise, fever, arthralgia, facial œdema or lymphadenopathy. Those who have been highly sensitised by previous administration react the most quickly and may develop angioneurotic œdema, laryngeal œdema or collapse. Scarlatiniform rash, erythema multiforme and erythema nodosum have been reported and, like sulphonamides and other drugs (Honey, 1956), penicillin has occasionally been suspected of causing polyarteritis nodosa or systemic lupus erythematosus. The most alarming reaction is anaphylactic shock. Its incidence has been calculated to be only about 0.1–0.3 per million injections, but by 1957 it had caused 1,000 deaths in the U.S.A. Extremely small amounts of penicillin, even in tablets, lozenges or ointment, have at times seemed capable of establishing the necessary sensitisation, and the latent period may be as short as a few weeks or as long as eight years. Likewise the precipitating dose, though almost always intramuscular, may be small or merely a skin test or a tablet. Usually the onset is immediate with paræsthesiæ in the mouth, sweating, angor animi, syncope and a variety of other symptoms. About

nine per cent of such patients die, generally within half an hour (Welch *et al.*, 1957). A rather similar syndrome was reported by Batchelor *et al.* (1951) and ascribed to accidental intravenous injection of procaine penicillin.

The treatment of minor reactions consists in the local application of steroids for contact dermatitis and the use of antihistamines or, if necessary, steroids systemically for serum-sickness-like reactions. Further exposure should be avoided. Patients should always be questioned about possible sensitisation, since premonitory symptoms may precede serious reactions. If anaphylaxis occurs, the patient should be laid flat and be given adrenaline and intravenous corticosteroid. A tourniquet to the injected limb and oxygen have also been recommended.

Penicillinase has been successfully used to neutralise penicillin causing sensitisation. The dose is 800,000 units, repeated in a few days if necessary (Becker, 1958). It cannot, however, be relied upon to act quickly enough in anaphylaxis. Furthermore, it is itself antigenic and has caused serious reactions (Hyman, 1959).

After confirmatory skin-testing with five units intracutaneously, patients may be desensitised by preparing serial dilutions of sodium penicillin that permit daily doses from about 100 units upwards. The process can be facilitated by the use of antihistamines or steroids, but patients vary greatly in their response and there is some risk of serious reactions.

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New Antibiotic Preparations

Blood Level Enhancement. Although the point of action of antibiotics is seldom in the bloodstream itself, serum levels are always taken as the most convenient index of therapeutic activity. Various new preparations have now been shown to produce better levels than their predecessors. With erythromycin propionate, a true ester, peak serum levels are higher and last longer than those obtained with conventional erythromycin tablets. Urinary excretion is approximately doubled. Therapeutically effective serum levels should, therefore, be more predictable and, as a result of the more complete absorption, the incidence of alimentary side-effects may be even lower (Griffith, 1959). Absorption is considerably diminished by food, as judged by the antibacterial activity of the serum (Hirsch and Finland, 1959a). Whereas erythromycin propionate is absorbed and acts as such, another new antibiotic derivative, triacetyloleandomycin, is de-acetylated in the alimentary tract and then absorbed better than the parent compound, food having little effect (Reisch *et al.*, 1958; Hirsch and Finland, 1959a). Of the two, erythromycin propionate produces the higher serum antibacterial activity.

It is surprising that the absorption of the tetracyclines was found only recently to be impaired by calcium and magnesium compounds, including milk and many antacids; for this reason, a number of earlier reports claiming improved blood levels with special preparations are invalid (Finland, 1958). An elaborate investigation conducted later by Kunin, Jones and Finland (1958), however, confirmed that a mixture of tetracycline hydrochloride and citric acid in equal parts gave significantly better serum levels and antibacterial activity than tetracycline hydrochloride alone. Both a mixture with glucosamine hydrochloride and a tetracycline-phosphate complex also gave somewhat better results than tetracycline alone. These improvements are welcome, but do not alter tetracycline therapy in any important respect.

A still more interesting development has been the discovery of demethyl-chlortetracycline, an analogue of chlortetracycline, produced by a mutant of the original *Streptomyces aureofaciens*. As a result of its greater stability to alkali it is absorbed as well, and probably better than, equal doses of either chlortetracycline or oxytetracycline in combination with glucosamine. Its absorption is not enhanced by citric acid. It gives much greater antibacterial activity in the serum, as it does *in vitro* (Kunin and Finland, 1958; Hirsch and Finland, 1959b), and the levels persist for much longer, since the renal clearance is only 43 per cent of that of tetracycline. After a single dose of 500 mg., serum antibiotic activity may last for as long as 120 hours (Sweeney *et al.*, 1959). These results give promise of better-sustained serum levels from less frequent and perhaps smaller total dosage, but the clinical efficacy and tolerance of demethyl-chlortetracycline can be confirmed only by further experience.

Newer Antibiotics. Apart from chloramphenicol, several of the newer antibiotics are of value for treating staphylococcal infections resistant to the more commonly used antibiotics and also for certain other conditions. For comparison, their salient features and limitations are set out in Table I. Like neomycin and streptomycin, with which it shows cross-resistance, kanamycin has a wide antibacterial spectrum embracing gram-positive and gram-negative organisms and the tubercle bacillus. It may have some value also for proteus infections and as an intestinal antiseptic, but it is not absorbed by mouth, and on injection it is oto-toxic in even modest doses (Yow, 1959). All the others listed have spectra rather like that of penicillin and can in theory be used for similar purposes. But staphylococcal resistance develops quickly to erythromycin and to the related but weaker oleandomycin and spiramycin. Cross-resistance between all three is common, so that use of the second two could rapidly lead to ineffectiveness of erythromycin, which at present remains a most useful reserve drug. Vancomycin and ristocetin are both bactericidal, and staphylococcal resistance to them develops unusually slowly. They are also effective against enterococcal infections. However, both have to be given intravenously and are apt to be toxic (Kirby *et al.*, 1959; Herting *et al.*, 1959).

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Table I

Some Newer Antibiotics

Name	C or S*	Dose	Staphylococcal Resistance	Remarks
NOVOBIOCIN Albamycin Biotexin Cathomycin	C/S	250–500 mg. q.i.d. or double b.d. Children 5–10 mg./kg. q.i.d.	Rapid used alone No cross-resistance	Exceptionally well absorbed and persistent in serum. Gastric symptoms, rashes, fever not rare; occasional yellow pigmentation.
ERYTHROMYCIN Erythrocin Ilotycin	S	250–500 mg. q.i.d. orally Children 6–8 mg./kg. q.i.d.	Rapid. Cross-resistance oleandomycin and spiramycin common, chloramphenicol occasional.	Spectrum like penicillin. Well tolerated. Mild alimentary symptoms.
OLEANDOMYCIN Evramycin Matromycin Romicil	S	250–500 mg. q.i.d. orally. Children 6–8 mg./kg. q.i.d.	Use encourages staphylococcal resistance to erythromycin (q.v.).	Like erythromycin but weaker. Well tolerated. Mild alimentary symptoms; occasional rashes.
SPIRAMYCIN Rovamycin	S	2 G. then 1 G. q.i.d. orally. Children 25 mg./kg. q.i.d.	See oleandomycin.	Like erythromycin but weaker. Well tolerated. Not well absorbed.
KANAMYCIN Kannasyn	C	Unabsorbed orally. 500 mg. i.m. b.d.	Resistance rapid. Cross-resistance neomycin complete, streptomycin partial.	Wide spectrum. Injection pain. Allergic symptoms, deafness, nephrotoxicity, especially above 20 mg./kg./day.
RISTOCETIN Spontin	C	I.v. drip only. 2 mg. /ml. 25–50 mg./kg. daily; less in elderly or if poor renal function.	Rare. No cross-resistance.	Thrombophlebitis. Neutropenia 5 per cent. Fever, rash, diarrhœa. Greater toxicity above 2 G. daily.
VANCOMYCIN Vancocin	C	Unabsorbed orally. 0.5–1 G. in 200 ml. dextrose i.v., 2–4 times daily.	Slow. No cross-resistance.	Thrombophlebitis, fever, rash, deafness, especially with serum levels above 20 μg./ml.

* C = bactericidal. S = bacteriostatic.