THE NAT[illegible]ICAL RESEARCH

CHEMOTHERAPY
WITH
ANTIBIOTICS AND ALLIED DRUGS

By

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and
Stanley W. Williams

N.H.M.R.C.

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Chemotherapy with Antibiotics and Allied Drugs

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PREFACE

A BRIEF survey of the present status of antibiotics and allied drugs in chemotherapy has been attempted.

There is still much that is unknown and much that is controversial, but a basic knowledge of the principles of chemotherapy is important, and ignorance of these has sometimes led to failure which could have been avoided.

The application of an accurate knowledge of the bacteriology of an infection, supported by a knowledge of established clinical experience in the treatment of similar infections with antibiotics, yields the most rewarding results in chemotherapy. When empirical therapy is necessary, such previous knowledge enables the clinician to select drugs wisely.

Recommendations on therapy are based on or supported by local experience in conjunction with a detailed study of the literature.

We at the Alfred Hospital owe much to Mr. I. H. Cuming, who stimulated and encouraged our interest in the correlation of clinical and bacteriological findings, and to Dr. R. S. Smibert and members of the Honorary and Resident Medical Staff, who over a period of years have invited our cooperation in chemotherapy.

The manuscript is based on notes on antibiotics issued in 1952 to medical students, and we wish to express our appreciation to Dr. Ewen Downie, who proposed extension and publication of that work.

The manuscript has been read by all the contributors and by Dr. Leonard Cox, Dr. Edgar Thomson (Sydney), Dr. H. McLorinan, Dr. A. V. Jackson and Mr. Robert Officer. The authors are indebted to them all for valuable criticism and advice. Particular sections of the work have been read by Dr. T. J. Cotter (Innisfail, Queensland), Dr. A. A. Ferris, Dr. E. S. Mancy, Dr. G. R. Stirling and Dr. J. Reich, and to them also we are grateful for helpful criticism. Mrs. Elizabeth ●dgers has helped us materially in tracing references.

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CHAPTER I

INTRODUCTION

It is apparent that authorities differ in their opinions as to the choice of antibiotics and the dosage given. Certain infections appear to respond equally well to any one of several drugs and it is common experience that different schedules of dosage may give similar results. Hence it would be foolish to be dogmatic; but it is reasonable to make general recommendations based as far as possible on controlled clinical and bacteriological experience rather than on individual clinical impressions. Such recommendations will need to be modified at times according to the special needs of certain patients.

Chemotherapy aims at rapid and efficient control of an infection with a minimum of risk and discomfort to the patient. As experience accumulates and new antibiotics become available, changes in the choice of drugs and their administration are naturally to be expected.

The use of antibiotics and the fact that different organisms vary in their sensitivity to different drugs has made bacteriological diagnosis far more important than before.

While it is possible in a number of cases to guess successfully at the best chemotherapy on clinical grounds alone, it is important to remember that a clinical entity is not necessarily a bacteriological entity. Thus any one of a variety of bacteria may cause an infection of the urinary tract or of a surgical wound. Hence chemotherapy is more likely to be successful when the bacteriology and sensitivity of the organisms are known.

In a seriously ill patient, chemotherapy cannot be withheld until the results of cultures are known, but every effort should be made to obtain specimens for investigation before commencing therapy so that modifications can be made later if necessary.

In less seriously ill patients it is desirable to establish a diagnosis before giving chemotherapy. The antibiotics often mask the bacteriology even when they do not effect a cure. This is exemplified in subacute bacterial endocarditis where aureomycin can suppress the bacteriæmia so that blood cultures are negative and the diagnosis is delayed, and in diphtheria where throat swabs taken after one or two injections of penicillin are negative and may be fatally misleading.

Laboratory tests which may aid diagnosis and methods for carrying out sensitivity tests are discussed in the Appendix.

Sensitivity tests have become a routine procedure in most laboratories. They are not highly accurate but if wisely used and interpreted with due consideration of the site and nature of the lesion, and of established clinical experience, they are invaluable. Close cooperation between the clinician and the bacteriologist is important.

It is sometimes stated that sensitivity tests *in vitro* are not a reliable guide to chemotherapy. The bacteriologist reports a penicillin-resistant organism; meanwhile the infection apparently has responded to penicillin. This discrepancy can usually be

explained. The recovery may have been natural and chemotherapy unnecessary, or the organism tested may not have been the cause of the infection. Certain regions of the body possess a natural flora, more or less numerous and diverse. This flora includes a number of species which may be harmless in one site but pathogenic or potentially so in another. Cultures of, for example, sputum, pus from open lesions, urine and fæces may therefore contain pathogenic organisms not related to the infection, and it is necessary for both bacteriologist and clinician to remember this. Such a situation does not arise when the causative organism is definitely known following isolation from blood, cerebrospinal fluid, a closed abscess. When sensitive organisms are shown to be present and chemotherapy with adequate dosage fails, the possibility of an underlying tuberculous lesion or a fungous infection should be considered.

Sensitivity testing, like every other bacteriological method, needs to be properly controlled if it is to yield satisfactory results.

CHAPTER II

THE SULPHONAMIDES

The first sulphonamide used in chemotherapy was Prontosil Rubrum, which was synthesized in 1932. Experimental results in animals were described by Domagk in 1935, and other workers described the successful treatment of hæmolytic streptococcal infections in man.

There are three clinically important groups of sulphonamides :

I. The readily absorbed or more soluble drugs.

Those considered here are :

Sulphanilamide.

Sulphacetamide (syn. Albucid)

Sulphapyridine (syn. M. & B. 693).

Sulphathiazole.

Sulphadiazine.
Sulphamerazine.
Sulphamezathine (syn. Sulphamethazine, Sulphadimidine).
Elkosine.
} The Sulphadiazine or Sulpha-pyrimidine Group.

Sulphamethazole (syn. Gantrisin, Urolucosil).

Sulphatriad (a mixture of sulphadiazine with sulphathiazole and sulphamerazine).

Sulphadital (a mixture of sulphadiazine with sulphamerazine and sulphacetamide).

II. The poorly absorbed sulphonamides.

Examples are :

Sulphaguanidine.

Succinyl sulphathiazole (syn. Sulphasuccidine).

Phthalyl sulphathiazole (syn. Sulphathalidine).

III. Sulphamar (syn. Marfanil), which differs fundamentally in chemical structure from the first two groups and is not inactivated by para-amino-benzoic acid or by pus. It resembles the first group in being readily absorbed.

I. THE READILY ABSORBED SULPHONAMIDES

Some sulphonamides affect a larger number of species of bacteria than others. Sensitivity tests are valuable because different strains within these species vary, some being sensitive and some resistant to therapeutic concentrations of the same drug. The use of sulphonamides over a period of years had led to the selection of resistant strains so that the empirical treatment of pneumonia, gonorrhœa, hæmolytic streptococcal and other infections is not as successful as it used to be. Penicillin is more reliable. The soluble sulphonamides are inactivated by pus and are unsatisfactory in the treatment of closed abscesses, appendicitis and general peritonitis, although they have some value in checking the spread of infection because of the high concentrations of the drugs (particularly sulphadiazine) which are obtained in most tissues. Treatment is very successful when drainage is present as in urinary tract infections, meningitis and conjunctivitis.

Sulphanilamide is structurally the simplest of the sulphonamides. It is active against some coliform strains and *Streptococcus pyogenes* but not against pneumococci or staphylococci.

Sulphacetamide has a wider range of activity than sulphanilamide, and is very soluble. It is active against pneumococci. It may be used in urinary tract infections and in local applications to the eye.

Sulphapyridine is also active against pneumococci, but is toxic and is not recommended.

Sulphathiazole has the greatest *in vitro* potency of the sulphonamides, being 50 times as active as sulphanilamide. It is effective against staphylococci as well as pneumococci. It is very rapidly excreted so that adequate blood concentrations are difficult to maintain. Drug fever and rashes are frequently encountered.

Sulphadiazine is not so potent as sulphathiazole *in vitro* but is more active *in vivo* owing to the high concentrations attained in the blood and tissues as a result of its ready absorption and slow excretion. It has the same bacterial spectrum as sulphathiazole. It penetrates readily into the cerebro-spinal fluid and is therefore useful for the treatment of meningitis. Toxic effects are rare, but owing to the sparing solubility of the drug in urine, hæmaturia and anuria may occur unless adequate fluids are given and alkalinity of the urine is achieved.

Sulphamerazine resembles sulphadiazine but is more toxic.

Sulphamezathine (Sulphadimidine) also resembles sulphadiazine but is much more soluble and is one of the least toxic of the sulphonamides. These qualities make it particularly suitable for routine use. However, it does not penetrate into the cerebro-spinal fluid as well as does sulphadiazine and is not satisfactory for the treatment of meningitis unless very large doses such as 3 grams 4-hourly are used.

Elkosine resembles sulphamezathine, but is not readily available and is not considered further.

Sulphamethazole is rapidly absorbed and excreted and very high concentrations of active drug are found in the urine. For this reason it has been recommended as the drug of choice for the treatment of infections of the urinary tract. This is based on the assumption that in such infections absorption from the urine into the tissues is more effective than the presence of the drug in the blood and kidney. In fact, even following large doses relatively low concentrations of sulphamethazole are found in the tissues, and while this sulphonamide has been used with success in infections with sensitive organisms, there is no real evidence that it is superior for routine use to sulphamezathine or to triple mixtures. Small doses of sulphamethazole sometimes induce clinical improvement in superficial infections but care should be taken that the infection is not merely suppressed (page 62).

While sulphamethazole is highly soluble in alkaline urine, its solubility is much less in acid urine and the high concentrations of drug excreted when the recommended dosage of at least 6 grams daily is given, may constitute a serious risk of blockage of the renal tubules unless alkali is also given. Hæmaturia and crystalluria have been reported. Other toxic effects common to the sulphonamides also occur.

Sulphatriad or similar mixtures containing several different sulphonamides may be used, particularly when dehydration is marked and the urinary output is low, or when only one kidney is functioning. The concentration of each drug in the urine, with dosage that is adequate, is insufficient to produce crystal formation, but the total blood concentration is ample for therapeutic results.

Administration and Dosage

Oral administration is the routine method. Ample fluids should be given, about one pint for each gram of sulphonamide up to a maximum of about 6 pints daily for an adult. The urine should be made alkaline to litmus and should be tested daily. Alkalinity can usually be achieved by giving 1·3 gram of sodium bicarbonate and 1·3 gram of sodium citrate with each dose of sulphonamide, but more may be required.

The drug recommended for sensitivity tests is sulphadiazine, because it is structurally the simplest of the sulphadiazine group and a great deal of information is available concerning its behaviour. Organisms resistant to sulphadiazine may be assumed resistant to other sulphonamides except sulphamar.

Suggested dosage schedules for sulphadiazine or sulphamezathine or triple sulphonamide mixtures for an adult of 10 stone weight are stated in Table 1.

An initial dose of from 2 to 4 grams (or more in severe infections) is given to raise the blood concentration rapidly to an effective level. In serious acute infections the initial dose should be given intravenously.

Preparations are available for intravenous and intramuscular injection. The sodium salts of sulphathiazole, sulphapyridine and the sulphadiazine group are conveniently given in 10% solution.

They are strongly alkaline and therefore irritating and cause some necrosis of the tissues, and should be given deeply into the muscle with the sites of injection well-spaced. Intravenous injections should be given slowly. They should not be combined with a blood transfusion as the alkaline fluid may produce changes in citrated blood. *They should never be administered intrathecally* because owing to their high alkalinity they may cause permanent damage to the nerve roots and spinal cord. Soluble sulphamezathine is the drug of choice. It

TABLE 1

SULPHADIAZINE

Sensitivity	Interpretation	Adult Dosage Oral)*
(1) 2·5 milligrams *per centum*	Very sensitive.	4 grams statim. 1 gram 4-hourly for 4 days.
(In very severe infecti	ons use Schedule 2).	1 gram 6-hourly for 2 days.
(2) Between 2·5 and 10 milligrams *per centum*	Sensitive.	6 grams statim. 1·5 gram 4-hourly for 3 days. 1 gram 4-hourly for 3 days.
(3) Between 10 and 20 milligrams *per centum*	Probably resistant.	Of doubtful value. Choose another drug if possible; or try (2) or even larger doses.
(4) More than 20 milligrams *per centum*	Resistant.	

Children, weight for weight, have a better tolerance than adults. For children of average build, give two-thirds adult dose for age 11 to 15; one-half for age 4 to 10; and one-third for age 0 to 3 years.

* The dosage schedules recommended here and elsewhere throughout this volume are in the main those in use at the Alfred Hospital, Melbourne.

is used in severe infections to give an immediate high concentration in the blood, and is invaluable when oral administration is impracticable. The dosage is from 3 to 4·5 grams statim with subsequent doses of from 1 to 2 grams 6-hourly.

Duration of therapy may extend to 7 days but should rarely proceed beyond this. A shorter period may be sufficient but treatment should continue for 2 or 3 days after the temperature has become normal.

II. THE POORLY ABSORBED SULPHONAMIDES

Sulphaguanidine is one of the less potent sulphonamides. It is rapidly but incompletely absorbed (about 50%). A dose of 6 grams followed by 3 grams 4-hourly, produces in an adult a blood level of about 5 milligrams *per centum*, but concentrations of from 300 to 4000 milligrams *per centum* are found in fæces. It is recommended in the treatment of bacillary dysentery because it produces a therapeutic concentration in the tissues as well as in the lumen of the bowel.

Succinyl sulphathiazole is of very low potency. It is very insoluble in water and is not absorbed to any appreciable extent as such. It owes its bacteriostatic activity to a slow liberation of

sulphathiazole in the intestine. An initial dose of 7 grams is followed by doses of 3·5 grams 4-hourly.

Phthalyl sulphathiazole has a bacteriostatic activity in the bowel some two to four times as great as that of succinyl sulphathiazole because relatively more of the phthalyl compound is converted into free sulphathiazole. The dosage recommended is 3 grams daily in 6-hourly doses. This drug is not considered to be as effective as sulphaguanidine or succinyl sulphathiazole in the treatment of bacillary dysentery. It is favoured for preoperative treatment in operations on the bowel (page 75).

III. SULPHAMAR

Sulphamar is not inhibited by *p*-amino-benzoic acid or by the presence of pus and can therefore be used, either alone or mixed with streptomycin, for local application to wounds. When administered by mouth it is rapidly absorbed and excreted. It is not readily available for systemic use. Organisms resistant to other sulphonamides such as sulphadiazine may prove sensitive to sulphamar.

Toxic Effects of Sulphonamides

The most common toxic effects of the sulphonamides including the sulphadiazine group are headache, mental depression and general malaise. Nausea and vomiting may also occur, but are rare with the sulphadiazine group. Cyanosis is common when sulphanilamide is used. However, these complications are not dangerous and therapy need not be discontinued.

Drug rash, drug fever and hæmaturia or renal pain are not uncommon side effects and if they occur it is wise to stop treatment.

Other complications are rare, but may be extremely serious. These are anuria, agranulocytosis, hæmolytic anæmia, aplastic anæmia, purpura, exfoliative dermatitis, peripheral neuritis and hepatitis. Therapy should be stopped at once.

Many toxic effects are due to sensitization, as for example drug fever, rashes, some cases of agranulocytosis, and it is important to enquire whether a patient is aware of previous sensitization. Sensitization may occur with any sulphonamide.

The usual toxic symptoms can occur following the administration of sulphaguanidine, but succinyl sulphathiazole and phthalyl sulphathiazole are practically non-toxic.

Amongst other sulphonamides the sulphadiazine group is the least toxic.

CHAPTER III

PENICILLIN

Penicillin was isolated from *Penicillium notatum* by Fleming in 1929, and was first used as a chemotherapeutic agent in 1940 by Chain and Florey and their co-workers.

There are five main varieties of penicillin, namely F, G, K, X and O.

Penicillin K is active *in vitro* but is useless therapeutically. The other varieties are all active *in vivo* as well as *in vitro*, but it is penicillin G, benzyl-penicillin, which has been most studied and commercially developed and which is the basis of the various forms of penicillin in common use. Recently penicillin O has become available commercially in the United States of America and may be used for patients who have become allergic to penicillin G.

The properties of penicillin G, in particular its bactericidal action (page 30), its low toxicity and the fact that high concentrations can be attained in the tissues and in foci of infection, make it by far the most reliable and satisfactory of all the antibiotics for the treatment of infections caused by bacteria which are sensitive to it.

All strains reported of certain species (*Treponema pallida*, *Clostridium welchii*, the gonococcus, meningococcus, pneumococcus, *Streptococcus pyogenes*, *Streptococcus viridans* and the various types of anaerobic cocci) are sensitive to therapeutic concentrations of penicillin, and provided that the identity of the organism is known, sensitivity tests can be dispensed with. However, different strains in these species vary in the degree of their sensitivity and higher dosage is required for relatively resistant organisms. Thus, failure of therapy can often be explained by inadequate dosage. When sensitivity-testing is not available, dosage should be increased empirically; if it is available it provides useful information for guiding dosage and may indicate whether inadequate dosage is in fact the cause of failure in a particular patient, or whether other causes should be sought. Sensitivity tests with penicillin are of the greatest importance for staphylococci because resistant strains are now common.

CRYSTALLINE PENICILLIN G

Crystalline penicillin G is the only kind of penicillin to be used for infections which may endanger life, because absorption (following intramuscular injection) is more reliable than with the procaine salt and much greater concentrations can be attained, with better penetration of foci of infection.

Administration and Dosage

Routine administration is by the intramuscular route. Various dosage schedules and time intervals have been used with success. The longer the interval, the larger is the dose required to produce the same effect, but the interval should never be longer than 12 hours.

Since treatment must often be initiated before the results of bacteriological investigation are known, it is useful to have a standard routine procedure. The minimum dosage recommended for adults is 100,000 units intramuscularly every 6 hours. In acute pneumococcal pneumonia and similar severe infections this dose should be given every 3 hours for the first 24 hours, after which, if there is a good clinical response, the interval may be 6 hours. If there is no clinical response in 24 hours, the dose should be increased to 500,000 units 3-hourly.

Dosage schedules suggested in relation to sensitivity tests when these are available are indicated in Table 2.

Continuous intramuscular or intravenous infusion may be given to avoid frequent injections, but contamination and infection with penicillin-resistant organisms may occur and these methods are not recommended. However, in special cases, such as infection with a staphylococcus resistant to the usual concentrations of all available drugs, intravenous infusion may be used to maintain high concentrations of penicillin in the blood in an attempt to overcome the effect of penicillinase, and may prove life-saving (54).

TABLE 2

CRYSTALLINE PENICILLIN G

Sensitivity	Interpretation	Adult Dosage (I.M.)
(1) Between 0·01 and 0·1 unit per millilitre	Very sensitive.	100,000 units 6-hourly, or 3-hourly for severe infections.*
(2) Between 0·1 and 1·0 unit per millilitre.	Sensitive (except staphylococci, which are resistant owing to penicillinase production).	500,000 units 6-hourly, or 3-hourly for severe infections.
(3) Between 1·0 and 10 units per millilitre.	Probably resistant.	Consider another drug or try 1 million units of penicillin 6-hourly or 3-hourly. Consider Benemid.†
(4) More than 10 units per millilitre.	Resistant.	

Children over 3 years may have one-half to two-thirds the adult dose; under 3 years, one-quarter the adult dose.

* Meningitis, subacute bacterial endocarditis and infections with resistant staphylococci require special schedules.

† Benemid (probenicid) suppresses the excretion of penicillin by the renal tubules and thus raises the blood concentration. It is administered by mouth in 0·5 gram doses 6-hourly. Its action is antagonized by salicylates.

Intrathecal injections may be given in meningitis (page 42) during the first few days of illness. The daily dose is 5,000 units for a child and 10,000 units for an adult in a concentration not exceeding 2,000 units per millilitre. The dose should never exceed 20,000 units or convulsions may result.

Oral administration is much less reliable than administration by injection in that absorption is irregular and there is great variation in the concentration attained in different patients. However, it is a useful adjunct in the treatment of minor infections provided that large doses of at least 200,000 units 4-hourly are given before meals, and that it *follows* treatment with one or more injections of crystalline penicillin G or of procaine penicillin. Oral administration has been used in the prophylaxis of rheumatic fever in children (page 72).

Duration of treatment with penicillin depends on the nature and severity of the infection. In acute infections, treatment should be continued for a few days after the temperature has returned to normal. Care should be taken that patients in hospital are not treated for long indefinite periods.

In meningitis, the time for which penicillin should be given appears to depend largely on the stage of the disease at which it is begun. When started early, treatment for 5 days may be sufficient, but intramuscular injections are usually continued for longer periods of two to three weeks.

In subacute bacterial endocarditis, treatment is given for a minimum period of four weeks, and in chronic actinomycosis it may be continued for many months.

PROCAINE PENICILLIN

Procaine penicillin is useful because absorption of penicillin is prolonged for a period up to 24 hours, and injections can be given at infrequent intervals.

It is usually stated by commercial firms that a certain dose of procaine penicillin maintains a "therapeutic concentration" of penicillin in the blood. It should be clearly understood that in order to be effective the concentration in the blood must exceed the concentration required to inhibit the organism. Since different strains of the same species vary in the degree of sensitivity and the rates of absorption and excretion vary in different patients, the dosage required is greater in some instances than in others.

(1) Aqueous suspensions such as "Penaquacaine G" or "Distaquaine" are suitable for minor infections with sensitive organisms such as tonsillitis due to *Streptococcus pyogenes*. An injection of 300,000 units maintains a level above 0·06 unit per millilitre in some patients for 24 hours, but owing to marked individual differences in absorption and in the sensitivity of strains, it is better to use a minimum of 500,000 units per dose in an adult.

(2) Fortified aqueous suspensions containing added crystalline penicillin G provide a much higher concentration in the blood for a few hours following each injection and are probably superior to ordinary aqueous suspensions, but the same dosage of procaine penicillin (at least 500,000 units) should be used.

(3) Oily suspensions containing procaine penicillin and 2% aluminium monostearate delay absorption even more than aqueous suspensions, so that injections may be given twice weekly, although daily injections of 500,000 units are more reliable. Oily suspensions have been favoured for the treatment of syphilis (page 55), but their viscosity makes them troublesome to handle and their use is not recommended in other infections.

ESTOPEN

Estopen (syn. neo-penil) is the hydriodide of the diethylaminoethyl ester of penicillin G. It is not itself active against bacteria, but it is claimed that it is hydrolysed in the body to liberate active penicillin. It appears to have a particular affinity for lung tissue, but there is no evidence that it is therapeutically more effective than crystalline penicillin provided that adequate doses of the latter are employed. Anaphylactoid reactions may occur, and this drug is not recommended.

D.B.E.D. PENICILLIN

Di-benzyl-ethylene-diamine penicillin (syn. D.B.E.D. penicillin ; penidural) is a relatively insoluble, stable salt of penicillin which when injected *intramuscularly* in a dose of 600,000 units can maintain a low concentration of penicillin in the blood for a period of one or even several weeks. It is already in use for the treatment of gonorrhœa and early syphilis (page 55), in which the organisms are particularly sensitive to penicillin and in which default from repeated treatments may occur. However, there are individual differences in the concentrations attained in the blood, and a mixture containing crystalline, procaine and DBED penicillin (as in " Bicillin all-purpose ") is more reliable than DBED penicillin alone. The mixture may be used in the treatment of other infections but it is unwise to depend on one injection which is likely to prove inadequate. Patients should at least be observed at frequent intervals. A safer schedule is the use of several daily injections of procaine penicillin followed by one injection of the mixture containing the DBED drug.

A high incidence of sensitization reactions has been reported with DBED penicillin.

DBED penicillin may be administered by the *oral* route in a dose of 300,000 units or more, but suitable concentrations are not maintained for periods longer than from 6 to 8 hours. However, there is some indication that absorption by the oral route is more reliable than is the case with crystalline penicillin G, and oral prophylaxis in rheumatic fever is under trial.

THE CHOICE BETWEEN CRYSTALLINE, PROCAINE AND DBED PENICILLIN

In general, crystalline penicillin G is used for infections endangering life, such as pneumonia, bacterial endocarditis and meningitis. Its superiority depends mainly on two factors :

(1) The high concentrations obtainable. Thus an organism might be insensitive to concentrations attainable with either procaine or DBED penicillin, yet sensitive to those attainable with large doses of crystalline penicillin. When it is stated that an infection has " failed to respond to penicillin ", it is important to know what form of therapy is implied.

(2) Its ability to penetrate a focus of infection or to reach a particular site. In subacute bacterial endocarditis a higher concentration of penicillin is usually required than in septicæmia. In meningitis, the concentrations attained with procaine penicillin are not sufficient to ensure passage into the cerebro-spinal fluid.

It is claimed that procaine penicillin can be used in severe infections, particularly following early diagnosis, but there is risk of failure and its use is not recommended. The convenience of administration once or twice daily naturally favours its choice in less serious infections such as acute tonsillitis, cellulitis and boils, and in these conditions it is more reliable than DBED penicillin. However, DBED penicillin, or preferably a mixture of DBED with crystalline and procaine penicillin, is now widely used in gonorrhœa and syphilis because injections can be given at weekly or bi-weekly intervals with

satisfactory results. Since DBED penicillin is a relatively new preparation it will be some time before its value is fully assessed.

Toxic Effects of Penicillin

One of the most valuable properties of penicillin therapy is its comparative freedom from ill effects. More than 20 million units daily have been given intramuscularly for a period of several weeks without harm. When reactions do occur there is no evidence that they are related to large dosage.

The most important toxic effect of penicillin is the production of allergic manifestations (22). The commonest of these is urticaria, but a serum-sickness type of delayed reaction and various dermatoses such as contact dermatitis of skin or mucous membrane, bullous eruptions and exfoliative dermatitis may occur. A number of fatal anaphylactoid reactions has been recorded. It has been suggested that accidental entry into a vein during intramuscular injection of procaine penicillin may have caused some deaths, probably by pulmonary embolism (6). Stomatitis appears to be related to contact dermatitis in that it rarely occurs except in patients taking penicillin by mouth.

Sensitivity reactions occur most frequently in patients who have had previous penicillin therapy and so are more commonly seen now than previously, but they may occur in subjects who have had no known previous contact with the drug. In severe cases the use of cortisone may be considered.

Sensitization of nursing and other members of hospital staffs to antibiotics has recently become a serious problem (48). Sensitivity may be acquired at what appears to be a first contact with the drug or the latter may be handled for months or years before sensitivity appears. In some cases it has followed an incident in which the antibiotic was splashed on the skin or squirted into the eye.

Various preventive measures have been suggested, such as the wearing of gloves, gowns, masks and eye-shields while preparing and giving injections, but some nurses have become sensitized in spite of special precautions.

The degree of sensitization varies considerably from a condition where improvement occurs (after avoidance of the drug for a brief period and following simple treatment such as the use of calamine lotion or anti-histamine), so that the nurse may again handle the drug with impunity, to a state in which she is unable to have any contact with the drug, and may be obliged to abandon her profession. Sensitization is often less serious if diagnosis is made early and treatment is established. There is a difference of opinion as to the value of a deliberate attempt at desensitization by appropriate administration of the drug, but successful results have been recorded.

Accurate diagnosis is important since dermatitis may be caused by contact with plants, cosmetics and drugs other than antibiotics such as procaine and P.A.S.

Herxheimer reactions to penicillin, though frequent in early syphilis, rarely appear to have serious consequences. In cardio-vascular and late neuro-syphilis, however, severe and dangerous effects may result.

Diarrhœa and *pruritus ani* sometimes follow oral administration.

CHAPTER IV

STREPTOMYCIN

Streptomycin was isolated from *Streptomyces griseus* by Waksman and his co-workers, and the first publication concerning this drug appeared in 1944. It is active against a number of species of bacteria, but there is extreme variation in the sensitivity of strains, so that sensitivity tests are necessary.

Dihydrostreptomycin is a synthetic derivative of streptomycin. It has the same activity against bacteria but differs in its toxic effects. It is occasionally used as a substitute for, or in a mixture with streptomycin.

Apart from its great importance in the treatment of tuberculosis (p. 56), the main use of streptomycin is as an adjunct to penicillin in the therapy of subacute bacterial endocarditis caused by *Streptococcus fæcalis* (page 62) and as an adjunct to sulphadiazine or chloramphenicol in the treatment of meningitis due to *Hæmophilus influenzæ* (page 44). It may also be of value in the treatment of pyogenic infections caused by penicillin-resistant staphylococci which are sensitive to it, or by sensitive strains of *Proteus* and other Gram-negative bacilli which are resistant to other drugs. It should always be combined with another drug if possible, but is occasionally effective clinically by itself.

Two factors militate against the use of streptomycin :

(1) Its high toxicity, which strictly limits the dosage.

(2) Highly resistant mutants exist which replace the original sensitive organisms and make continued treatment useless. This effect can be overcome to some extent by administering simultaneously another drug *to which the organism is sensitive*, e.g. para-amino-salicylic acid (P.A.S.) in tuberculosis and sulphamezathine in pyogenic infections. The second drug reduces the number of organisms, so that mutation is less frequent, and is also able to deal with resistant organisms as they appear.

Administration and Dosage

Routine administration is by the *intramuscular* route. The interpretation of sensitivity tests on pyogenic bacteria is stated in Table 3.

Duration of therapy with intramuscular injections of streptomycin in ordinary pyogenic infections is limited to from 5 to 7 days owing to the toxic nature of the drug, but streptomycin may usually be expected to exert its maximum effect within this period. In pyogenic infections it is better to give 6-hourly injections rather than single daily injections.

In infections which endanger life, treatment is prolonged and the risk of toxic effects must be taken. In subacute bacterial endocarditis treatment with 2 grams per day is continued for 4 weeks. In meningitis caused by *Hæmophilus influenzæ* or other sensitive Gram-negative bacilli and in brucellosis, a course of several weeks may be necessary. The dosage and duration of therapy in tuberculosis are discussed on pages 57 and 59.

Intrathecal injections of from 25 to 50 milligrams of streptomycin daily may be given in meningitis if necessary, but owing to the toxicity of the drug are to be avoided if possible. In meningitis caused by *Hæmophilus influenzæ* their use is recommended (for a period of from 3 to 5 days only) on account of their apparent value clinically (page 44). In tuberculous meningitis this method of treatment has been found unnecessary since isoniazid became available. The intrathecal injection of dihydrostreptomycin is not advised.

TABLE 3

STREPTOMYCIN*

Sensitivity	Interpretation	Adult Dosage (I.M.)
(1) 1 microgram (μg) per millilitre.	Very sensitive.	0·5 gram 6-hourly.
(2) Between 1 and 10 μg per millilitre.	Sensitive.	0·5 gram 6-hourly.
(3) Between 10 and 20 μg millilitre.	Probably resistant.	Choose another drug if possible.
(4) More than 20 μg per millilitre.	Resistant.	

Children over 3 years may have one-third to one-half the adult dose ; under 3 years, one-quarter the adult dose.

* Benemid does not suppress the excretion of streptomycin.

Oral administration has been used in the treatment of bowel infections due to *Shigella sonnei*. Streptomycin is very poorly absorbed from the gastro-intestinal tract, and large concentrations of the drug are attained in the bowel contents. This has led to its use in prophylaxis prior to operations on the colon, but owing to the emergence of resistant strains its effect is unreliable.

Toxic Effects of Streptomycin and Dihydrostreptomycin

Prolonged intramuscular administration of streptomycin or dihydrostreptomycin or high dosage over a short period may produce damage to the eighth nerve. Vestibular function is affected more commonly than hearing, but most patients achieve satisfactory vestibular function by compensatory mechanisms. However, if deafness occurs it may persist in some degree. Deafness is more likely to occur with dihydrostreptomycin than with streptomycin ; vestibular dysfunction is more common with streptomycin. A mixture containing equal parts of the two drugs is obtainable and is thought to reduce the risks of toxicity (27, 57). Streptomycin is preferred to dihydrostreptomycin although when the usual dosage schedules for pulmonary tuberculosis are employed, e.g. 1 gram every other day, toxic reactions with either drug are considered negligible.

Allergic skin rashes and urticaria occur and may be severe. Contact dermatitis may develop in nurses giving repeated injections of streptomycin, and its management is the same as for penicillin (page 17). Desensitization may be attempted.

CHAPTER V

CHLORAMPHENICOL

Chloromycetin was isolated by Burkholder from *Streptomyces venezuelæ* and was first described in 1947. In 1948 the drug was synthesized as chloramphenicol.

It is active against many different types of Gram-positive and Gram-negative bacteria and against some rickettsiæ. Its special value lies in the treatment of typhus and typhoid fevers. It has been used with success in the treatment of meningitis caused by *Hæmophilus influenzæ* and of meningitis and other serious infections caused by staphylococci resistant to other antibiotics. In minor infections with sensitive cocci or bacilli it is as effective as the tetracycline drugs but its use carries the risk of more serious toxic manifestations. It is sometimes of value in brucellosis but is usually ineffective in subacute bacterial endocarditis. Claims for its value in the treatment of psittacosis and other virus infections have not been substantiated.

Administration and Dosage

Routine administration is by the *oral* route. The interpretation of sensitivity tests is given in Table 4.

TABLE 4
CHLORAMPHENICOL

Sensitivity	Interpretation	Adult Dosage (Oral)
(1) 2 micrograms (μg) per millilitre.	Very sensitive.	About 50 milligrams per kilogram per day or 3 grams per day in 6-hourly doses.
(2) Between 2 and 10 μg per millilitre.	Sensitive.	
(3) Between 10 and 20 μg per millilitre.	Probably resistant.	Choose another drug if possible or try 100 milligrams per kilogram per day.
(4) More than 20 μg per millilitre.	Resistant.	

Children may have 50 milligrams per kilogram per day, or those over 3 years about one-half and under 3 years one-quarter adult doses.

Chloramphenicol palmitate is a palatable preparation suitable for children, but it does not give satisfactory blood concentrations for the treatment of typhoid fever. It is not recommended if digestion is defective.

A special solution for *intramuscular and intravenous* use is available commercially. The dosage is 50 milligrams per kilogram of body weight per day administered by deep intramuscular injection at 6-hourly intervals. The solution may be used intravenously provided that it is diluted at least fifty-fold in physiological saline or 5% glucose solution. When preparing dilutions the chloramphenicol solution should be added rapidly under the surface of the diluent or precipitation may occur. The rate of intravenous injection should not exceed 2 millilitres per minute.

Duration of therapy depends on the severity and type of illness. In typhus fever 36 hours is often sufficient, but in pyogenic infections a minimum period of 5 days is recommended. In view of the toxic properties of the drug it is advised that the period of treatment should not exceed 10 days unless adequate blood studies are performed. Periods longer than 10 days are usually necessary in typhoid fever, brucellosis and meningitis.

Toxic Effects of Chloramphenicol

Gastro-intestinal disturbances are much less common than with the tetracycline compounds, possibly owing in part to the fact that little active chloramphenicol is present in the lower bowel (24).

Depression of bone marrow function occasionally occurs. A number of fatal cases of aplastic anæmia has been attributed to the drug as well as a large number of cases of depression of marrow function with recovery after discontinuing the drug. Most cases, but not all, have followed prolonged continuous or intermittent therapy. All of the marrow elements, red cells, granulocytes and platelets may be involved. The incidence of serious blood disorders is low, but chloramphenicol should be used with caution.

CHAPTER VI

THE TETRACYCLINE COMPOUNDS

The tetracycline compounds are aureomycin (chlortetracycline), terramycin (oxytetracycline) and the parent compound, tetracycline (syn. achromycin, tetracyn).

Aureomycin was isolated by Duggar from *Streptomyces aureofaciens* and a series of articles on experimental and clinical investigations appeared in 1948.

Terramycin is produced by *Streptomyces rimosus*, and was first reported by Finlay and his co-workers in 1950.

Tetracycline was prepared independently at Lederle Laboratories from aureomycin and at Pfizer Laboratories from terramycin, and was reported in 1953.

The tetracycline drugs resemble each other and chloramphenicol in the wide range of their antimicrobial activity, and they are sometimes grouped with chloramphenicol as the *broad spectrum antibiotics*. They are active against some rickettsiæ, but have no specific effect in virus diseases with the exception of trachoma. Some activity against *Endamœba histolytica* in acute intestinal amœbiasis has been demonstrated, but these drugs are useless in the systemic and chronic form of the disease. Terramycin is sometimes useful in the treatment of tuberculosis.

The pneumococcus, hæmolytic streptococcus and *Hæmophilus influenzæ* are usually sensitive to the tetracycline compounds, but strains of *Staphylococcus aureus*, coliform bacilli* and other organisms vary considerably, so that sensitivity tests are important. It is

* *Bacterium coli* and related lactose-fermenters.

common to find that an organism resistant to aureomycin is resistant to terramycin and to tetracycline. However, cross-resistance is by no means invariably seen and it is desirable, at least for the time being, to include all three drugs in sensitivity tests. There is no cross-resistance between the tetracycline drugs and chloramphenicol.

Since tetracycline itself has been available for only a short time, its clinical value is not fully established, but there is no reason to believe that it will be less effective than aureomycin or terramycin.

The tetracyclines are bacteriostatic antibiotics (page 30) and are not highly effective in chronic diseases. The course of brucellosis is arrested, but relapse frequently occurs. The drugs are not of much use in the treatment of subacute bacterial endocarditis (page 62).

Administration and Dosage

Routine administration is by the *oral* route. The interpretation of sensitivity tests is stated in Table 5.

TABLE 5

THE TETRACYLINES

Sensitivity	Interpretation	Adult Dosage (Oral)
(1) 1 microgram (μg) per millilitre.	Very sensitive.	About 15 milligrams per kilogram per day or 1 gram daily in 6-hourly doses.
(2) Between 1 and 5 μg per millilitre.	Sensitive.	About 25 milligrams per kilogram per day or 1·5 to 2 grams daily in 6-hourly doses.
(3) Between 5 and 10 μg per millilitre.	Probably resistant.	Choose another drug if possible. In critically ill patients consider I.V. therapy.
(4) More than 10 μg per millilitre.	Resistant.	

Children may have the same dosage by weight as adults, or those over 3 years about one-half, and under 3 years one-quarter of the adult doses. Palatable forms are available.

In meningitis the adult dosage may be increased to 3 grams per day, with corresponding increases for children. Large doses over 2 grams per day do not as a rule provide higher blood concentrations, but since there are marked individual differences in absorption, their use is justified in serious infections. Penetration of these drugs into cerebro-spinal fluid occurs slowly following oral medication and intravenous therapy is desirable in the early stages of treatment of meningitis.

Intravenous preparations are available commercially. The dosage is from ½ to 1 gram per day. A maximum of 2 grams per day for an adult should never be exceeded, or liver damage may result. Unfortunately, thrombophlebitis is likely to occur, and appears to be more frequent when the antibiotics are administered by slow intravenous drip than when given by separate injection. Each ampoule of 250

milligrams should be dissolved in at least 100 millilitres of sterile saline or distilled water. Methods of administration in order of preference are:

(1) Separate injections given 12-hourly over at least a 5-minute period according to volume. The rate of injection should not exceed 100 millilitres in 5 minutes.

(2) Addition of the drug to the drip tube of an intravenous infusion set followed by rapid flushing with the infusion.

(3) Incorporation of the drug in an intravenous infusion, e.g. glucose, saline or blood, together with 1,000 units of heparin per litre bottle.

An *intramuscular* preparation of terramycin is available commercially and consists of equal parts of terramycin hydrochloride and magnesium chloride in 2% procaine hydrochloride. The dosage for an adult is 100 milligrams (in a volume of 2 millilitres) administered at 8-hourly intervals. Children may have from one-quarter to one-half adult doses according to age. Since pain and induration occasionally occur at the site of injection, administration is by *deep* intramuscular injection in gluteal muscle, and injection sites are alternated. Intramuscular treatment with terramycin is indicated when oral therapy is not feasible. Its value is established, but intravenous therapy is still preferred in the early stages of acute illness such as meningitis and general peritonitis.

Duration of therapy depends on the severity of the illness. Clinical response usually occurs within 48 hours, but in pyogenic infections the minimum period of treatment recommended is 5 days. In meningitis treatment is continued for from 2 to 3 weeks or for longer if indicated.

Toxic Effects of Tetracyclines

The most common toxic effects following the use of aureomycin and terramycin are gastro-intestinal symptoms such as nausea, heartburn, epigastric distress and vomiting. These may sometimes be avoided by the patient drinking fluid, especially very cold milk, at the rate of about one glassful per capsule. More troublesome is diarrhœa, often associated with *pruritus ani*, or vaginitis, which may persist for a considerable time after treatment has stopped. Tetracycline produces the same effects as aureomycin and terramycin, but they occur less frequently and are usually less severe.

Occasionally staphylococcal enteritis develops, caused by a secondary infection with staphylococci resistant to the drug in use, and may be fatal (59).

Owing to the suppression of the normal flora, mouth or skin lesions due to *Monilia albicans* may develop. Fatal cases of pulmonary moniliasis in patients with a pulmonary abscess or bronchiectatic cavity have been reported. However, the mere presence of *Monilia albicans* in lesions is not proof of its ætiological role and it now seems likely that this complication of antibiotic therapy, while it may occur, has been over-emphasized (28).

Stomatitis, skin eruptions and vertigo have been observed. Fever, chills, general malaise and vomiting may occur but do not necessarily interfere with treatment.

Some patients tolerate aureomycin better than terramycin, and vice versa. Intolerance to either drug might suggest a trial of tetracycline.

The possibility of liver damage and of thrombophlebitis following intravenous therapy has already been mentioned.

CHAPTER VII

ERYTHROMYCIN AND CARBOMYCIN

ERYTHROMYCIN

Erythromycin (syn. ilotycin, erythrocin) is produced by *Streptomyces erythreus* and was isolated by McGuire and his co-workers in 1952.

It is active against Gram-positive and Gram-negative cocci and Gram-positive bacilli, but not against the common Gram-negative bacilli. However, some activity has been demonstrated against strains of *Hæmophilus influenzæ*, *Brucella melitensis* and *Brucella suis* (but not *Brucella abortus*) and against *Endamœba histolytica* and certain rickettsiæ.

Good clinical results, but not better than with penicillin, aureomycin or terramycin, have been obtained in the treatment of pneumococcal pneumonia and of hæmolytic streptococcal infections such as tonsillitis and scarlet fever. Erythromycin has also been used successfully in the treatment of diphtheria carriers resistant to penicillin therapy (23). The treatment of gonorrhœa has been less satisfactory. However, the main use of erythromycin is in infections caused by staphylococci resistant to other antibiotics, in which it may be life-saving. Whenever possible this drug should be reserved for patients in whom laboratory studies of the organism can be made. It should not be used unnecessarily in the community and should rarely be used empirically for the following reasons :

(1) Organisms resistant to therapeutic concentrations of the drug may develop rapidly (even within 36 hours) during treatment, so that continued therapy with the drug is useless. Erythromycin is therefore not as reliable a drug as penicillin for the treatment of infections with penicillin-sensitive organisms, nor as reliable as the broad spectrum antibiotics in infections with organisms which are sensitive to them.

(2) Since erythromycin is not active against coliform and related Gram-negative bacilli, it is a bad choice for the empirical treatment of an infection which might be due either to a Gram-positive coccus, a Gram-negative bacillus, or to both. A wiser choice would be either penicillin combined with sulphamezathine (and possibly with streptomycin), or one of the broad spectrum antibiotics.

(3) It has already been reported that within one month of the adoption of erythromycin for general use in a hospital, strains of staphylococci resistant to it appeared in nose and throat cultures from the staff. After five months the carrier rate of resistant strains was 75%. This implies a high risk to patients, of " hospital infection " with resistant strains for which there may be no specific treatment. Fatalities from such infections have occurred (29).

The dissemination of resistant strains can be greatly delayed by restricting the use of this now valuable antibiotic. However, each case is to be reviewed on its merits and if a serious staphylococcal infection is encountered, the use of erythromycin must be considered (page 64).

Administration and Dosage

Routine administration is by the *oral* route, and the interpretation of sensitivity tests is stated in Table 6. Tablets with an acid-resistant coating are used, but unfortunately these are not always digested. Tablets containing erythromycin stearate are said to be superior. A palatable syrup containing erythromycin stearate is obtainable for children. It may be administered by Rehfuss tube to patients who are unable to swallow.

TABLE 6
ERYTHROMYCIN

Sensitivity	Interpretation	Adult Dosage (Oral)
(1) 1 microgram (μg) per millilitre.	Sensitive.	About 25 milligrams per kilogram per day or 1·5 gram per day in 6-hourly doses.
(2) Between 1 and 5 μg per millilitre.	Moderately sensitive.	In seriously ill patients, increase oral dosage to a maximum of 4 grams per day and consider I.V. therapy.
(3) Between 5 and 10 μg per millilitre.	Probably resistant.	Consider bacitracin.

Children over 3 years of age may have one-half, and children under 3 years one-quarter adult doses.

An *intravenous* preparation of erythromycin is available overseas.

Duration of therapy depends on the nature of the illness. A response may be expected within 48 hours. The usual course is 5 days, but in some infections a longer period may be necessary.

Toxic Effects of Erythromycin

The only toxic effects so far reported are nausea, vomiting and occasionally diarrhœa, and these are said to be infrequent with a dosage less than 2 grams per day.

CARBOMYCIN

The isolation of carbomycin (syn. magnamycin) from *Streptomyces halstedii* was reported by Tanner and his co-workers in 1952.

Although carbomycin is similar to erythromycin in its activity against bacteria *in vitro*, clinical reports suggest that it is not of much

value in the treatment of infections. Low concentrations of the drug are found in the blood and urine, and it is possible that carbomycin is rapidly inactivated in the body. Moreover, organisms which become resistant to erythromycin show cross-resistance to carbomycin.

CHAPTER VIII

BACITRACIN

Bacitracin was isolated in 1945 by Johnson, Anker and Meleney. It is produced by a bacillus closely related to *Bacillus subtilis*.

Owing to the toxicity of the drug its parenteral administration is strictly limited, but it has proved a life-saving agent in certain infections where other drugs have failed. It should only be used for patients in hospital where toxic manifestations can be detected readily.

Its antibacterial spectrum covers Gram-positive organisms and Gram-negative cocci, but not the common Gram-negative bacilli, and probably the only infections in which its systemic use is justified are those caused by staphylococci which are sensitive to it but resistant to other antibiotics. Staphylococcal septicæmia, endocarditis and meningitis have all been treated with success, but owing to the restricted use of the drug few clinical reports are available.

Administration and Dosage

Administration is usually by the *intramuscular* route. Organisms sensitive to 0·1 microgram per millilitre are regarded as very sensitive to therapy; those resistant to 0·1 but sensitive to 1 microgram per millilitre as sensitive, and those resistant to 1 but sensitive to 10 micrograms per millilitre as probably resistant.

Recommendations regarding dosage are as follows:

Bacitracin is administered intramuscularly* in a dosage of 10,000 units 6- or 8-hourly for an adult, or at the rate of 200 units per kilogram of body weight 6- or 8-hourly for a child. If the clinical response is not satisfactory the dosage may be increased to a maximum of 20,000 units every 6 hours for an adult or at the rate of 400 units per kilogram of body weight for a child. A single dose should never exceed 25,000 units and the total daily dose should never exceed 100,000 units. The concentration should not exceed 10,000 units per millilitre. The drug should be dissolved in 2% procaine in normal saline. The site of injection usually becomes painful and two injections should not be given in the same spot.

Duration of therapy is for a minimum period of 5 days, but in the absence of toxic effects it may be continued for several weeks, or for longer if necessary.

If *intrathecal* injections are necessary, bacitracin may be administered at 12-hourly intervals in a concentration of 1,000 units per millilitre in a volume of from 1 to 10 millilitres of saline according to the age of the patient. Procaine must not be added, so a separate solution must be prepared.

Bacitracin cream for *topical* application is available commercially and is very satisfactory for staphylococcal infections which are confined to the skin and require the use of an antibiotic. It is claimed that bacitracin rarely causes sensitization.

* It is important to use the specially prepared sterile bacitracin which is now available in Australia, as the powder supplied for topical application is of unknown purity and its activity is lost by Seitz filtration.

Toxic Effects of Bacitracin

The most important toxic effect of bacitracin is damage to the renal tubules. The daily output of urine must be maintained above 1 litre per day. If it falls below this, bacitracin should be discontinued except in desperate circumstances.

The urine should be examined before beginning treatment, and thereafter every second or third day, for the presence of albumin, casts and cellular elements. These usually appear on the second or third day, reach a low peak from the fifth to the seventh day, and then decline with continued treatment.

The blood urea nitrogen shows some variability during treatment, but the test is not essential unless there is oliguria. However, if possible the test should be done before commencing treatment and at weekly intervals.

Loss of appetite, nausea and vomiting may occur, but may be controlled with andramine, 25 milligrams, administered before each dose of bacitracin. Treatment should not be discontinued unless there is interference with fluid intake.

CHAPTER IX

POLYMYXIN

Polymyxin is derived from various strains of *Bacillus polymyxa* and was first described by Benedict and Langlykke in 1947.

Like bacitracin, polymyxin is a nephrotoxic drug, and the same precautions should be taken in its administration (see above).

There are five varieties of polymyxin, designated A, B, C, D and E. Of these, polymyxin B (aerosporin) and polymyxin E are the least toxic. Polymyxin B is the variety generally used for systemic therapy, but polymyxin E has been used recently with equal success and with the production of fewer side-effects. The polymyxins are active *in vitro* against a very limited number of Gram-negative bacilli, for example some strains of coliform bacilli, *Salmonella*, *Shigella* and occasionally *Proteus*, and many strains of *Pseudomonas pyocyanea*. Their main use clinically is in the treatment of infections with strains of *Pseudomonas pyocyanea* which are resistant to other antibiotics and to the sulphonamides (page 66). They are not active against Gram-positive cocci.

Administration and Dosage

Routine administration is by *intramuscular* injection with procaine added to the diluent. The interpretation of sensitivity tests is stated in Table 7.

The *intrathecal* route may be used in meningitis, and the dosage recommended is as follows: Children under 2 years of age may receive 2 milligrams every day or 2·5 milligrams every other day. When giving 2 milligrams every day the dosage may be continued for 3 or 4 days, and then 2·5 milligrams may be given every other day. The dosage for children over 2 years and for adults is 5 milligrams every day for 3 or 4 days, then 5 milligrams every other day.

TABLE 7
POLYMYXIN

Sensitivity	Interpretation	Adult or Child Dosage (I.M.)
(1) 5 micrograms (μg) per millilitre.	Sensitive.	1·5 to 2·5 milligrams per kilogram per day in 6-hourly doses.*
(2) Between 5 and 10 μg per millilitre.	Probably resistant.	Try 2·5 milligrams per kilogram per day.
(3) More than 10 μg per millilitre.	Resistant.	

The maximum dosage should never exceed 200 milligrams per day.

* It will be noted that the dosage is much less than that recommended for other antibiotics.

Therapy should be continued for at least 3 days after the cerebrospinal fluid has become sterile and may be continued for several weeks when necessary.

It is important that procaine should not be injected intrathecally. Hence a special solution should be prepared and kept separately from the solution for intramuscular injection.

Duration of intramuscular therapy is usually for 5 days, but in the absence of serious toxic effects it may be continued for several weeks if indicated clinically.

Toxic Effects of Polymyxin

Renal damage may occur, producing albuminuria and sometimes increased nitrogen retention, but in patients with normal renal function such changes are transient and it is considered that polymyxin may be administered with safety provided that the maximum dosage of 2·5 milligrams per kilogram per day is not exceeded. In patients with renal disease treatment should proceed with great caution.

Pain and induration at the site of intramuscular injection (relieved by the addition of procaine to the diluent), and drug fever are also observed, and are said to be less frequent with polymyxin E than with polymyxin B.

Neurotoxic symptoms of varying intensity may occur and consist of circumoral and peripheral paræsthesiæ, moderate dizziness and a feeling of weakness without objective signs. All these effects are usually transient and disappear when injections are discontinued.

CHAPTER X

TYROTHRICIN, NEOMYCIN AND VIOMYCIN

TYROTHRICIN

Tyrothricin has considerable historical interest. It was isolated from cultures of *Bacillus brevis* and was described by Dubos in 1939. It is a mixture of two antibacterial substances, gramicidin and tyrocidine, and is active *in vitro* against Gram-positive cocci such as pneumococci, streptococci and staphylococci. There is great variability in the sensitivity of different strains of these organisms. The drug is inactive against Gram-negative bacilli. Tyrothricin is a highly active poison and its systemic use can never be considered. It has been used with some success in the topical treatment of minor lesions, but its value is limited and its use is now outmoded by the discovery of less toxic and more active antibiotics.

NEOMYCIN

Neomycin was isolated from *Streptomyces fradias* by Waksman and Lechevalier in 1949. It is a much more toxic drug than either polymyxin or bacitracin and its systemic use can rarely be justified. It might be used in the treatment of septicæmia caused by a strain of *Proteus* resistant to other antibiotics and to sulphonamides. A dosage of 1 gram per day intramuscularly may be given for brief periods. The drug is nephrotoxic and neurotoxic. Neomycin is bactericidal against a variety of Gram-positive and Gram-negative bacteria, and against acid-fast bacilli. On this account and because of its low absorption from the gastro-intestinal tract, some authorities favour its use by oral administration as a preoperative measure in bowel surgery. It may be used as a topical application to the skin.

VIOMYCIN

Viomycin is produced by *Streptomyces punicans* and was described by Finlay and his co-workers in 1951. It is active against the tubercle bacillus but not against other organisms. It has been used in the treatment of tuberculous infections in which the organisms were resistant to streptomycin.

Renal disturbances and eosinophilia may occur and vestibular dysfunction has been reported, but if treatment is administered in the usual dosage of 1 gram intramuscularly night and morning every three days, toxic effects are usually minor and transient (45).

Viomycin should be given in conjunction with isoniazid for preference, or with P.A.S.

CHAPTER XI

ACTIDIONE

Actidione is an antibiotic produced, in addition to streptomycin, by *Streptomyces griseus*. It was isolated by Whiffen, Bohonos and Emerson in 1946. It is inactive against bacteria but inhibits the growth *in vitro* of certain fungi including *Torula histolytica* (*Cryptococcus neoformans*). *Monilia albicans* and the fungi causing ringworm are not affected.

Actidione shows little promise in the treatment of torulosis but it might still be tried in an infection with a highly sensitive strain of *Torula histolytica.*

Administration and Dosage

Actidione may be administered by intramuscular, intravenous or intrathecal routes, but its high toxicity limits the dosage. Doses up to 480 milligrams intravenously, twice daily, have been used in an infection with a strain of average sensitivity, with no benefit but with severe toxic effects (8). The administration of 20 milligrams daily by the intrathecal route has also been tried.

Toxic Effects

Nausea and vomiting, which can be controlled with andramine, are produced by intramuscular injections of even 20 milligrams 6-hourly. Large doses may be followed by confusion, disorientation and a fall in the prothrombin concentration. Intrathecal injections may produce severe spinal root pains.

CHAPTER XII

SYNERGISM AND ANTAGONISM

Broadly speaking, antibiotics may be classified as either bactericidal or bacteriostatic. The term bacteriostasis implies merely inhibition of bacterial growth in that the number of viable bacteria remains practically constant; bactericidal action is progressive lethal action. Both activities can be demonstrated with the sulphonamides and with all of the antibiotics, depending on the concentration of the drug relative to the sensitivity of the test organism. However, in the concentrations of a drug which are usually attainable in the blood, penicillin and streptomycin stand out as being rapidly bactericidal, since each is capable of reducing the numbers of a sensitive bacterial population by 50% in two or three hours, and of virtually sterilizing a culture in from 8 to 24 hours.

On the other hand the sulphonamides and the broad spectrum antibiotics usually act much more slowly, so that there is virtually no reduction in the numbers of bacteria during the first few hours (bacteriostasis) and it may require about 24 hours for the population to be reduced by 50% (slow bactericidal action). However, sensitive bacteria are ultimately destroyed if the concentration of the drug is adequate, and each of these bacteriostatic drugs used alone can exercise a life-saving effect in certain infections. This is aided in the patient by phagocytosis, etc.

Jawetz and Gunnison and their co-workers have proposed grouping the antibiotics on the basis of their rapidly bactericidal or bacteriostatic (and slowly bactericidal) action, as follows:

Group 1 (bactericidal): Penicillin, streptomycin, bacitracin, neomycin (and polymyxin).

Group 2 (bacteriostatic): Aureomycin, terramycin, chloramphenicol (and the sulphonamides). Tetracycline and erythromycin should also be included.

It is known that antibiotics act on bacteria by blocking various essential metabolic activities. If organisms are simultaneously in contact with two drugs, any slight alteration in their metabolism induced by commencing action of one drug may render them less vulnerable to the other drug, and vice versa. The consequence may be that the organisms escape effective action by either drug and the clinical result may then be worse than that which would have been achieved by either drug alone. This type of *antagonism* has been demonstrated with some of the antibiotics and has been defined by Jawetz and Gunnison (33) as " a large decrease in the rate of early bactericidal action and a reduction in the rate of cure of infections below that observed with the single more active drug ".

The converse process, *synergism*, has also been observed, and has been defined by these workers as " a large increase in the rate of early bactericidal action and in the rate of cure of infections beyond that obtainable by simple additive effects of the agents ".

Experimental Observations

Jawetz and Gunnison found that members of Group 1 were frequently synergistic with each other, occasionally indifferent, but never antagonistic. Mixtures of Group 2 drugs showed only additive effects.

Combinations of the two groups were often antagonistic, the Group 2 drug interfering with the bactericidal action of the other but not itself suffering interference except on rare occasions.

The antagonistic effect of chloramphenicol, aureomycin or terramycin on the bactericidal action of penicillin was evident within two hours, but when sulphadiazine was combined with penicillin the lethal action of the latter was able to proceed for four hours before interference occurred.

In animal experiments, antagonism resulting in a high mortality rate was demonstrated between the broad spectrum antibiotics and penicillin or streptomycin, and between sulphadiazine and penicillin.

Clinical Applications

(*a*) *Synergism*

The beneficial effect of combining streptomycin with penicillin in the treatment of subacute bacterial endocarditis caused by *Streptococcus fæcalis* has been established in patients treated unsuccessfully by penicillin alone.

It has been assumed that combinations of any of the members of Group 1 would be equally valuable in suitable cases.

(*b*) *Antagonism*

Since delay in recovery from an infection may often be ascribed to any one of a number of causes, it is difficult to determine the clinical effect of antagonism between drugs unless an increase in mortality can be demonstrated.

There is no clinical evidence of antagonism between penicillin and the sulphonamides or between streptomycin and the sulphonamides and experience has shown that these combinations are useful in therapy.

There is no clinical evidence of antagonism between streptomycin and chloramphenicol in the treatment of meningitis caused by *Hæmophilus influenzæ*, and indeed this combination gives good clinical results. So also do combinations of streptomycin with the tetracycline drugs in the treatment of brucellosis.

However, antagonism resulting in increased mortality has been recognized following the combination of penicillin with aureomycin in the treatment of pneumococcal meningitis. Thus Lepper and Dowling (37) found that 30% of patients treated with penicillin alone died, while of those treated with penicillin and aureomycin 79% died. Yet Ahern and Kirby (1) could find no evidence of antagonism between these drugs in the treatment of pneumococcal pneumonia.

(*c*) *Conclusions*

No rigid rule can be applied regarding the combination of Group 1 with Group 2 drugs. When it is known from clinical experience, as in the examples cited, that combinations are harmless or probably beneficial, these may safely be recommended. However, the observations of Lepper and Dowling cannot be ignored, and the use of aureomycin combined with penicillin in the treatment of pneumococcal meningitis is unnecessary and unwise.

Experimental observations have shown that antagonism occurs only when there are certain relative concentrations of each drug in relation to the sensitivity of the infecting organism. Such concentrations depend on dosage, and are less likely to be found when large doses of both drugs are given.

Combinations of drugs, while often unnecessary, are probably harmless in mild infections. In severe infections where the time factor is all-important, the risk of antagonism is a real one because the action of the bactericidal drug may be delayed by the bacteriostatic drug. Hence, it is recommended that if combined therapy is deemed desirable, the bactericidal drug should be administered in large doses a few hours before the bacteriostatic drug.

CHAPTER XIII

THE CHOICE OF AN ANTIBIOTIC AND THE USE OF COMBINATIONS OF DRUGS

The choice of an antibiotic is governed chiefly by two factors :

(1) The sensitivity of the infecting organism. If an organism is resistant to the highest concentration of a drug which can be attained in the body, at the site of infection, then therapy with that drug will fail. Thus an infection with a coliform bacillus cannot be treated with penicillin.

(2) Established clinical experience which has indicated that in certain diseases, although the organism is sensitive to a number of drugs, one drug gives better clinical results than the others. This is well illustrated in subacute bacterial endocarditis where *Streptococcus viridans* is sensitive to sulphadiazine, to all the broad spectrum antibiotics, and to penicillin ; yet penicillin is the drug of choice because it gives the most dependable clinical results. This may possibly be explained by its greater bactericidal action, or it may have a greater capacity than the other drugs to diffuse into a focus of infection.

It is in the patient's interest to attempt to make an early accurate bacteriological diagnosis and to carry out sensitivity tests, particularly in an infection which is or might become serious. In such infections therapy need not be withheld, but it may subsequently be modified if necessary. Cultures should be made before commencing chemotherapy, which sometimes masks the bacteriology, although the infection may not be controlled (page 7).

Penicillin Alone

There are certain species of bacteria in which all strains are sensitive to penicillin, although some being relatively more resistant than others, may require larger dosage for the treatment of the infection. These species are : *Treponema pallida* of syphilis, *Streptococcus pyogenes* (hæmolytic streptococcus, group A), *Streptococcus viridans*, the gonococcus, meningococcus and pneumococcus, the anaerobic cocci and *Clostridium welchii*.

If empirical treatment with large doses of penicillin fails in infections thought to be caused by these organisms, the accuracy of the bacteriological diagnosis may well be questioned. Thus tonsillitis may occur in glandular fever ; cellulitis assumed to be streptococcal may be caused by a staphylococcus resistant to penicillin.

When an organism is sensitive to penicillin, there is usually no advantage in adding a second drug. Failure is nearly always due to inadequate dosage. Crystalline penicillin administered frequently is desirable for infections which endanger life. Procaine penicillin or mixtures containing DBED penicillin may be used for less serious infections. Penicillin given by injection is the most reliable and the least toxic of all the antibiotics.

Sulphonamides Alone

It appears that all strains of the meningococcus are sensitive to sulphadiazine, a drug which penetrates readily into the cerebro-spinal fluid. Hence when the diagnosis is known, meningococcal meningitis may be treated with sulphadiazine alone. Sulphamezathine, which is more soluble and which is the drug recommended for routine use, may be used provided that large doses are given of from 9 to 12 grams daily for an adult. Sulphamethazole is not advised because the blood concentration attained is only about one-half of that found with sulphadiazine, and the concentration in the cerebro-spinal fluid is likely to be insufficient.

Strains of other species such as the pneumococcus, hæmolytic streptococcus, gonococcus, staphylococcus and various Gram-negative bacilli vary in sensitivity, and the sulphonamides are such useful drugs that it is worth including one (e.g. sulphadiazine) in routine sensitivity tests. The sulphonamides are often used empirically with success in pneumonia, tonsillitis or infections of the urinary

tract, but therapy will fail if the strain happens to be resistant. Infections of the urinary tract are usually systemic infections and should be treated as such with adequate dosage.

Since the sulphonamides are inactivated to some extent by pus, they are useful in the presence of pus only where there is drainage, as in the urinary tract, the conjunctival sac, the meninges, etc. They are not recommended to be used alone in pneumococcal meningitis in which excessive purulent exudates are produced, or in general peritonitis, or in closed abscesses.

The availability of soluble sulphamezathine for patients who cannot have oral medication is important.

Streptomycin Alone

There are very few pyogenic organisms which are resistant to sulphonamides and the broad spectrum antibiotics, yet sensitive to streptomycin. Hence there is no advantage in using streptomycin alone unless it is known specifically from sensitivity tests that one is dealing with such an organism. Moreover, the odds are weighted against therapeutic success because resistant strains are likely to emerge before the infection is controlled. Streptomycin is a valuable drug best reserved for an emergency. If it must be used, it is always desirable to combine it with other active drugs which prevent or delay the appearance of resistant organisms. Whether it is used alone or in combination, streptomycin is not usually effective in pyogenic infections when given in single daily doses; the dosage should be 2 grams daily in 6-hourly doses, continued for not longer than from 5 to 7 days. Prolonged therapy is unnecessary and may induce toxic effects.

If streptomycin is used in subacute bacterial endocarditis or in brucellosis, a calculated risk of toxic effects is taken.

Chloramphenicol or Aureomycin or Terramycin or Tetracycline Alone

The choice of any particular one of these drugs rather than another depends primarily on the sensitivity of the organisms, which at least with the staphylococci and most of the Gram-negative bacilli is unpredictable.

When an organism is sensitive to all four, as is often the case, choice is based on clinical experience, as for example in typhoid fever in which chloramphenicol has been proved effective, although it is possible that the tetracycline compounds have not received adequate trial.

Chloramphenicol should also be preferred in meningitis due to *Hæmophilus influenzæ* or penicillin-resistant *Staphylococcus aureus*, because this drug passes readily into the cerebro-spinal fluid, and its clinical value in these conditions is well established. In less serious infections chloramphenicol might be avoided because of the possibility (though rare) of blood dyscrasia.

There are individual differences in gastro-intestinal tolerance to the three tetracycline compounds. This might influence the choice of one rather than another. Although side-effects are less common with tetracycline, all three drugs can induce diarrhœa

and pruritus, which may persist for months. Hence it should not be forgotten that there are many infections in which the sulphonamides are equally effective antibacterials.

Cross-resistance occurs among the tetracycline drugs, so that frequently (though not always) an organism resistant to one is resistant to the others. Hence if empirical therapy with aureomycin fails it is probably better to change to chloramphenicol rather than to terramycin or tetracycline.

Penicillin with Sulphonamides

As already stated, it is unnecessary to combine these drugs (although it is common practice) when it is known that the infecting organism is sensitive to one of them. However, they are often useful in combination for mixed infections, and are recommended in puerperal infections (page 53) and in early meningitis of unknown origin (page 45).

A vast amount of clinical experience has shown that in general the drugs are not antagonistic, but it should be remembered that the sulphonamides are bacteriostatic and may interrupt the bactericidal action of penicillin. It is suggested therefore that when time is important as in fulminating meningococcal septicæmia, penicillin should be used alone in massive doses.

Streptomycin with Sulphonamides

It is well known that the administration of para-amino-salicylic acid (P.A.S.) together with streptomycin in the treatment of tuberculosis prevents or delays the emergence of organisms resistant to streptomycin, providing that the infecting strain of tubercle bacillus is sensitive to both drugs. In pyogenic infections the addition of a soluble sulphonamide to streptomycin has the same effect provided that the infecting organism is sensitive to both drugs.

This combination is sometimes successful in eradicating an infection as, for example, in the urinary tract, which was only arrested by sulphonamides alone. It has been used successfully in the treatment of brucellosis, but in this disease it is not as effective as a combination of streptomycin with one of the broad spectrum antibiotics.

Penicillin with Streptomycin

The synergism of streptomycin with penicillin has been established *in vitro* and is confirmed *in vivo* in the successful treatment of subacute bacterial endocarditis caused by *Streptococcus fæcalis*, which does not respond to either drug alone. Similar success with combined therapy has been reported in actinomycosis (4). This has led to the production commercially of mixtures of the two drugs and to the impression that a mixture must be superior to penicillin alone. Apart from the examples cited, there is no clinical evidence for this. If the organism is fully sensitive to penicillin, therapy with that drug should be successful if the dosage is adequate. The use of streptomycin may cause sensitization of the patient and prohibit its subsequent administration.

Sometimes the combination is used empirically with the idea of dealing with an infection caused either by a Gram-positive coccus or

a Gram-negative bacillus ; but even if the organism happens to be a Gram-negative bacillus sensitive to streptomycin, the added penicillin cannot prevent the emergence of a strain resistant to streptomycin, and the value of the therapy may be lost. A better combination would be penicillin with sulphonamides or, in severe infections, penicillin with sulphonamides and streptomycin. Sulphonamides alone, or one of the broad spectrum drugs, might also be effective.

Penicillin with Streptomycin and Sulphonamides

This combination is compatible and probably synergistic and usually obviates the problem of resistant strains emerging because many Gram-negative bacilli are sensitive to both streptomycin and sulphonamides. It is recommended in serious acute infections such as purulent meningitis when the identity of the organism is unknown and either cocci or bacilli may be involved. All three drugs can be administered by injection, and their use is recommended in general peritonitis if intravenous preparations of the tetracycline drugs are not available.

The combination is not advised if an infection is likely to be staphylococcal in origin, since strains resistant to all these drugs are now common.

Penicillin with Chloramphenicol or One of the Tetracycline Drugs

The evidence for antagonism between these drugs has been discussed above and their combination is not recommended. In any event there appears to be no good reason for their combination in treatment. There are extremely few bacteria which are sensitive to penicillin and resistant to all the broad spectrum drugs. Hence if the presence of penicillin-resistant organisms were suspected it would be reasonable to use one of the other drugs alone.

Streptomycin with Chloramphenicol or One of the Tetracycline Drugs

Antagonism between streptomycin and the broad spectrum antibiotics has been demonstrated in the treatment of experimental infections in animals, but if it has occurred in man it appears not to have been recognized. Streptomycin combined with chloramphenicol is recommended in the treatment of meningitis due to *Hæmophilus influenzæ*, and a combination of streptomycin with one of the tetracycline drugs is advised in the treatment of brucellosis. In other infections where the use of such combinations is not supported by clinical trials, caution should be exercised and the combinations avoided when possible.

Chloramphenicol with the Tetracycline Drugs and/or Sulphonamides

There is no known objection to these combinations which could be used in mixed infections if indicated by sensitivity tests. It should be remembered, however, that both chloramphenicol and sulphonamides can depress bone-marrow function.

Erythromycin Alone

Erythromycin should be reserved for infections with staphylococci which are resistant to other drugs and for treatment of diphtheria carriers. It would be used empirically in a serious infection arising in hospital and believed to be staphylococcal, but it is not a good choice generally for empirical therapy, because it is inactive against Gram-negative bacilli. It is not as reliable a drug as penicillin because resistant organisms may appear rapidly before the infection is controlled. There is cross-resistance with carbomycin, but the clinical value of the latter is not established so in any case its use is not recommended.

Erythromycin in Combination

Erythromycin is a bacteriostatic drug. It can be combined with any of the broad spectrum antibiotics or with sulphonamides. It has been used occasionally in combination with penicillin and streptomycin, but it is suggested that such mixtures should be avoided if possible, particularly in the treatment of meningitis.

Bacitracin Alone

Bacitracin is a toxic antibiotic and should be reserved for infections with staphylococci resistant to other drugs, including erythromycin. It is satisfactory if used alone for the treatment of known staphylococcal infections, but is less valuable for empirical therapy because of its inactivity against Gram-negative bacilli.

Bacitracin in Combination

Bacitracin is a bactericidal drug which may be combined with streptomycin or with penicillin, although this should rarely be necessary. On theoretical grounds its combination with bacteriostatic drugs should be avoided, but there is as yet no information regarding the clinical effect of mixtures.

Polymyxin Alone

Since polymyxin has a very limited bacterial spectrum and is a toxic drug, it is used only for infections with sensitive strains of *Pseudomonas pyocyanea* and related organisms which are resistant to other drugs.

Polymyxin in Combination

Polymyxin is a bactericidal drug which could be used in combination with other bactericidal antibiotics in the treatment of mixed infections with *Pseudomonas pyocyanea* and another species. Owing to its narrow spectrum and its toxicity its use in empirical therapy is not advised.

CHAPTER XIV

THE PLACE OF CHEMOTHERAPY IN TREATMENT AND THE ABUSE OF ANTIBIOTICS

It is now ten years since penicillin became freely available, and much has been learned of the properties of antibiotics generally. Some of this knowledge has been summarized in the preceding pages. Before embarking on recommendations for the treatment of specific infections it is fitting to consider the place of chemotherapy in the treatment of disease.

There are certain infections such as tonsillitis, gonorrhœa and syphilis, where chemotherapy is often the only form of treatment necessary. There are other infections such as diphtheria, tetanus and gas gangrene where treatment with the appropriate antiserum is more important than chemotherapy and where other measures may also be required. Finally there is a large group of infections in which chemotherapy is usually necessary or at least desirable, but in which a successful outcome depends primarily on medical or surgical management. Thus the treatment of shock and of dehydration in acute infections, such as meningococcal septicæmia, is of the first importance. In severe gastro-enteritis, replacement of fluids and proper electrolyte control are essential. Maintenance of the hæmoglobin at a high level is necessary in the management of infections with anaerobic streptococci in puerperal and abortional sepsis. While nursing care and the maintenance of nutrition are always important, they may be life-saving in such diseases as whooping cough and typhoid fever.

In some infections, such as osteomyelitis, antibiotics administered very early in the course of the infection may prevent the lesion becoming a surgical problem, but in so-called surgical infections chemotherapy is always secondary to surgical management. Abscesses must be adequately drained and foreign bodies and dead tissue must be removed, and if these principles are observed chemotherapy is often unnecessary. In the urinary tract infection frequently follows obstruction, due perhaps to stricture, calculus, tumour or prostatomegaly, and chemotherapy cannot be expected to succeed unless the obstruction is removed.

The enormous sale of antibiotics bears witness to the general observation that these drugs are often used unnecessarily.

There is evidently a strong temptation to treat minor ailments with antibiotics, and an intelligent appraisal is needed of the undesirability of chemotherapy in most cases.

There is considerable wastage in hospitals both in the amounts of antibiotics used and in the time spent in dispensing drugs and giving injections. Enthusiasm might well be tempered with judgment on many occasions and the patient spared.

However, when it has been decided that chemotherapy is really necessary an adequate dosage and period of therapy should be ensured.

Of late, much has been written concerning the abuse of antibiotics. The following aspects of the subject are important:

(1) Antibiotics and sulphonamides are not universal antipyretics and should not be used without careful consideration, because

(*a*) they may mask important signs and symptoms so that diagnosis is delayed, sometimes with serious results;

(*b*) they may sensitize the patient so that the drug cannot be used on a later occasion when it might save his life;

(*c*) they may have persistent side-effects which are more unpleasant than the infection itself.

Efforts should be made to inform the public concerning these facts.

(2) When chemotherapy is given, the dosage should be adequate.

(*a*) Small doses are usually not effective, although they may appear so in minor self-limiting infections which would have recovered spontaneously.

(*b*) Small doses may merely suppress an infection which thus becomes more deeply entrenched and more difficult to eradicate.

(*c*) Organisms resistant to the drug may replace the initially sensitive strain.

(3) The duration of the period of chemotherapy should be adequate, but should not be unduly prolonged.

(*a*) Prolonged therapy is unnecessary and extravagant except in certain diseases such as subacute bacterial endocarditis.

(*b*) If there is no clinical response to adequate dosage within 48 hours it is usually better to try another drug.

(*c*) Toxic effects, and particularly the serious blood dyscrasias which can be produced with the sulphonamides or chloramphenicol, are more likely to occur after prolonged or repeated treatment.

(*d*) Secondary infection (so-called super-infection) with another species of bacterium resistant to the drug is likely to occur.

It is very important to review chemotherapy at least at weekly intervals.

(4) The use of streptomycin combined with penicillin is undesirable in empirical therapy unless sulphadiazine is given as well (page 36).

(5) The use of combinations of drugs which may be antagonistic, such as penicillin and aureomycin in the treatment of meningitis, is to be avoided (page 32).

(6) Antibiotics should not be used prophylactically in clean operations to cover inadequate aseptic surgical technique (page 73).

(7) Topical applications should not be used in deep infections where systemic therapy is necessary, or in those superficial infections in which antiseptics such as vioform give equally good results (page 70).

CHAPTER XV

REASONS FOR FAILURE IN CHEMOTHERAPY

The reasons for failure in chemotherapy may be summarized as follows :

(1) Incorrect assumptions regarding bacteriological diagnosis may lead to the choice of the wrong antibiotic.

(2) Late treatment. If a patient already has an overwhelming toxæmia or a very extensive lesion, chemotherapy is less likely to succeed, although it should always be tried. When the patient has what appears to be a fulminating infection, delay in instituting massive chemotherapy must be avoided.

(3) Inadequate dosage with failure to penetrate the lesion in sufficient concentration.

(4) An inadequate period of therapy. Relapse may occur in typhoid fever, subacute bacterial endocarditis, etc.

(5) Neglect of other forms of treatment, such as drainage.

(6) Choice of the wrong method of administration, e.g. the use of topical applications when the lesion is not superficial or of systemic therapy alone when the blood supply to the lesion is unsatisfactory.

(7) The presence of a previously unsuspected underlying infection or lesion, e.g. tuberculosis of the urinary tract or a fungous infection of the skin.

(8) An increase in the resistance of the infecting organism during treatment. This should be watched for and either the dosage increased or the drug changed.

(9) Secondary infection. This implies a new infection with an organism which is resistant to the drug in use, e.g. infection with a coliform bacillus or a resistant staphylococcus in a patient receiving penicillin, or with *Monilia albicans* in a patient receiving one of the broad spectrum antibiotics.

(10) The use of a combination of antibiotics which may be mutually antagonistic. The clinical significance of using such combinations is still not fully evaluated.

(11) In certain infections such as whooping cough and gastro-enteritis, where the organisms persist in spite of chemotherapy, the reasons for failure are not clear. It may be that the distribution of the drugs in the body is such that the focus of infection escapes effective concentrations.

CHAPTER XVI

THE TREATMENT OF INFECTIONS

TONSILLITIS AND OTHER INFECTIONS WITH STREPTOCOCCUS PYOGENES

In the treatment of tonsillitis it is common to use sulphonamides, but it is doubtful whether these drugs do more than reduce the incidence of complications (26). In severe infections, including those in patients who have had rheumatic fever, penicillin is preferred because it produces more rapid clinical improvement. Whenever practicable a throat swab should be taken *before* commencing chemotherapy, so that diphtheria is not missed (see below).

In severe suspected streptococcal infections procaine penicillin or fortified procaine penicillin is advised in single daily injections containing 300,000 units of procaine penicillin for a child or 600,000 units for an adult. Treatment should be continued for at least 5 days. A course of 7 days may be required to eradicate the hæmolytic streptococcus. Similar treatment may be given in scarlet fever, *otitis media*, paronychia and cellulitis.

If tonsillitis is treated with a single injection of DBED penicillin or of a mixture of DBED, procaine and crystalline penicillin (such as " Bicillin All-Purpose "), the patient should be examined again after a day or two so that diphtheria and glandular fever are not overlooked. The reliability of one injection in eradicating the hæmolytic streptococcus is not yet established and its efficacy should be checked by throat swab.

Treatment with DBED penicillin by mouth has given promising results but is still under trial.

Any one of the tetracycline drugs may be administered if there is any reason for avoiding the use of penicillin.

DIPHTHERIA

The administration of antitoxin is still the most important single measure in treatment. To prevent complications and to reduce the carrier rate crystalline penicillin should be given in a dosage of 100,000 units 6-hourly for 48 hours, then 12-hourly for 5-days.

Swabs taken for diagnosis after chemotherapy has been instituted are likely to yield negative results and fatality may result if antitoxin is inadvertently withheld (page 79).

Erythromycin is of value in the treatment of diphtheria carriers (23).

ACUTE PNEUMONIA

In 1951, the British Medical Research Council (47) surveyed 267 cases of clinical pneumonia in which special bacteriological investigations were made, and found that penicillin by injection was at least as good as, if not better than, any other drug for empirical therapy. This is borne out by local experience. The commonest cause of failure is probably inadequate dosage.

In the first 24 hours, crystalline penicillin should be given in doses of from 100,000 to 500,000 units 3-hourly according to the age of the patient. If there is a good clinical response, the same dose may then be given 6-hourly for a few days, then 500,000 units 12-hourly. Subsequently, fortified procaine penicillin (200,000 units of crystalline plus 600,000 units of procaine penicillin) is given once daily. The minimum period of treatment is 5 days, but a longer period is usually desirable.

If there is no response to penicillin within 24 hours, one of the tetracycline drugs may be administered in the standard dosage stated in Chapter VI. However, an attempt to isolate the causative organism should be initiated before therapy is changed. The sensitivity of most bacteria causing pneumonia, with the exception of the pneumococcus, is unpredictable. Sputum cultures, while subject to the defects discussed in the Appendix, may indicate the most suitable drug by the time it becomes apparent that the drug chosen has not been effective.

Sulphamezathine is frequently effective in the treatment of pneumococcal pneumonia.

Erythromycin should be considered in the empirical treatment of staphylococcal pneumonia (page 64).

MENINGITIS

Two important questions govern the management of chemotherapy in meningitis. These are the sensitivity of the organism and the capacity of drugs to diffuse adequately into the cerebro-spinal fluid.

Bacteriological diagnosis is of great importance, since the type of organism determines the choice of drug. Organisms may often be identified in smears of cerebro-spinal fluid, but whether they are found or not cultures should be made and sensitivity tests carried out. *Meanwhile chemotherapy is urgent and must not be delayed.*

The passage of the drugs under discussion through the normal meninges is slight and irregular, but in the presence of inflammation diffusion usually occurs provided that the systemic dose is large enough. There are marked individual variations in the concentration attained, which is only a fraction of the concentration in the blood.

Sulphadiazine or *sulphamezathine* administered orally in a large initial dose reaches the lumbar theca within about an hour, and even more rapidly if the intravenous route is used. These drugs must not be injected intrathecally.

Penicillin given intramuscularly in a large dose of 1 million units of crystalline penicillin can be detected in the cerebro-spinal fluid after 2 hours in most patients and almost always reaches a satisfactory concentration within 8 hours. Some authorities have therefore abandoned intrathecal injections. However, since failures in therapy still occur when these are omitted, and since this method provides immediately a high concentration of penicillin in the cerebro-spinal fluid, daily intrathecal injections are recommended at least for the first two or three days of treatment.

Streptomycin injected intramuscularly in a dose of 0·5 gram is more slowly absorbed than penicillin and takes longer to penetrate into the cerebro-spinal fluid in therapeutic concentrations. Daily intrathecal injections are recommended for the first few days in cases where early treatment with streptomycin is deemed desirable. Streptomycin hydrochloride is preferred. Dihydrostreptomycin should not be injected intrathecally because of its toxicity. The use of intrathecal therapy has been abandoned in tuberculous meningitis because satisfactory concentrations of isoniazid are obtained in the cerebro-spinal fluid following oral administration of that drug.

Chloramphenicol administered by the oral route can be detected 3 hours later in the cerebro-spinal fluid. An initial dose of from 1 to 3 grams according to age is recommended so that a high blood level is rapidly attained.

The antibiotics of the tetracycline group are perhaps the least satisfactory of the more common drugs for the treatment of meningitis, although they have been used with success. When given orally the maximum dose absorbed is about 0·5 gram, which gives a relatively low blood concentration. Passage into the cerebro-spinal fluid occurs, but it may require 24 hours or longer before satisfactory concentrations are found there. The newly described member, tetracycline, is said to penetrate more readily than aureomycin and tetramycin.

If treatment with these drugs is necessary, the use of intravenous therapy for the first day or two is advised.

Erythromycin is advised only for resistant staphylococcal infections. When administered orally in the usual dosage of from 1·5 to 2 grams daily, penetration into the cerebro-spinal fluid occurs, but it may take some time before a satisfactory concentration develops. If a suitable preparation is available, intravenous therapy is suggested for the first few days.

Bacitracin and polymyxin are used only in special cases. Since both are toxic drugs, instructions as to dosage should be followed meticulously (pages 26, 27).

Meningococcal Meningitis

Meningococcal meningitis is usually amenable to treatment if diagnosed in time, and responds to maximum doses of sulphonamides alone. Sulphadiazine gives higher concentrations in the cerebro-spinal fluid, but if sulphamezathine is preferred very large doses are required, e.g. 2 grams statim and 1 gram 4-hourly for a child under 3 years. Initial therapy may be given intravenously. Treatment with crystalline penicillin is also advised in a dosage of 1 million units intramuscularly every 2 or 3 hours according to the severity of the infection, together with one intrathecal injection daily of 10,000 units (5,000 units for a child) for the first few days. As the patient improves, the interval between intramuscular doses may be lengthened to 6 hours, and later to 12 hours, but the size of the dose should be maintained. Systemic treatment is continued for at least 4 days after the temperature has subsided and for at least 7 days from the commencement of illness. In the presence of the Waterhouse-Friderichsen syndrome, antibiotic therapy is not sufficient and the treatment of shock is vital.

Pneumococcal Meningitis

Pneumococcal meningitis is difficult to combat owing to the excessive production of pus and fibrinous adhesions. The mortality was formerly 100%; the sulphonamides reduced it but little. Sulphonamides combined with intrathecal penicillin and moderate doses of penicillin intramuscularly produced a large reduction in mortality (39, 51). Later it was shown that penicillin injected intramuscularly or intravenously in large doses would reach the

cerebro-spinal fluid in almost all cases (7) and therapy based on such results gave a further reduction in mortality (18).

However, it appears that the risk of not obtaining an adequate concentration of penicillin in the cerebro-spinal fluid in even a few cases outweighs the disadvantages of intrathecal therapy, and a combination of the two methods is advised.

Pneumococcal meningitis is usually secondary to another lesion such as *otitis media*, pneumonia, sinusitis or fracture of the skull. It is noteworthy that in the best results published by those interested in the question of intrathecal therapy, close attention has been paid to the eradication of the primary infection and the prevention and control of impending relapse or complications (36, 51).

The following treatment is recommended:

Intramuscular injections of 1 million units of crystalline penicillin should be given 2-hourly and *this dosage and interval should be maintained for several days or longer if indicated.* Subsequently the interval may be lengthened. A period of about 20 days of intramuscular injections is recommended to prevent relapse. Intrathecal injections of 10,000 units daily for at least the first 3 days are advised.

Sulphadiazine or sulphamezathine may be given in addition to penicillin, but should not be used alone as some strains of pneumococci are resistant.

Penicillin combined with aureomycin is *not* advised.

Hæmophilus Influenzæ Meningitis

Strains of *Hæmophilus influenzæ* may vary in their sensitivity to different drugs such as sulphadiazine, streptomycin, chloramphenicol, the tetracycline group and penicillin, but treatment must usually be commenced before this is known. Most strains are sensitive to chloramphenicol, and this drug should always be included if it is available. A useful ancillary form of treatment is antibacterial rabbit serum. It is impossible at the early stage of this infection to be certain how severe the illness will be, and it is advised that all useful forms of treatment be used at the outset. If sensitivity tests indicate the desirability of changing the drugs used, this should be done at once.

The following combined treatment is suggested:

(1) Streptomycin by intramuscular injection: for a child 100 milligrams 3-hourly for 24 hours, then 250 milligrams 6-hourly for 24 hours, then 12-hourly for from 10 to 12 days. Adults may have 2 grams daily in 3- or 6-hourly doses. Streptomycin intrathecally: 25 to 50 milligrams daily for from 3 to 5 days.

(2) Antibacterial rabbit serum intramuscularly or by continuous intravenous drip in 5% glucose solution in a dose of from 30 to 120 millilitres.

(3) Chloramphenicol orally at the rate of 100 milligrams per kilogram for an adult, or up to 200 milligrams per kilogram for an infant.

The minimum period of treatment is 10 days. The dosage may usually be reduced by one-third after 5 days.

If chloramphenicol is not available, sulphadiazine or sulphamezathine should be used instead in maximum dosage.

It is considered that the use of the tetracyclines in combination with streptomycin should be avoided in the treatment of meningitis on account of possible antagonism (page 31). If it is necessary to use the tetracyclines, intravenous therapy is suggested at least for the first two doses, e.g. 100 to 500 milligrams intravenously followed 12 hours later by the same dose, followed in 6 hours by an oral dose at the rate of about 40 milligrams per kilogram, which is repeated at 6-hourly intervals.

Various combinations of drugs such as chloramphenicol and sulphadiazine (2) are advocated in the literature, but in our experience the combination of streptomycin with antibacterial serum and chloramphenicol gives good results, with a low incidence of subdural effusion and residual cerebral damage.

Meningitis due to Coliform Bacilli

Meningitis due to *Bacterium coli* or related organisms is the commonest form of meningitis in infants under the age of 6 weeks. It occurs occasionally in older children and in adults. Treatment is the same as for *Hæmophilus influenzæ* meningitis with the omission of antibacterial serum.

Sensitivity tests are extremely important and should be carried out without delay. Tests with polymyxin B should be included.

Other Forms of Purulent Meningitis

Occasionally infection occurs with *Streptococcus pyogenes*, *Staphylococcus aureus*, or various Gram-negative bacilli such as *Proteus*, *Salmonella* or *Pseudomonas* species. Direct smears may give guidance to therapy. If a streptococcus is seen, penicillin and sulphonamides should be given, but if a Gram-negative bacillus is present a combination of streptomycin, chloramphenicol and sulphamezathine is suggested while awaiting the laboratory report on the identity and sensitivity of the infecting organism. Staphylococcal infections are discussed on page 63.

If there is no immediate clue from the examination of smears as to the identity of the organism, and *purulent* meningitis is suspected, immediate combined therapy with crystalline penicillin, streptomycin and sulphamezathine is recommended. If *tuberculous* meningitis is a possibility, but unproven, the streptomycin, but not the other two drugs, may be withheld for 24 hours, when the results of investigations may be assessed and a decision made regarding diagnosis and the most suitable chemotherapy.

No drug should be injected intrathecally without careful consideration. A *faintly* turbid cerebro-spinal fluid does not necessarily mean purulent meningitis (page 76), and intrathecal therapy should not be commenced until information is received regarding the cytology, biochemistry and the result of the examination of smears. However, if the fluid is *frankly purulent* penicillin may be injected intrathecally at once.

Intramuscular therapy may be commenced immediately the fluid has been obtained if urgency is indicated.

Tuberculous Meningitis

The treatment recommended is the concurrent use of streptomycin intramuscularly and P.A.S. and isoniazid by mouth in the dosage stated on pages 57, 58. Intrathecal injections of streptomycin are not necessary and are not advised.

Tuberculous meningitis sometimes provides a problem in bacteriological diagnosis (page 76). Every effort should be made to establish a diagnosis rapidly because of the benefits of early specific therapy. However, if tubercle bacilli cannot be demonstrated in smears of cerebro-spinal fluid and there is evidence of the possibility of tuberculous meningitis, chemotherapy for tuberculosis should not be unduly delayed. The subsequent course of the disease and the bacteriological findings will usually confirm or refute the clinical diagnosis.

If there is any suspicion that the meningitis is early pyogenic rather than lymphocytic in type, penicillin and sulphamezathine in adequate dosage should be administered immediately as a precaution.

WHOOPING COUGH

Although *Hæmophilus pertussis* is sensitive *in vitro* to a number of antibiotics, including erythromycin, there is as yet no chemotherapeutic cure for whooping cough. Careful nursing is still the most important feature in treatment. However, chemotherapy lessens the danger of complications. The antibiotic of choice is terramycin in a dose of 4.0 milligrams per kilogram of body weight. The palatable form is best to administer if it is available.

Treatment is usually continued for from 7 to 10 days, or longer if indicated by the chest signs. If excoriation of the mouth or buttocks occurs, therapy should be stopped.

CONJUNCTIVITIS

The pathogens most commonly isolated in conjunctivitis are *Staphylococcus aureus*, the pneumococcus and *Hæmophilus influenzæ*. Sulphacetamide ointment may be used empirically after cultures have been made. Failure of therapy reflects resistance of the infecting strain to sulphacetamide, which is not uncommon. In this event treatment with an ointment containing one of the broad spectrum antibiotics is usually effective. Bacitracin ointment is useful in staphylococcal infections.

The use of penicillin drops (5,000 units per millilitre) is sometimes advocated. Since the penicillin is rapidly diluted, it should be applied every few minutes for the first hour and every hour for the next eight hours.

SINUSITIS

Many cases clear without treatment other than nasal hygiene and inhalations.

A great variety of organisms may cause this infection, and the selection of the correct antibiotic depends on their sensitivity. It is helpful to make cultures from the purulent discharge before commencing chemotherapy.

In acute cases, systemic therapy with penicillin either alone or combined with streptomycin and sulphamezathine is often successful.

If there is no clinical response a broad spectrum drug may be used, the choice being guided by the bacteriology when this is known.

In subacute and chronic cases systemic or local chemotherapy can be used, but drainage may be necessary.

OTITIS MEDIA

The commonest organism concerned is probably *Streptococcus pyogenes*, but the pneumococcus, *Staphylococcus aureus* and *Hæmophilus influenzæ* are also important. If there is a purulent discharge a swab should be taken and cultures and sensitivity tests performed.

Most early cases respond well to penicillin therapy in similar dosage to that used for acute tonsillitis. Paracentesis may be necessary.

ULCERS OF THE MOUTH

Ulceration of the oral cavity is not necessarily the result of infection, and it is a mistake to treat this condition empirically with antibiotics.

Syphilis should always be considered because of its great importance, although it is now uncommon. When suggested clinically it is most important to confirm the diagnosis by dark-ground examination or Wassermann test first, and then to treat the patient adequately with penicillin injections (page 55).

Severe infections of the mouth caused by *Vincent's organisms* should be treated with injections of crystalline penicillin given 6-hourly. Less severe infections usually respond to local applications of hydrogen peroxide or may be treated with daily injections of about 600,000 units of procaine penicillin. Ulcers of the gums should be treated thoroughly with applications of chromic acid and hydrogen peroxide. When the acute condition has subsided attention to oral hygiene with the removal of foci due to pockets and overhanging fillings is essential if the infection is to be eradicated.

Topical therapy with antibiotics in the form of lozenges or troches has been used successfully in the treatment of acute Vincent's infection, but is not advised because sensitization may occur associated with stomatitis which is slow to resolve.

The presence of occasional spirochætes or fusiform bacilli in smears from the mouth is not evidence of infection.

In *thrush* or *moniliasis* there is no specific chemotherapy, but lesions usually respond to applications of gentian violet. *Monilia albicans* is sometimes associated with the ulceration and stomatitis which occasionally occur during systemic therapy with antibiotics, and it is then uncertain whether the ulcers are primarily due to a sensitivity reaction or to a monilial infection. Withdrawal of the drug concerned is the most important measure. The presence of a few monilia in the absence of lesions is not evidence of infection.

With the exception of thrush, *herpes simplex* stomatitis is the most frequently occurring infection in infants and children. It commences as clusters of vesicles which may break down to form white ulcers on the tongue or gums, spreading to the lips, and is associated with fever and irritability. The course of infection lasts for from 7 to 10 days. There is a tendency for these ulcers to recur

under stimulus of fever or infection. Antibiotics are of no value. Palliative treatment is the use of gentian violet locally and occasionally of trochets containing benzocaine.

In non-specific ulcers of the mouth bacteria, usually Gram-positive cocci, can always be demonstrated, but their causal relationship is doubtful. Antibiotics appear to be useless. The ulcers may disappear spontaneously or following improved nutrition. Iodoglycerol (Mandl's paint) applied after removing saliva and mucus with cottonwool is sometimes effective treatment. Occasionally the ulcers are intractable.

INFECTED WOUNDS AND ULCERS OF THE SKIN

The primary approach to the management of infected wounds is that of applying surgical principles, for example, removal of foreign bodies and dead tissue, provision of effective drainage, promotion of adequate blood supply, reduction of œdema, adequate lavage, correction of anæmia and hypoproteinæmia, prevention of reinfection, etc.; antibiotic therapy is ancillary to these and is usually not required.

However, there are a few instances where chemotherapy is more important—either

(1) because the infection endangers life:

(*a*) in consequence of the pathogenicity of the organism, or

(*b*) in consequence of the site rather than the nature of the lesion

or (2) because the infection is rapidly progressing.

These are chiefly instances where rapid arrest or control of the infection is desirable; other measures may be applicable if time is gained by the use of antibiotics. In many of these conditions where empirical therapy is needed penicillin is clearly indicated.

In general, temporary sterilization by antibiotics of a wound which, for reasons not bacteriological, does not heal at a normal rate, is of little avail since it is usually followed by invasion of the lesion by bacteria resistant to the antibiotic.

For this reason, if for no other, chemotherapy should be co-ordinated with surgical measures and used at the time when it will be most effective.

Choice of an antibiotic is guided by the bacteriology of the lesion. Frequently several species of bacteria are present and their relative importance may not be clear. In such cases it is preferable to take action against species known to be more pathogenic, such as *Streptococcus pyogenes* and *Staphylococcus aureus*, rather than to use multiple antibiotics.

Bacillus anthracis and the clostridia causing gas gangrene are sensitive to penicillin. Cellulitis is usually caused by *Streptococcus pyogenes* which is sensitive to penicillin, or occasionally by *Staphylococcus aureus* of unpredictable sensitivity.

In post-operative spreading gangrene of the skin the causative organisms are usually *Streptococcus pyogenes* in combination with *Staphylococcus aureus* or one of these species in combination with *Proteus vulgaris* or *Pseudomonas pyocyanea*. Anaerobic or micro-aerophilic streptococci may also be concerned in this and related conditions.

Staphylococcus aureus is the most frequent cause of post-operative and probably of all wound infections (page 63). Coliform bacilli, *Proteus vulgaris* and *Pseudomonas pyocyanea* (page 66) are frequently found and other species may occur. Treatment is in accordance with the results of sensitivity testing. These bacteria are sensitive only to a restricted and variable range of antibiotics, and empirical treatment is without beneficial effect in many cases.

In most wound infections where chemotherapy is necessary or desirable, systemic administration is required. However, in superficial infections, and particularly in the treatment of ulcers of the leg where, despite remedial measures, the blood supply remains poor, topical applications may be advantageous. Simple measures such as swabbing with ether in superficial infections due to Gram-negative bacilli (particularly *Proteus*), and the application of 1% acetic acid in infections caused by *Pseudomonas* are sometimes overlooked.

Tetanus and gas gangrene require the administration of antitoxin as well as penicillin.

TYPHOID FEVER

By J. A. Forbes

Chloramphenicol is at present the drug of choice in typhoid fever. Following adequate dosage in the early stages of the disease, the patient usually becomes afebrile within 3 or 4 days, the blood stream is cleared of organisms and complications are minimized, although ulceration and perforation of the bowel occasionally occur. When the infection is diagnosed late, the clinical benefit of chloramphenicol is much less striking.

Relapses occur in a small proportion of cases usually from 4 to 10 days after the cessation of treatment, but as a rule they respond to a second course of chloramphenicol. The incidence of relapse is related to the duration of the period of therapy and the following regimen is recommended. Chloramphenicol is administered orally at the rate of 50 milligrams per kilogram of body weight daily, in divided doses at 6- or 8-hourly intervals. The initial period of treatment is 2 weeks. This is followed by a rest period of 5 days, and a further 10-day course of treatment. The use of chloramphenicol palmitate is not advised because it does not provide an adequate blood concentration of chloramphenicol.

In patients with typhoid fever the stools are not cleared of organisms as rapidly as the blood stream, and in healthy carriers the excretion of the organism is not affected by large doses of chloramphenicol.

Chloramphenicol has been preferred in treatment to aureomycin and terramycin because most strains of *Salmonella typhi* are more sensitive to it *in vitro* and because it causes less gastro-intestinal disturbance. However, we have seen a few strains which were equally sensitive to all three drugs, and both aureomycin and terramycin administered intravenously have been used successfully in therapy.

The therapy of typhoid fever was recently reviewed by Woodward and his co-workers (61).

GASTROENTERITIS AND BACILLARY DYSENTERY

Although the most important lines of therapy are fluid replacement and rest for the bowel by diet restriction, chemotherapy has its place.

Many infections abate rapidly whether treated or not. In those which persist specimens of fæces or rectal swabs should be taken whenever practicable and despatched to a laboratory without delay.

In the acute stage of illness while awaiting the bacteriological report, treatment with one of the sulphonamides is recommended. Sulphaguanidine is preferred because it produces a high concentration in the lumen of the bowel and is absorbed to some extent into the tissues. Alternatively sulphamezathine which is readily absorbed may be used, or either phthalyl sulphathiazole or succinyl sulphathiazole, both of which are only slightly absorbed. Success depends on the sensitivity of the infecting organism and the nature and extent of the lesion, which may be confined to the mucosa or not.

Suitable dosage schedules for adults are :

Sulphamezathine :	4 grams statim and 1 gram 4-hourly.
Sulphaguanidine :	6 grams statim and 3 grams 4-hourly (a palatable form is available).
Succinyl sulphathiazole :	7 grams statim and 3·5 grams 4-hourly.
Phthalyl sulphathiazole :	3 grams daily in 6-hourly doses.

Children may receive one-quarter to one-half of these doses.

Treatment should be continued for a few days after diarrhœa has ceased.

Frequently *no pathogens are discoverable* and the patient recovers rapidly. If, however, there is no clinical response to treatment with the sulphonamides within 48 hours, one of the broad spectrum antibiotics may be tried in standard dosage although their value is doubtful.

In *proven Shigella flexneri infections* treatment with sulphonamides may be continued if there is good clinical response. If not, one of the broad spectrum drugs may be given in accordance with results of sensitivity tests, if these are available. All of these drugs have been shown to be effective. During the war, infections with *Shigella flexneri* were amenable to treatment with sulphonamides, but now resistant strains are sometimes found.

Most infections with *Shigella sonnei* are mild. Severe cases do not respond to sulphonamides which are also ineffective in clearing the carrier state. Treatment with streptomycin by mouth is often successful and has no side-effects because it is not absorbed. Neomycin administered by mouth may be effective if streptomycin-resistant strains are present. The broad spectrum antibiotics may be used if desired.

Gastroenteritis caused by *Salmonella* species is still a chemotherapeutic problem. Most patients recover spontaneously but severe and even fatal infections occur. Antibiotics do not produce a dramatic improvement in severe infections and there is difference of opinion as to whether they should be prescribed. The tetracycline drugs may have an undesirable effect in that they may themselves induce diarrhœa. The administration of fluids and biochemical and especially electrolyte control appear to be the most important measures.

A new antibiotic, synnematin B, has been shown to be more effective than other antibiotics in the treatment of mice and chicks infected with *Salmonella* species (44). Clinical trials have not yet been reported.

If severe enteritis develops in a patient receiving treatment with antibiotics for any infection (particularly with the tetracycline drugs), the possibility of a secondary infection with *Staphylococcus aureus* should be considered (59). The organism, which is present in the fæces (page 81), is certain to be resistant to the drug in use. If sensitivity tests are not available erythromycin should be tried.

AMŒBIASIS

By J. E. Clarke

The course of amœbiasis may be altered in two ways : (1) by drugs such as emetine and carbasone exerting a direct amœbicidal action, and (2) by drugs which, by their action on the organisms in the bowel, alter the intestinal flora making it unfavourable for the survival of amœbæ. Chloroquin, another amœbicide, is concentrated in the liver and is effective in amœbic hepatitis, but less effective against amœbæ in the colon.

The perfect amœbicidal drug has not yet been found ; and it remains true that whatever treatment schedule is adopted there will be relapses, sometimes years later. Adequate follow-up is therefore essential.

Penicillin was the first antibiotic used by Hargreaves in 1945 as an adjunct to other forms of treatment. It was suggested that penicillin, by dealing with certain secondary infectors, prepared the way for a successful attack by amœbicidal drugs, otherwise ineffective.

Various antibiotics have been investigated for their amœbicidal activity, and it seems clear that those of the tetracycline group are actually amœbicidal as distinct from their effect in changing the intestinal flora. Aureomycin and terramycin may therefore have some place in the treatment of amœbiasis, particularly in clearing the gut of amœbæ or cysts. However, they seem quite ineffective in the treatment of systemic amœbiasis, e.g. hepatitis.

In the present state of our knowledge the following schedules are advised :

(*a*) *Intestinal amœbiasis with symptoms.* Emetine hydrochloride, 1 grain daily, subcutaneously for from 8 to 10 days, followed by carbasone, 0·25 gram, by mouth twice daily for 10 days. To eradicate the infection from the bowel there is a choice of a wide range of drugs ; probably the best is still emetine bismuth iodide, 3 grains, by mouth, sometimes combined (although these seem unnecessary) with quinoxyl retention enemata, daily. Aureomycin or terramycin may

be used 0·5 gram four times daily for 10 days, or one of the quinoline compounds, such as diiodoquin, 0·6 gram, three times daily for 10 days.

(*b*) *Intestinal amœbiasis without symptoms* ("cyst passers"). Emetine hydrochloride, 1 grain, daily for from 3 to 4 days, followed by emetine bismuth iodide by mouth for 10 days, and other drugs as detailed in (*a*).

(*c*) *Hepatitis.* Emetine hydrochloride, 1 grain, daily for from 10 to 12 days; this can be preceded by, or combined with, chloroquin phosphate, 0·5 gram (0·3 gram of base) twice daily for 2 days, then 0·5 gram daily for 12 days. This treatment must be followed by the use of drugs as outlined in (*a*) to eradicate the infection from the bowel.

BRUCELLOSIS

Brucellosis continues to be a problem in chemotherapy. Both the acute and chronic forms of the disease are prone to relapse, possibly because the organisms are inaccessible to the antibiotics used.

Aureomycin, terramycin and chloramphenicol have all been used singly with excellent initial response but a very high rate of relapse. When streptomycin is given in addition the relapse rate is considerably reduced, but not abolished (41). Duration of therapy is important and treatment should continue for 2, or preferably 3 weeks.

The following regimen for an adult is recommended:

Streptomycin: 2 grams daily in 6-hourly doses for 2 weeks, combined with terramycin or aureomycin: 3 grams daily in 6-hourly doses for 1 week, followed by 1·5 gram daily for 2 weeks.

After two weeks' rest the course of treatment may be repeated in an attempt to avoid relapse, on this occasion using terramycin or aureomycin alone.

If repeated relapses occur, their clinical manifestations may be prevented by anticipatory treatment with terramycin or aureomycin for three or four days, commencing just prior to the period when relapse is expected.

The effect of treatment of chronic brucellosis when the patient may have vague symptoms and little fever is not as dramatic as in the more acute disease. The above regimen affords relief in a number of patients; in others the gastro-intestinal disturbance so often induced by the tetracycline drugs merely adds to their distress.

PUERPERAL AND ABORTIONAL INFECTIONS

By A. M. Hill

Puerperal Infections

The bacteria responsible for at least 75% of puerperal infections are the anaerobic streptococci, usually in association with Gram-negative anaerobic bacilli (Bacteroides). Most often responsible for the remainder are coliform bacilli, *Staphylococcus aureus*, *Streptococcus fæcalis* and *Streptococcus pyogenes*. Bacteriological investigations are discussed on page 84.

The combination of penicillin and sulphonamide is almost invariably effective against the non-sporing anaerobes and *Streptococcus pyogenes*. It is also often valuable in puerperal infection due to the other bacteria listed, but resistant strains of these occur, and when this is the case the broad spectrum antibiotics are required.

Penicillin

For all severe and moderately severe infections crystalline penicillin should be used, the dose varying from 30,000 units to 100,000 units every 3 hours, according to the nature and severity of the infection. Although many use larger doses, it is exceptional for an obstetric infection to require more than 100,000 units every 3 hours. When the infection is under control, the intervals between doses may be increased (e.g. 100,000 units every 6 hours) and therapy continued at this level until at least 2 days after apparent clinical cure.

The use of depot penicillin should be limited to the treatment of clinically mild infections due to penicillin-sensitive bacteria such as *Streptococcus pyogenes* and the anaerobic cocci, and to treatment which has to be conducted outside hospital. Fortified penicillin containing 600,000 units of procaine penicillin with 200,000 units of crystalline penicillin is recommended, the mixture being given twice daily until infection is controlled, then once daily.

Sulphonamides

A triple sulphonamide is used to minimize the danger of crystalluria and toxic reactions. For moderately severe infections the average dosage is from 2 to 3 grams initially, followed by from 1 to 2 grams every 4 hours until the acute phase has resolved, then 1 gram every 6 hours. For severe infections this dosage will need to be increased by 50% until the acute phase is controlled. Alkalis should be given and the fluid intake raised to ensure a urinary output of at least 2 pints daily.

Tetracyclines and Chloramphenicol

These drugs are employed only when penicillin and sulphonamides have failed to control infection or when bacteriological investigations indicate the need. Terramycin and aureomycin are the compounds most often required, the dosage being from 25 to 30 milligrams per kilogram of body weight daily, or, in general, 500 milligrams every 6 hours. When chloramphenicol is used the dosage is 50 milligrams per kilogram daily. Treatment is continued for at least two days after apparent resolution.

Streptomycin

Owing to the speed with which bacteria become resistant to it, streptomycin has a limited place in the treatment of obstetric infections. At times, however, it has been of value against penicillin-resistant staphylococci or sulphonamide-resistant coliform bacilli. The dosage is 0·5 gram every 6 hours, and if response is not definite within 3 days it is waste of time to continue therapy.

Most mild infections do not require chemotherapy. It should be given, however, if the infection does not resolve reasonably rapidly ; if the patient has a surgical wound (e.g. episiotomy, Cæsarean section) ; or if the bacteria are infectious to others (e.g. *Streptococcus pyogenes*, *Staphylococcus aureus*).

Prophylaxis

Antibacterial agents may be used to prevent infection of mother and baby before delivery. Chief indications are long-standing rupture of the membranes, prolonged labour, infective vaginal discharge, and contemplated surgery. Investigation of the vaginal flora should precede and guide prophylaxis, but if this is not possible a full penicillin and sulphonamide cover should be given. The only reliable and therefore satisfactory form of penicillin for prophylaxis is the crystalline.

Summary

The principles to follow in the treatment of puerperal infection are these :

(1) Restore the patient's blood volume and hæmoglobin level to normal. Blood is a more common immediate requirement than antibiotics, and its early and adequate use will reduce, and at times eliminate, the need for chemotherapy.

(2) When facilities are available, make a bacteriological diagnosis as a basis for therapy. In serious infections, combined penicillin and sulphonamide therapy should begin as soon as vaginal swabs have been taken for smear and cultural examinations, and adjustment of therapy can await the return of the bacteriological findings.

(3) Give a large initial dose of the agent chosen, maintain a high dosage throughout, and continue therapy until at least 2 days after the infection appears controlled.

(4) Do not treat the patient longer than necessary for this increases the danger of secondary infection.

(5) If clinical improvement is not evident within 48 hours, question the value of continued therapy with the same agent and dosage.

(6) The broad spectrum antibiotics should not be used at the same time as bactericidal agents such as penicillin.

(7) Avoid the common dangers of indiscriminate therapy and inadequate dosage. At times these have been responsible for the death of a patient admitted to hospital after treatment outside.

Abortional Infections

The management of abortional infections differs from that of puerperal infections in two main requirements :

(1) The treatment of *Clostridium welchii* infections (bacteriological diagnosis by direct smears, page 86), which, in Melbourne, are the commonest cause of deaths from infected abortion.

(2) The common need for uterine curettage which, particularly in anaerobic infections, should be performed as soon as is compatible with safety.

The treatment of severe *Clostridium welchii* infections involves the immediate application of a number of measures : administration of antitoxin, chemotherapy, treatment of shock, uterine curettage, replacement of blood loss and management of renal failure. Chemotherapy consists of 100,000 units of penicillin every 3 hours, together with moderate doses of sulphonamides when indicated. Penicillin is unreservedly the antibiotic of choice. Without the early and adequate use of antitoxin, however, the gravest cases will die.

It must be remembered that although immediate uterine curettage is usually desirable in infected abortion it should not be attempted until the patient has recovered sufficiently from shock, and restoration of blood loss and chemotherapy have begun.

Gonorrhœa

Penicillin is the drug preferred. One intramuscular injection of 600,000 units of procaine penicillin with 100,000 units of the crystalline salt added will effect a cure in a number of cases, but daily injections for five days are advised to prevent relapse.

One injection of DBED penicillin to which has been added procaine and crystalline penicillin has also proved effective.

It is important to consider before starting treatment for gonorrhœa whether the patient may be suffering from syphilis, which requires a much more prolonged treatment.

Syphilis

Penicillin has produced excellent results in the treatment of syphilis. Modifications in treatment are required for the different forms of the disease, and results vary according to the chronicity. Syphilis is the chief condition where procaine penicillin in oil with 2% aluminium monostearate added is used. The dosage of this preparation is :

(*a*) Early syphilis : 2,400,000 units in one injection or in equally divided doses in each buttock, followed four days later by 600,000 units. This dose is repeated at four-day intervals for four injections.

(*b*) Late and latent syphilis : 600,000 units twice weekly for 5 weeks.

(*c*) Neuro-syphilis : 600,000 units twice weekly for 10 weeks.

(*d*) Congenital syphilis : 150,000 to 300,000 units twice weekly for 6 weeks.

After from 6 to 8 weeks' rest, serological tests are done and the course of penicillin repeated if necessary.

Serological tests should be carried out monthly for the first year, quarterly for the second year, and then annually. In all forms of chronic syphilis the cerebro-spinal fluid should be examined before a cure is claimed.

If a relapse occurs, or if the two courses of treatment fail to achieve a satisfactory serological response, the older methods of treatment may be combined with a course of penicillin injections. In such cases the use of large doses of crystalline penicillin is suggested. The failure rate in therapy is about 10%.

It is likely that the oily preparation of penicillin will be replaced by either DBED penicillin, 600,000 units, or a mixture of DBED penicillin, 600,000 units, with procaine penicillin, 300,000 units, and crystalline penicillin, 300,000 units. This dose will be given in one injection at weekly intervals. However, in a disease such as syphilis it requires several years before the efficacy of a new form of therapy can be assessed.

In patients treated with any form of penicillin a Herxheimer reaction may occur. This is usually shown by a rise in temperature and an exacerbation of joint pains and skin lesions which rapidly subside. However, in cardio-vascular syphilis a Herxheimer reaction may be fatal and some authorities prescribe a preliminary course of bismuth and iodides before penicillin is given. Serious reactions can also occur in late neurosyphilis.

Aureomycin and terramycin have been used with success in the treatment of syphilis, but are not as reliable as penicillin. Large doses of at least 2 grams, or preferably 3 grams, daily have been recommended.

TUBERCULOSIS

By D. B. Rosenthal

The manifestations of tuberculosis are so various that the details of the management of individual cases, including the duration of treatment, may require the advice of a specialist, and surgical intervention may be necessary.

In the field of chemotherapy, rapid changes in the choice and administration of drugs have occurred, and further developments are to be expected as experience accumulates and new drugs become available.

At the time of writing, the drugs most important in chemotherapy are, in order of preference: streptomycin, isonicotinic acid hydrazide (I.N.A.H., isoniazid) and para-amino-salicylic acid (P.A.S.).

It is generally held that one drug should *not* be used alone but that two or even three drugs should be given concurrently to prevent or delay the emergence of resistant bacilli and to obtain a better therapeutic effect. This view is supported by clinical and bacteriological evidence that if streptomycin is used alone bacterial resistance develops rapidly and the therapeutic value of the drug is probably lost. If it is combined with either P.A.S. or isoniazid or with both, the emergence of resistant organisms is delayed.

Recent work (17) suggests that in certain patients isoniazid may be used alone for a long period of up to 12 months. Organisms resistant to this drug may emerge, but this is less serious than is the case with streptomycin. Some (but not all) isoniazid-resistant bacilli are of lower virulence for guinea-pigs, and therefore presumably for man than are sensitive bacilli. It is further suggested by the same workers that when isoniazid is used alone, particularly in the early stages of therapy, the combination of streptomycin and P.A.S. or other drugs is then available for patients in whom clinical response proves unsatisfactory. But it is not established that treatment with isoniazid alone is superior to treatment with isoniazid in combination.

Until the situation is clarified it is recommended that:

(1) In general, one drug should *not* be used alone.

(2) A long period of therapy is essential and should be continued *well beyond the time when the disease appears on clinical and radiological grounds to have been arrested.*

(3) There should be no interruption in the administration of drugs.

The simultaneous use of streptomycin, isoniazid and P.A.S. is recommended in the acute disease, such as miliary or meningeal tuberculosis, or acute forms of pulmonary tuberculosis.

In the subacute and chronic forms of the disease, streptomycin and P.A.S. may be alternated with streptomycin and isoniazid. The combination of P.A.S. and isoniazid is convenient for administration to ambulatory patients.

Isoniazid appears able to penetrate tissues more fully than does streptomycin, and it is excreted in the urine. It enters the cerebrospinal fluid and is therefore useful in tuberculous meningitis.

In this last condition the treatment of choice is the use of streptomycin intramuscularly, together with P.A.S. and isoniazid by mouth. If oral administration is impracticable, P.A.S. may be given intravenously and isoniazid by rectal injections. It is neither desirable nor necessary to administer streptomycin by the intrathecal method.

In primary tuberculosis, evidence of infection may be shown early by the conversion of the tuberculin reaction, with or without demonstrable pulmonary lesions of a "primary complex" type. Any combination of the drugs listed above may be used in the treatment of this condition, but the use of isoniazid alone for a period of from 3 to 12 months has been advised by several authorities, including Walgren of Sweden, and Lincoln, Waring and Middlebrook of the United States of America.

Administration, Dosage and Toxic Effects

(1) **Streptomycin**

Dosage

(*a*) For all forms of tuberculosis (including renal tuberculosis) other than the acute generalized or meningeal disease, 1 gram in a single dose intramuscularly on alternate days, or twice weekly if long continued.

(*b*) For the acute generalized or meningeal disease 1 gram intramuscularly once or twice daily.

Toxic Effects

(1) Disturbance of vestibular function, usually compensated.

(2) Deafness.

(3) Skin rashes.

Toxic effects are rare in the dosage advised.

The advantages of a mixture of streptomycin and dihydrostreptomycin in reducing toxicity (page 19) must be weighed against the possible advantage of reserving dihydrostreptomycin for use in streptomycin-sensitive patients (30).

(2) Para-amino-salicylic Acid

P.A.S. may be given orally as the sodium salt in solution, or as the acid or as the salt of sodium or calcium, in tablets or granules. Preparations are also available for intravenous and intrapleural therapy, but their use is rarely advised.

Dosage

12 grams of the acid or 16 grams of one of the salts administered after meals. The drug should not be given on an " empty stomach ".

Toxic Effects

Nausea, vomiting, diarrhœa, and occasionally fever and skin rashes. The latter are usually mild, but exfoliative dermatitis may occur.

(3) Isonicotinic Acid Hydrazide

Many forms are available from manufacturing chemists. All appear to be equivalent and are termed collectively " I.N.A.H. " or isoniazid. They are usually given orally in tablets of 50 milligrams, but preparations are available for intrapleural and other parenteral administration.

Dosage

The commencing dosage is from 2 to 4 milligrams per kilogram of body weight, which may be rapidly increased to from 8 to 16 milligrams if no untoward effects are observed. A useful rule as commencing dosage is 200 milligrams daily if the patient's weight is below 10 stone and 300 milligrams daily if it is above 10 stone. The drug is administered as 2 tablets after meals night and morning or 2 tablets after meals three times daily.

Toxic effects are not commonly observed, but the following reactions may occur :

Vertigo, twitching of the lower limbs, increase in reflexes, retention of urine, dryness of the mouth, asthma (rare), drowsiness (rare). " Peripheral neuritis " may develop in the later stages of therapy, but is usually not severe nor of long duration. The relation to a possible vitamin B2 deficiency is undecided but the administration of pyridoxine (vitamin B6) is advised.

(4) Other Drugs

The following drugs are less commonly used, but are available when standard forms of chemotherapy are unsatisfactory.

(1) *Viomycin* (page 29). The dosage is 1 gram night and morning every third day, administered by intramuscular injection. Isoniazid or P.A.S. should be given concurrently.

(2) *Pyrazinamide*, a derivative of nicotinic acid. The dosage is 1 gram, three times a day, by mouth. Hepatitis and liver failure may occur.

The drug is used in combination with isoniazid.

(3) *Terramycin* (page 21). The dosage is 4 grams daily by mouth and the drug is given in combination with isoniazid.

Duration of Chemotherapy

The administration of drugs used in the treatment of tuberculosis should be continued, without remission, depending on the clinical condition. The period should be not less than twelve months for meningitis. The limitation of usefulness of drugs may be indicated by the loss of bacterial sensitivity to the individual drug. If organisms are not available for testing, and toxic effects are not observed in the patient, drug treatment may be continued for a variable time of a minimum of six months to a reasonable optimum period of two years.

Tuberculosis in Infants and Children

The general principles presented above apply equally well for children.

In the early stages of treatment of acute miliary or meningeal tuberculosis and tuberculosis of bones and joints, the dose of streptomycin for infants is 250 milligrams once daily, and for a child from 3 to 6 years, 0·5 gram.

The dosage of P.A.S. for a child is from 3 to 5 grams daily, and of isoniazid (as for an adult) from 2 to 4 milligrams per kilogram of body weight, which may be increased rapidly to from 8 to 16 milligrams in the absence of toxic effects.

Cortisone in Tuberculosis

Cortisone is considered undesirable in the therapy of tuberculosis because of its action in suppressing the normal inflammatory response to infection. However, in certain conditions when the patient can be placed under close observation the administration of cortisone may be valuable, e.g.

(1) In acute and persistent severe tuberculous infections, such as pleurisy with effusion, pericarditis, meningitis, when the response to conventional therapy is unsatisfactory (31). Chemotherapy must be continued during the exhibition of cortisone (page 71).

(2) In the treatment of hypersensitivity reactions to streptomycin or P.A.S. In patients with severe reactions, cortisone may be needed to save life. Large doses are usually necessary, but only for a limited period. In such cases, the antituberculous drugs should be stopped. Minor reactions may be offset by the temporary or intermittent use of adrenal steroids without discontinuing the exhibition of the drug (31).

(3) In any tuberculous patient for whom cortisone may be indicated to save life or sight in diseases which are amenable to therapy with adrenal steroids, e.g. pemphigus, *polyarteritis nodosa*, iridocyclitis, or when warranted in acute or chronic non-tuberculous arthritic disease by the severity or progression of the condition. The concurrent administration of the standard anti-tuberculous drugs is essential.

LEPROSY

By J. A. Forbes

No specific cure for leprosy has yet been found, and the assessment of drugs is hampered by inability to cultivate Hansen's bacillus.

Chaulmoogra and hydnocarpus oils, the traditional remedies, are still used in some places, usually administered by intramuscular or local injection in conjunction with more modern drugs, but they are generally considered to be of little specific value in treatment.

Various modern drugs which inhibit the growth of *Mycobacterium tuberculosis in vitro* are being used in the treatment of leprosy; of these, the sulphones and thiocetazone (syn. thiosemicarbazone) appear to have the most favourable effect.

Administration, Dosage and Toxic Effects

(1) Sulphones

The various forms of diaminodiphenyl sulphone appear to provide the most effective treatment for leprosy at present.

Remissions, particularly in cases of lepromatous leprosy, appear to be more common with sulphone administration, but recrudescence occurs frequently at varying intervals of time.

Dosage

The dosage varies according to the type of sulphone.

(*a*) *Solapsone* may be given orally in tablets or by subcutaneous or intramuscular injection. The initial dose is usually about 1·5 gram a day, gradually increasing to a maximum dosage of 5 grams a day.

(*b*) *Dapsone* may be administered orally or by intramuscular or subcutaneous injection. The initial dose is usually 100 milligrams twice weekly and may be increased cautiously to 300 milligrams daily.

(*c*) *Promin* may be given orally or intravenously. It is rather more toxic than the former two types and small initial doses may be necessary, gradually increasing to an optimum dose of 5 grams a day. Signs of toxicity may prevent the dose from being increased beyond 2 grams.

Toxic effects are gastro-intestinal upsets, anæmia; at times, acute hæmolytic anæmia. These drugs at times appear to provoke exacerbations of the disease, dermatitis, lepra reactions, leprous neuritis and iritis, most of which clear up with the temporary withdrawal of the drug.

(2) Thiocetazone

This drug is administered orally in tablet form.

Dosage

Initially 25 to 50 milligrams daily, gradually increased to 150 or 200 milligrams daily.

Toxic Effects

Liver damage and depression of bone marrow may occur; mild toxic effects are gastro-intestinal disturbances, conjunctivitis and skin rashes.

Isoniazid is commonly used in similar dosage as for tuberculosis, in conjunction with the sulphones.

The *duration of treatment* is at least several years with occasional rest periods, and may continue for life.

BACTERIAL ENDOCARDITIS

Unless the patient is dangerously ill it is most important to obtain a positive blood culture. This is usually easy in the acute form of the disease, but in subacute bacterial endocarditis it may be necessary and is desirable to make several attempts at daily or shorter intervals before commencing chemotherapy. A positive blood culture often clinches the diagnosis. Moreover, once empirical therapy is given, blood cultures are likely to be negative, yet the physician is committed to a long course of treatment.

In both the subacute and acute forms of the disease penicillin-sensitive organisms are usually found, but infections with penicillin-resistant cocci, *Hæmophilus influenzæ* and other Gram-negative bacilli occasionally occur, and a knowledge of the identity of the organism and its sensitivity to antibiotics is often invaluable in controlling therapy.

If no organisms are isolated from blood cultures a presumptive diagnosis is sometimes warranted, and penicillin (given always as crystalline penicillin G by injection) is the drug of choice, since in general more than 90% of infections are amenable to treatment provided that adequate dosage is given.

Penicillin Alone

When the infecting organism is sensitive to penicillin, as in subacute bacterial endocarditis caused by *Streptococcus viridans*, the best form of treatment is penicillin alone, although strains vary considerably in their sensitivity to penicillin and in the dosage required.

The duration of treatment is extremely important, and Christie (13) showed that while patients might occasionally respond satisfactorily to a course of ten days' duration, relapse was frequent. Christie recommended a course of 500,000 units of crystalline penicillin daily in 3-hourly doses for 28 days. In 1949 (14), with due regard to the varied resistance of organisms, he recommended a *minimum course of 2 million units a day for a month or 6 weeks*. Larger doses are required if the organism is very resistant or if there is no clinical response. The extent and degree of organization of the lesion varies in different patients, and larger doses may be required to achieve penetration. In our experience injections at 6-hourly intervals are satisfactory.

Treatment with procaine penicillin injected twice daily in combination with benemid to raise the blood concentration of penicillin has been used with success, but the reliability of this regimen is not established and it is not recommended.

Penicillin with Streptomycin

It was first demonstrated by Hunter (32) and has since been confirmed (12) that the administration of penicillin with streptomycin was more effective than penicillin alone in the treatment of

subacute bacterial endocarditis due to *Streptococcus fæcalis*. The two drugs are synergistic and are effective even when the organism is relatively resistant *in vitro* to streptomycin.

The dosage of streptomycin recommended is 2 grams daily in 6-hourly doses, and is given for the whole period of 4 to 6 weeks. A course of streptomycin of 2 grams daily for the first 10 days only has been suggested, but its value remains to be determined. Streptomycin may be mixed with penicillin and injected at the same time.

Streptomycin alone is not recommended because of the rapid emergence of resistant organisms, although occasional successes in therapy have been reported.

Sulphadiazine or aureomycin or terramycin or chloramphenicol alone are reported as having been used with success on occasion in early cases, but relapses are common.

Streptomycin with sulphadiazine or aureomycin or terramycin or chloramphenicol might provide a suitable combination for an infection with a penicillin-resistant organism provided that the organism was sensitive to both the drugs used.

Whatever treatment is selected, present knowledge suggests that a prolonged course is desirable.

INFECTIONS OF THE URINARY TRACT

The organisms most commonly responsible for infections of the urinary tract are Gram-negative bacilli, especially coliform bacilli and species of *Proteus* and *Pseudomonas pyocyanea*. It is well known that the sensitivity of these organisms to antibiotics and sulphonamides is unpredictable, so that treatment guided by sensitivity tests is desirable. This applies also to staphylococcal and streptococcal infections.

Since these drugs are all excreted in the urine in much higher concentrations than are attainable in the blood, it is sometimes held

(*a*) that very sensitive organisms can be eliminated by the use of small doses, and

(*b*) that infections with organisms resistant to blood concentrations yet sensitive to urine concentrations of a drug are amenable to treatment with moderate or large doses.

These views may not be valid. While they may apply in superficial infections such as cystitis, where the inflamed mucous membrane may absorb quantities of the drug (as is established in topical therapy with sulphonamides), it is unlikely that they would hold in lesions which extend more deeply into the tissues. It is therefore probably advisable to choose a drug to which the infecting organism is so sensitive that requisite blood concentrations are readily obtainable.

It is desirable to make microscopical and cultural examinations of urine several days after treatment has ceased to ensure that the infection is cured and not merely suppressed. Successful therapy cannot be expected in the presence of obstruction brought about by stricture, tumour, calculus, prostatomegaly, etc.

The sulphonamides, streptomycin, chloramphenicol, aureomycin and terramycin have all been used separately with success in susceptible infections. The use of streptomycin alone is not recommended owing to the probable emergence of resistant strains, but in combination with sulphonamides or with one of the broad spectrum antibiotics it may eradicate an infection which was only clinically suppressed by the use of one drug alone.

Penicillin is useful in the treatment of staphylococcal and streptococcal infections when the organisms are sensitive, but other drugs, such as aureomycin, often give better results in infections with *Staphylococcus aureus* or *Streptococcus fæcalis*.

The recommended dosage of the different drugs according to the results of sensitivity tests has already been stated.

Sulphonamides are preferred in empirical therapy and when the organisms are shown to be sensitive to a number of drugs including sulphonamides.

The treatment of tuberculous infections of the urinary tract is considered on page 57.

STAPHYLOCOCCAL INFECTIONS

Staphylococcal infections present the major problem in chemotherapy owing firstly to the unpredictable variation in the sensitivity of different strains of staphylococci to antibiotics, and secondly to the fact that even when the organisms are sensitive the infection is not always amenable to treatment. Cultures and sensitivity tests are of great importance.

Some 50% of strains initiating infection outside hospital are sensitive to penicillin as well as to other drugs. In such cases, penicillin is the drug of choice, at least in severe infections such as osteomyelitis and staphylococcal endocarditis, in which it is more effective clinically than the broad spectrum antibiotics. However, the widespread use of penicillin has led to the selection of strains of staphylococci which can resist the action of penicillin. These organisms possess a destructive enzyme, penicillinase, which accounts for their resistance to penicillin. Different strains vary in the amount or rate of penicillinase production. Some may be overcome by massive doses of penicillin; others defy all forms of therapy with this drug.

Most strains initiating infection inside hospitals today and many strains causing infection in out-patients are penicillin-resistant. Some are sensitive to sulphadiazine and to streptomycin, but neither of these drugs is recommended by itself, since sulphonamides are inactivated by pus and are not effective unless drainage is present, and streptomycin-resistant organisms appear rapidly following treatment with that drug. However, their possible value as adjuvants to other drugs or in combination with each other should not be forgotten.

Many of these penicillin-resistant strains are sensitive to one or other of the broad spectrum antibiotics. Provided that an organism is sensitive to them, all these drugs appear to have the same therapeutic value and the same limitations. They are effective in the treatment of boils, staphylococcal septicæmia, acute staphylococcal broncho-

pneumonia and urinary tract infections, but the treatment of osteomyelitis is less satisfactory than in patients who can be treated with penicillin. Moreover, the treatment with the broad spectrum antibiotics of patients with bacterial endocarditis or with such lesions as metastatic abscesses of the lungs usually fails, with clinical and bacteriological relapse as soon as the drug is withdrawn.

Other penicillin-resistant strains are resistant to all of the broad spectrum antibiotics so that therapy with them fails even in minor infections. Severe infections with such strains as in enteritis (page 51), as well as severe infections with strains sensitive to, but not amenable to treatment with the broad spectrum antibiotics, are a cause of anxiety. Erythromycin and bacitracin are both active against *Staphylococcus aureus** and at present most strains are sensitive to both drugs. However, both drugs suffer from disadvantages. Erythromycin is a bacteriostatic drug not effective in bacterial endocarditis, for example, and resistant organisms soon appear. Bacitracin, although bactericidal, is toxic, and its use is limited.

The initial choice between erythromycin and bacitracin depends on the nature and severity of the infection, and erythromycin may often be tried first.

If neither drug is available, recourse is had to massive intravenous therapy with penicillin in an attempt to overcome the production of penicillinase by the organism. Such treatment has proved life-saving on occasions (54).

The use of combinations of drugs such as streptomycin with penicillin or penicillin with bacitracin may also be tried in an attempt to obtain an additive or a synergistic effect.

Recommendations regarding therapy may be summarized as follows :

(1) Minor staphylococcal lesions do not usually require treatment with antibiotics. However, when they are a source of infection to others, as in nurseries, treatment is desirable. If antiseptics fail or are unsuitable, use topical applications of bacitracin.

(2) In more severe infections, make cultures and carry out sensitivity tests even when it is felt that empirical therapy cannot be withheld. The information gained may subsequently prove invaluable if empirical therapy fails.

(3) If sensitivity reactions are known :

(*a*) If the organism is known to be sensitive to penicillin and to other drugs, use penicillin, because it is the most effective and least toxic drug. When the infection is not severe, treatment with the procaine salt in a dosage of about 600,000 units for an adult or 300,000 units for a child administered once daily, should suffice. When the infection is serious, such as septicæmia, osteomyelitis, endocarditis or pneumonia, use *crystalline penicillin*, preferably in large doses of 1 million units 3-hourly. If osteomyelitis is treated early, complete

* *Staphylococcus pyogenes.*

resolution of the local lesion may be obtained without drainage. Treatment is continued for one week after systemic and local signs have subsided. If the necessity for drainage is evident, it should be carried out under cover of chemotherapy. However, in the chronic form of the disease clinical judgment and surgical technique take precedence and chemotherapy cannot follow any preconceived plan.

(*b*) If the organism is resistant to penicillin but sensitive to one or other of the broad spectrum antibiotics, use the appropriate drug in standard doses by the oral route. In infections which endanger life consider intravenous therapy.

(*c*) If the organism is resistant to penicillin and to all the broad spectrum antibiotics but sensitive to erythromycin, give erythromycin by mouth, or intravenously if indicated.

(*d*) If the organism is also resistant *in vitro* to erythromycin *or* if there has been no clinical response to erythromycin *or* if the infection is deep-seated, as in staphylococcal endocarditis, and is unlikely to respond to erythromycin give bacitracin intramuscularly.

(*e*) If the use of erythromycin or bacitracin is indicated and neither is available, try continuous intravenous infusion with penicillin in a dosage of 100 million units per day. In addition, give streptomycin intramuscularly in a dosage of 0·5 gram 6-hourly. If continuous intravenous infusion is impracticable, give 2-hourly intravenous or intramuscular injections of penicillin with as large doses as possible, and give benemid by mouth to raise the concentration in the blood. The administration of antiserum may also be considered.

(4) If the infection is known to be staphylococcal but drug sensitivity reactions are not known, treatment is influenced by considerations which include the severity of the infection, the likelihood of it being controlled by a particular drug and the toxicity of the various drugs.

Of 850 strains of staphylococci tested during the year 1954, 15% were resistant to chloramphenicol, 25% to aureomycin and 28% to terramycin. Higher percentages were resistant to streptomycin, sulphadiazine and penicillin, in that order. Far fewer tests have been done with tetracycline which appears very similar to aureomycin. 8% were resistant to all these drugs.

While other records compiled from different sources may show results more or less similar, it is obvious that a particular strain of staphylococcus may be sensitive to one, several, all or none of the drugs. In view of this fact, empirical treatment is inadvisable. Minor infections should not be treated with antibiotics under these circumstances and infections of moderate severity should be investigated. Since staphylococci are hardy and on serum-treated swabs

will survive transmission through the post, the sensitivity of the strain can be determined and treatment with antibiotics instituted on logical grounds.

(*a*) If circumstances render it desirable to treat incapacitating but not dangerous infections while awaiting sensitivity results, then penicillin is recommended because of its low toxicity and its superior efficiency against strains sensitive to it and other drugs. If penicillin should be found ineffective, sensitivity reactions should by that time be known, but if they are delayed one of the tetracycline drugs would be the next choice.

(*b*) In a minority of cases the prognosis is such that immediate treatment is necessary. The higher toxicity of chloramphenicol is then discounted, and it becomes the drug of choice. However, sensitivity testing should be initiated before it is administered. If the infection is still progressing 48 hours later and if the sensitivity report is not available, then the use of either erythromycin or bacitracin is indicated. If one of these is not immediately obtainable, aureomycin may be tried, since in our experience, about one-third of the strains resistant to chloramphenicol are sensitive to it. See also 3 (*c*, *d*, *e*).

INFECTIONS WITH PROTEUS VULGARIS OR PSEUDOMONAS PYOCYANEA

Infections with the Gram-negative bacilli, *Proteus vulgaris* and *Pseudomonas pyocyanea*, occur most commonly in the urinary tract or in lesions of the skin such as wounds or burns. More serious infections such as septicæmia and meningitis occur occasionally and may be fatal.

The sensitivity of different strains varies considerably, and is therefore unpredictable, so that sensitivity tests are important and should be carried out with sulphadiazine, streptomycin, chloramphenicol, the tetracyline drugs, polymyxin B and sulphamar.

In our experience some 40% of strains of both organisms isolated from routine cultures have proved sensitive to low concentrations of sulphadiazine. Strains resistant to this drug are often sensitive to one or more of the antibiotics in concentrations attainable by systemic therapy. A minority of strains requires the high concentrations which are only obtainable in topical applications. Most strains of both organisms are sensitive to sulphamar, which is very suitable for topical therapy.

Many strains of *Pseudomonas pyocyanea* are sensitive to polymyxin B, but *Proteus vulgaris* is usually resistant. *Proteus* may be sensitive to neomycin, but the toxicity of this drug prohibits its systemic use except as a life-saving measure.

PYREXIA OF UNKNOWN ORIGIN

Investigations and treatment depend on the severity and duration of the infection. In seriously ill patients in whom it is felt chemotherapy cannot be withheld, a total and differential leucocyte count, blood culture, and micro examination and culture of urine should be undertaken first, even if it is not possible to wait for the laboratory reports.

In children who are acutely ill with no detectable cause, lumbar puncture should always be considered, as this is often the only way that an early diagnosis of meningitis can be made.

In subacute cases of persistent pyrexia chemotherapy should be withheld until diagnostic tests have been completed.

Empirical therapy suggested for severely ill patients with pyrexia of unknown origin is a combination of :

Crystalline penicillin G : 500,000 units 3-hourly.

Streptomycin : 0·5 gram 6-hourly.

Sulphamezathine : 6 grams statim and 1·5 gram 4-hourly if given orally ; or 4·5 grams statim and 1·5 gram 6-hourly if given by intravenous or intramuscular routes.

Meanwhile every effort should be made to establish a diaguosis (page 87).

The use of chemotherapy in the minor acute febrile illnesses of unknown origin as seen in private practice depends on clinical judgment. Each case is to be considered on its merits, but penicillin or sulphamezathiue should usually be tried first. It is in the patient's interest to reserve the other drugs if possible, for more severe infections.

LEPTOSPIROSIS

Five types of pathogenic leptospira are known to cause human infections in Australia. These are *Leptospira icterohæmorrhagiæ* (the cause of classical Weil's disease), *Leptospira australis A* and *Leptospira australis B* which are classified as the canefields leptospiroses, and *Leptospira pomona* and *Leptospira mitis*, which are grouped as the mild leptospiroses. These infections have been described in detail by Johnson (34).

The treatment recommended by Cotter (15) for leptospirosis is crystalline penicillin in a dosage of 500,000 units 3-hourly for a period of 3 or 4 days. Patients are usually afebrile within 48 hours and there appear to be no sequelæ, at least when infections are treated early.

Aureomyciu and terramycin have also been used in early treatment. However, there is doubt as to the value of any form of chemotherapy in the later stages of the disease ; mild cases recover without treatment and severe infections may be fatal despite it (55). Further clinical trials are required.

The use of sulphonamides is not advised because of the risk of aggravating renal damage and causing anuria.

RICKETTSIAL DISEASES

Typhus Fever. The typhus fevers known to occur in Australia are scrub typhus (Queensland), murine typhus (Western Australia, Queensland, South Australia, New South Wales, Victoria) and North Queensland tick typhus (Queensland).

All varieties of the disease respond to treatment with the broad spectrum antibiotics, but occasionally treatment with a particular drug fails. This may reflect variation in the sensitivity of different strains of rickettsiæ.

Dosage schedules recommended (15) are as follows :

Chloramphenicol : 3 grams statim followed by 0·25 gram at 3-hourly intervals until a total of 6 grams has been given, or for longer if clinically indicated.

Aureomycin or terramycin : 1·5 gram statim followed by 3 grams daily in divided doses at 3- or 6-hourly intervals, administered until the patient's temperature has been normal for 24 hours. Intravenous therapy with 0·5 gram of either drug at 12-hourly intervals may be given if necessary.

While a short course of any of these drugs is usually adequate, relapse may occur and is thought to be related to insufficient antibody production at the particular stage of the disease. Relapse is prevented if treatment is continued for 5 days after the patient's temperature has returned to normal (50).

Q Fever occurs in Queensland and in South Australia, and laboratory infections have been reported in Victoria. The treatment recommended is the same as for typhus fever, but the response to antibiotics appears to be less clear-cut.

The treatment of other rickettsial diseases is reviewed by Valentine and Shooter (55).

VIRUS DISEASES

Antibiotics do not specifically influence virus infections (trachoma being a notable exception), and their use is confined to the prevention of complications.

Measles. In severe cases of measles it is common practice on the second day of the rash to give sulphamezathine in a dosage of from 1 to 3 grams daily for 5 days ; or if a child is vomiting, fortified procaine penicillin containing 300,000 units of procaine penicillin administered in one injection and repeated daily for 3 days.

Chicken Pox, Mumps and Rubella. Patients receive symptomatic treatment and do not need antibiotic therapy.

In *poliomyelitis*, if respiratory paralysis occurs, pulmonary infection readily ensues and tetracycline is the antibiotic of choice.

In " *virus pneumonia* " and *psittacosis* early reports of the specific value of the broad spectrum antibiotics have not been substantiated.

Trachoma. Good clinical results have been obtained in this disease by treatment with sulphonamides, penicillin, aureomycin, terramycin and chloramphenicol.

The apparent anomaly of a virus being susceptible to this array of drugs is probably related to the fact that the organism differs from typical viruses in other respects.

The treatment advised is that used by Mann (42), which was modified from the World Health Organization's recommendation :

(1) Sulphatriad or sulphadiazine by mouth, for an adult 4 grams statim, 1·5 grams 3 times a day, up to 30 grams.

(2) Aureomycin or terramycin ointment (in a concentration of at least 1%) applied under the upper lid every 4 hours for 6 weeks.

Additional measures (surgery, etc.) may be needed for the cicatricial sequelæ of trachoma.

FUNGOUS DISEASES

Actinomycosis

Penicillin is the drug of choice in actinomycosis, but owing to the fibrotic nature of the lesions and to the presence of colonies of the organisms in the " sulphur granules ", large doses administered over a long period are necessary.

The minimum dosage recommended is 500,000 units of crystalline penicillin intramuscularly at 6-hourly intervals for a period of 4 weeks, and for longer if indicated. Potassium iodide may be given concurrently. If the clinical response is not satisfactory streptomycin in a dosage of 0·5 gram 6-hourly should be combined with penicillin (4).

Patients who are allergic to penicillin may be treated with aureomycin in a dosage of 2 grams daily for a minimum period of 3 weeks.

It is desirable to cultivate the organism and to carry out sensitivity tests if possible.

Nocardiosis

Treatment is the same as that prescribed for actinomycosis.

Torulosis

Actidione is active *in vitro* against *Torula histolytica* but benefit has been claimed in only a small proportion of cases of torulosis (page 30). There is no other specific antibiotic.

Moniliasis

Various antibiotics, fungicidin, candicidin, candidin, ascosin and trichomycin are active *in vitro* against *Monilia albicans*, but their clinical value in relation to their toxicity remains to be determined.

CHAPTER XVII

TOPICAL CHEMOTHERAPY

Topical applications with ointments, creams or solutions have some place in chemotherapy. They are of particular value

(*a*) in situations where the blood supply is poor,

(*b*) in situations where diffusion from the surrounding tissues of drugs administered systemically may be inadequate, as in the eye (22),

(*c*) in cases where the infecting organism is resistant to drug concentrations obtained by systemic administration, but sensitive to higher concentrations, and the lesion is wholly accessible to local applications,

(*d*) in infections confined to the skin and not amenable to treatment with antiseptics.

Sensitization of the patient may occur following the application of any antibiotic to the skin and is not uncommon with sulphonamides, penicillin and streptomycin, particularly in the type of patient who is prone to affections of the skin.

When infections are confined to the skin and sensitive organisms such as staphylococci or coliform bacilli are present, the application of a bland antiseptic such as vioform or monacrin is often sufficient, and sensitization to antibiotics is thus avoided.

Creams containing one or other of the antibiotics and sometimes combinations of them in high concentrations are available commercially and are frequently used empirically. Failure may be expected if the lesion is not the result of bacterial infection or if the organisms happen to be resistant to the drug chosen. Penicillin, bacitracin and tyrothricin are active only against coccal infections; polymyxin only against *Pseudomonas pyocyanea* and occasional strains of coliform bacilli. An infection such as *otitis externa* caused by *Pseudomonas pyocyanea* may even be stimulated by treatment with penicillin. The broad spectrum antibiotics have a wide range of activity against both cocci and bacilli but strains vary in sensitivity, and such organisms as *Proteus vulgaris* and *Pseudomonas pyocyanea* are usually resistant. Neomycin appears to be of particular value owing to its bactericidal properties, its wide range of activity and the fact that it can rarely be used systemically. The use of streptomycin alone is not as a rule advocated owing to the rapid emergence of resistant strains.

If it is desired to use solutions rather than creams, these may be prepared in the following concentrations:

Penicillin: 5,000 units per millilitre in 0·5% sodium citrate solution.

Streptomycin: 2% in 0·5% sodium citrate solution.

Sulphamar: 5% (available commercially).

Chloramphenicol: 10% in propylene glycol is available commercially. It may be prepared from capsules of the drug, but these contain lactose powder which does not dissolve (16).

The application of solutions of the tetracycline drugs to the skin is not advised because of their irritant properties.

The use of lozenges prepared from antibiotics for the treatment of infections of the mouth and throat is not advised. It is not a reliable method of therapy, and sensitization readily occurs.

In the treatment of conjunctivitis, however, the value of topical applications of sulphacetamide and of various antibiotics, usually in the form of ointments, is established. Instillation into the nasal sinuses of solutions of penicillin either alone or in combination with streptomycin is also an accepted method of therapy.

It is recommended that whenever possible cultures and sensitivity tests should be carried out before commencing topical therapy. Unsatisfactory empirical treatment often merely suppresses the infection and masks the bacteriology.

Clinical response should be apparent within a few days, and treatment should not generally be continued for longer than one week. Prolonged topical treatment may lead to sensitization of the patient and to the emergence of resistant strains.

If an infection is not wholly superficial, systemic therapy may be required.

CHAPTER XVIII

THE ROLE OF ADRENOCORTICAL HORMONES IN INFECTIONS

By Bryan Hudson

It has been known for many years that the secretions of the adrenal cortex play some part in the reaction of the host to those diseases caused by bacteria. Thus, an infection in a person with Addison's disease or in an experimental animal which has been subjected to adrenalectomy is associated with a high mortality. Similarly, in patients with Cushing's syndrome a common cause of death is intercurrent infection.

Since the introduction of cortisone and related steroids into clinical medicine, there has been additional clinical observation and experimental work on the relationship of these hormones to infectious processes. Most experimental infections in animals are aggravated by cortisone and corticotrophin (A.C.T.H.), as are many infections in man. Moreover, during treatment of patients with these hormones spontaneous infections may arise with organisms that are of low virulence or even saprophytic, and latent infections such as tuberculosis may be rendered active.

The fact that cortisone and A.C.T.H. are non-specific antipyretics and produce an appearance and feeling of well-being in spite of advancing infection may have serious consequences, because a need for a change in the management of the disease may pass unrecognized.

There are probably several reasons for the action of adrenal steroids in depressing resistance:

(*a*) Cortisone may occasionally suppress the formation of antibodies, although in clinical doses (75 to 300 milligrams per day) this is unusual.

(*b*) There is a suppression of the inflammatory response to a wide variety of noxious agents including trauma, burns, chemical irritants and others. This suppression probably involves both the vascular and the cellular components of the inflammatory response and the tissues which participate in reparative processes (38).

(*c*) These hormones probably also inhibit the capacity of the reticulo-endothelial system to inactivate or to remove bacterial toxins from tissues.

It is possible that the exhibition of adrenal hormones may facilitate the treatment of deep-seated infective lesions as in tuberculosis (page 59), by making them more accessible to antibiotics. However, this concept requires further experimental proof and its practice may be fraught with danger.

Recommendations may be summarised as follows:

(1) If a serious infection develops in a patient receiving cortisone for the treatment of, for example, rheumatoid arthritis, hormone therapy should be reviewed.

(2) If the use of cortisone or A.C.T.H. is indicated in any clinical condition, the possibility of a concurrent, latent or subsequent infection must be kept in mind and the administration of antibiotics considered.

(3) In any infection, if cortisone or A.C.T.H. is given, the efficiency of antibiotics is reduced, so that a dosage larger than usual may be required.

The subject of adrenocortical hormones in infection and immunity has been reviewed in detail by Kass and Finland (35).

CHAPTER XIX

PROPHYLAXIS

Rheumatic Fever

Sulphonamides

The value of small doses of sulphonamides is established in the prophylaxis of rheumatic fever in children who have suffered from the disease (26).

In 1953, the American Heart Association (3) recommended for the prophylaxis of rheumatic fever the administration of sulphadiazine in a dosage of from 0·5 gram for children under sixty pounds in weight to 1·0 gram for larger children and adults. The drug was to be taken each morning throughout the year and continued until the age of eighteen, or in older persons for five years after the attack of rheumatic fever.

Toxic reactions are infrequent and usually minor. Any rash or sore throat should be regarded as a possible toxic effect, especially during the first eight weeks of prophylaxis. Leucopenia is a more serious reaction and administration of the drug should be stopped if the leucocyte count falls below 4,000 and the polymorphonuclear cells below 2,000. Weekly leucocyte counts are advised during the first 2 months and subsequently at 2 or 3 monthly intervals. It is desirable to test the urine microscopically on occasion to make sure that the drug is being taken. Sulphamezathine has been used prophylactically with apparent success.

It should be noted that although sulphonamides are usually satisfactory in prophylaxis, penicillin is preferred for the *treatment* of streptococcal infections in patients who have had rheumatic fever (page 41).

Penicillin

Penicillin administered orally represents an alternative to sulphonamides for the prophylaxis of rheumatic fever, although its value is less well-established and it is more costly. The dosage recommended is 250,000 units twice daily, taken one-half to one hour before a meal and at bedtime.

Injections of DBED penicillin (page 16) at weekly or longer intervals have been given prophylactically and the oral administration of this form of penicillin is also under trial.

Sensitization to any form of penicillin can occur, and oral medication sometimes induces persistent diarrhœa and *pruritus ani*, particularly in adults.

The Extraction of Tonsils and Teeth

In patients with rheumatic or congenital disease of the heart, prophylaxis with penicillin during the extraction of tonsils or teeth is essential. The important period is the time of extraction when bacteriæmia is likely to occur. Suggested prophylaxis is one dose of fortified procaine penicillin containing at least 200,000 units of crystalline penicillin and 500,000 units of procaine penicillin administered a quarter of an hour before operation. Additional daily injections may be given if desired. It is doubtful whether it is wise to give penicillin for an appreciable time *before* dental extraction because the bacterial flora of the mouth rapidly becomes penicillin-resistant, at least as a result of selection, and a more formidable endocarditis may develop.

Cellulitis of the face or osteomyelitis of the jaw may be associated with an infected tooth. The causative organism is likely to be *Streptococcus pyogenes* or *Staphylococcus aureus*, and while the former is always sensitive to penicillin provided that adequate dosage is given, infections with *Staphylococcus aureus* may require the use of other drugs (page 63). The acute infection should be treated before extraction of the tooth, which can subsequently be removed under cover of chemotherapy.

The use of prophylaxis before extraction in less serious infections is a matter for clinical judgment, but should not usually be necessary.

Clean Surgical Operations

Antibiotics should not be used prophylactically in clean surgical operations. If operative technique does not reach the necessary standard of asepsis, it is better that this should be recognized and remedied. When technique is satisfactory, few wounds become infected, and if infection occurs it is likely to be amenable to chemotherapy. But if infection arises in patients receiving prophylaxis, the organisms are likely to be resistant to the drugs used.

If in special cases prophylaxis is deemed desirable, it is important to use drugs which will prevent infection with either Gram-positive or Gram-negative organisms. The use of crystalline penicillin, 100,000 units, streptomycin, 0·5 gram, and sulphamezathine, 2·0 grams, all of which may be given by injection if desired, is recommended. Administration should commence just prior to operation and should be repeated at 6-hourly intervals for 24 hours. These three drugs will not prevent occasional "hospital infection" with resistant strains of staphylococci. In our experience, however, the tetracycline drugs may produce vomiting and diarrhœa in the period immediately following operation. Moreover, drugs administered orally in the period prior to operation or to anæsthesia are frequently retained in the stomach and hence are not absorbed for some time.

Surgical Operations in Infected Areas

Surgical interference with any infected area, for example in osteomyelitis or infected wounds or the urinary tract, may produce bacteriæmia with subsequent infection in tissues remote from the site

of operation. Hence, prophylaxis is often desirable during the period of operation and is essential in patients with rheumatic or congenitally diseased hearts and in diabetics.

In elective operations, cultures and sensitivity tests should be carried out and appropriate antibiotics given after due consideration of the problems mentioned above.

The application of sulphonamide powder to the peritoneal cavity is not necessary and is not advised because cyanosis, probably associated with methæmoglobinæmia, may develop within a few hours of operation. This condition is reversible in time without treatment, but is likely to cause concern to the clinician. The presence of powders in the peritoneal cavity may induce the formation of adhesions.

If circumstances requiring chemotherapy arise during operation, systemic treatment is more reliable than topical application.

Lacerated Wounds and Burns

When a lacerated wound requires prophylaxis before operation systemic administration is more satisfactory than local applications because it allows penetration to all parts of the wound. If a blood clot forms after operation it should then contain the drugs which are more effectively distributed than they would have been following a surface application of, for example, penicillin and sulphanilamide powder.

If the use of adjuvant topical application is insisted on in particular instances, consideration should be given to drugs such as sulphamar or neomycin, which are not generally used systemically, so that if sensitization develops or resistant organisms appear, subsequent systemic therapy is not jeopardized.

Systemic prophylaxis recommended is the use of crystalline penicillin administered by injection a quarter of an hour before operation to ensure a high concentration in the blood. It is best combined with procaine penicillin. Injections may be repeated daily for a few days. Alternatively a mixture of crystalline, procaine and DBED penicillin may be administered in one injection, but DBED penicillin should not be used alone. One injection of sulphamezathine may be given concurrently with the penicillin, followed by administration by mouth for a few days.

Although in the management of burns the treatment of shock and the replacement of fluids are of paramount importance, intramuscular injections of tetracycline or terramycin are suggested for prophylaxis and should be given as soon as practicable. If suitable preparations of these drugs are not available, daily injections of from 500,000 to 900,000 units of procaine penicillin should be adequate to prevent invasion by the hæmolytic streptococcus, which is the most serious infection to be feared.

The sulphonamides should not be used unless a daily urinary output of at least one litre is ensured, and care should be taken to choose a soluble drug such as sulphamezathine. The oral administration of the tetracycline drugs is not recommended in prophylaxis because they may cause serious loss of fluid and electrolytes if they induce diarrhœa. However, they would be used if necessary, for the treatment of a seriously infected burn. Burns treated by the exposure method are certain to become contaminated with pathogenic organisms. Infection does not necessarily develop, although it should be watched for. Cultures should be made at intervals for information.

The use of antibiotic creams solutions in prophylaxis is not advised.

Operations on the Bowel

The risk of peritonitis following operations on the large intestine is thought to be appreciably reduced by pre-operative treatment with sulphonamides or antibiotics. This diminishes the number of bacteria in the bowel, but it should be realized that it does not sterilize the bowel contents.

The drug recommended is phthalyl sulphathiazole, administered orally for one week before operation in a dosage of from 4 to 8 grams daily in 6-hourly doses. If desired, a retention enema consisting of 100 millilitres of a solution containing 4 grams of phthalyl sulphathiazole, 1 gram of streptomycin and 200,000 units of penicillin in 1 pint of saline, may also be administered daily for the three days preceding operation (43).

Succinyl sulphathiazole or streptomycin given by mouth may be used, but they are less active against the bowel flora than phthalyl sulphathiazole.

Neomycin has a powerful bactericidal action against a variety of bacteria, and its administration by mouth is favoured by some surgeons.

The tetracycline drugs may all be used preoperatively, but they are not advocated because if infection arises despite their use, whether it be peritonitis or staphylococcal enteritis, the organisms concerned are likely to be drug-resistant and difficult to control. The occasional development of infection with organisms resistant to phthalyl sulphathiazole is less serious because they are usually still sensitive to the tetracycline drugs.

APPENDIX

THE VALUE OF SOME LABORATORY TESTS IN THE DIAGNOSIS OF INFECTIONS

In any study of chemotherapy, the paramount importance of accurate bacteriological diagnosis soon becomes evident.

In some infections the clinical findings are so distinctive that there is little if any room for doubt. In others laboratory tests are needed either to provide clues or to determine the diagnosis.

It must be reiterated that early diagnosis and early treatment with the appropriate drugs yields the best results. Of first importance is to diagnose or exclude acute infections which endanger life.

MENINGITIS

The Examination of Cerebro-spinal Fluid

Adults with meningitis usually present with clinical signs, but this is often not the case in young children. In children who appear to be seriously ill without obvious cause, lumbar puncture should always be considered.

A slightly turbid cerebro-spinal fluid is not itself evidence of meningitis, but may indicate the presence of blood in the fluid or of debris in the test tube. It is imperative that a proper cell count of the number and type of cells per cubic millimetre be made immediately. The cell count may be dispensed with only if the fluid is frankly purulent, in which case smears should be made and stained by Gram's method. Organisms can often be recognized in such smears, and the appropriate chemotherapy instituted (page 42). Cultures should always be made for confirmation and sensitivity tests. If it is not practicable to make a cell count and Gram smear immediately, empirical therapy should be given (page 45) without delay. However, it is still important to identify the organism because the chemotherapy may need to be modified. Hence, the specimin of cerebro-spinal fluid should be sent forthwith to a laboratory or should accompany the patient to hospital. In subsequent specimens the bacteriology may be masked by the chemotherapy. Serological tests on cerebro-spinal fluid are available for the diagnosis of meningitis caused by *Hæmophilus influenzæ* (56).

In lymphocytic meningitis in which tuberculosis, torulosis and virus meningitis, including early poliomyelitis, must be considered, it is most important to diagnose or exclude tuberculous meningitis as rapidly as possible.

It is usual to examine smears of any pellicle or clot in the cerebro-spinal fluid for tubercle bacilli, but Smith and Vollum (52) recommend prolonged centrifugation at high speed and examination of thick smears of the deposit. If no organisms are found they recommended that about 2 millilitres of the fluid be incubated at 37° C. for several days and examined in the same way. Cultures should also be made. Biochemical tests on the cerebro-spinal fluid are often helpful, particularly the finding of a lowered sugar content which usually occurs in tuberculous and in torular meningitis but never in virus infections. Collateral tests such as X-ray of the chest should be carried out and the examination of sputum, gastric contents and urine for tubercle bacilli should be considered. A total and differential blood leucocyte count is sometimes useful when there is doubt as to whether the meningitis is lymphocytic or early pyogenic. A high count usually suggests a pyogenic infection and suitable chemotherapy should be given. However, counts above 20,000 cells have been recorded occasionally in tuberculous meningitis.

SEPTICÆMIA

Blood Cultures

In a patient with a persistent temperature, blood culture should be made *without delay*, since organisms may disappear from the blood stream. The early diagnosis of typhoid is of great importance since it can be treated specifically with chloramphenicol. Moreover, isolation of the organisms from the blood is more reliable diagnostically than serological tests (see below) and can be achieved earlier in the course of the disease.

In staphylococcal septicæmia, the early isolation of the causative organism and the determination of its sensitivity reactions may indicate life-saving measures.

Brucellosis can develop into a prolonged debilitating illness incurable with antibiotics, but if diagnosed early it responds well to chemotherapy. Blood cultures for *Brucella abortus* should be incubated aerobically in an atmosphere of 5% carbon dioxide, e.g. in a candle-jar.

Blood culture media should always include anaerobic broth as well as aerobic broth, so that infections with anaerobic streptococci are not missed. These arise not only in puerperal infections but in infections following trauma to the bowel. Anaerobic Gram-negative bacilli (*Bacteroides*) are often associated with anaerobic streptococci.

The ready isolation of organisms from the blood depends on the numbers present, and repeated attempts at blood culture may be desirable without of necessity awaiting the results of earlier ones. This is particularly important in subacute bacterial endocarditis, which often exhibits a bacteriæmia rather than a septicæmia, so that few organisms are present.

Blood cultures often show growth after 24 hours' incubation or less. If no growth occurs, the culture may be reported "negative" after three days, but should be reincubated for one week or for one month if the patient has received antibiotics. Cultures of *Brucella abortus* should not be declared negative until they have been incubated for one month.

PNEUMONIA AND RELATED CONDITIONS

The Examination of Sputum

In acute pneumonia it is now the practice to treat the patient empirically with penicillin (page 41) without examining the sputum, but it is desirable to make this examination if possible.

In patients who fail to respond to adequate doses of penicillin or in whom there is reason to suppose that the illness is not pneumococcal in origin (as in pneumonia associated with fibrocystic disease of the pancreas in children) it is important to examine the sputum by Gram-stain and culture, but the findings should be interpreted with great caution.

Sputum always contains bacteria. Unless the specimen has been obtained by bronchoscopic aspiration, it is always contaminated with mouth organisms, chiefly *Streptococcus viridans*, sundry Gram-negative cocci and diphtheroid bacilli; harmless commensals which have not been incriminated as a cause of pneumonia. Sometimes other organisms such as *Staphylococcus aureus*, coliform bacilli or *Pseudomonas pyocyanea*, which are potential pathogens, are also found. If the specimen is not perfectly fresh multiplication of organisms is likely to occur, so that the observer may be falsely impressed with the presence of large numbers. Moreover, the species of organisms present may simply reflect previous treatment antibiotic in that organisms sensitive to that drug have disappeared

and have been replaced by resistant but still probably harmless species. The bacteriologist is obliged to report the presence of potentially pathogenic bacteria and their sensitivity reactions because they may have some clinical significance, but this is rarely the case.

However, in a patient acutely ill with bronchopneumonia, the detection of large numbers of bacteria such as staphylococci in smears of fresh sputum should be used as a guide to empirical therapy and cultures and sensitivity tests should be carried out so that treatment can be confirmed or changed.

The possibility of acute tuberculous bronchopneumonia should be kept in mind.

In subacute and chronic infections of the lungs, the examination of sputum for pyogenic organisms seems rarely to be of value but may be carried out if due regard is paid to the interpretation of the results as already indicated.

In any infective lesion, whether pyogenic, tuberculous or fungal, the demonstration of the causative organism in sputum can hardly be expected unless rupture of the lesion into a bronchus has occurred. Hence it may be desirable to make repeated bacteriological examinations, and it is probably better to extend these over a period than to abandon them after specimens have been examined on three consecutive days. These remarks apply particularly to the diagnosis of tuberculosis. It should be remembered in this regard that cultural methods and the inoculation of guinea-pigs are more sensitive instruments of detection than are smears alone.

The most important fungal disease of the lungs occurring in Australia is torulosis. Torulæ may be recognized by direct examination of sputum either with India ink if the specimen is not too viscous, or in smears stained with methylene blue. Torulæ found in the tissues (or sputum) are quite different in appearance from *Monilia albicans*, and there should be no difficulty in distinguishing them. Cultures for torulæ may be made on Sabouraud's medium, which inhibits sundry bacteria.

Monilia albicans is frequently demonstrable in sputum both by means of smears and of cultures on Sabouraud's medium, but it is usually a secondary invader. True moniliasis of the lungs is an extremely rare condition, and such a diagnosis should be made with caution.

Histoplasmosis has been reported from Queensland. No other systemic fungal diseases have yet been found in Australia.

INFECTIONS OF THE THROAT, ETC.

The Examination of Swabs

The use of serum-treated swabs (swabs dipped in normal ox serum before autoclaving) (49) is recommended because diphtheria bacilli and hæmolytic streptococci remain viable on them for longer periods than on plain swabs. Nevertheless, delay in transit should be avoided.

(1) *Diphtheria*

The examination of direct smears is unreliable for diagnosis, and the results of cultures are not usually available within less than 18 hours. Hence if diphtheria is suspected clinically the patient should be sent to hospital, or after taking a throat swab should be treated with antitoxin and penicillin without waiting for bacteriological confirmation. The anginose form of glandular fever may be confused clinically with diphtheria, but if there is any doubt it is safer to treat the patient for diphtheria.

If the patient is not very ill it may be wise to exclude the diagnosis of diphtheria by taking a throat swab and then treating the patient with penicillin alone until the laboratory report is available.

It must be realized that if diphtheria is not considered until *after* the patient has had penicillin and a throat swab is then taken, the diphtheria bacilli will not be found. A negative report will be returned which may be false, and fatalities have occurred through a resulting failure to give antitoxin.

(2) *Streptococcal Tonsillitis*

The presence of numerous colonies of hæmolytic streptococci may be reported within 18 hours of receiving the swab, and when associated with clinical tonsillitis is presumptive evidence for the diagnosis. It requires, however, from 36 to 48 hours before the organisms can be declared Group A (*Streptococcus pyogenes*). Occasionally Groups C or G may be implicated in tonsillitis.

The presence of only a few hæmolytic streptococci is probably not diagnostic in acute conditions, although it is significant in the detection of carriers.

In patients who have received chemotherapy, throat swabs commonly yield negative results which may be misleading.

(3) *Glandular Fever*

Glandular fever (page 83) should be considered particularly in patients who fail to respond rapidly to chemotherapy.

(4) *Vincent's Angina*

This condition is diagnosed by the examination of direct smears stained with carbol fuchsin. Smears should be made at the bedside and sent to the laboratory, as swabs are prone to dry in transit. Cultures are unsatisfactory.

(5) *Ulcers of the Mouth*

The bacteriology of ulcers of the mouth has already been discussed (page 47). Smears should be made and sent for examination.

(6) *Whooping Cough*

Special fine nasopharyngeal swabs made of wire and cotton wool treated with serum are better than cough plates. The swab can be passed along the floor of the nose until it touches the posterior wall of the nasopharynx. It is best to inoculate the medium, a Bordet-Gengou plate containing penicillin, at the bedside. Demonstration of *Hæmophilus pertussis* is often possible up to the fourth week of illness, even if the child has received chemotherapy (20).

INFECTIONS OF THE URINARY TRACT

The Examination of Urine

When infection of the urinary tract is suspected, micro examination of a fresh specimen of urine is made. It is desirable to examine, if possible, an early morning specimen, which is likely to be more concentrated than later ones. A volume of from 5 to 10 millilitres may be centrifuged for 5 minutes and a wet preparation of the deposit examined microscopically.

The presence of polymorphs to the extent of four or more per high power field may indicate infection (except in non-catheter specimens from adult females) and cultures should be made.

Requirements for culture are clean midstream specimens from males, catheter specimens from females, and non-catheter specimens from children.

Pyogenic bacteria most commonly found in infections of the urinary tract are Gram-negative bacilli such as coliform bacilli, *Proteus vulgaris* and *Pseudomonas pyocyanea* ; *Streptococcus fæcalis* and other streptococci, and staphylococci including *Staphylococcus albus* associated with stone. Infection with more than one species is not uncommon, especially in cystitis.

The importance of sensitivity tests has already been stressed.

Failure of chemotherapy with a drug to which the infecting organism is sensitive may reflect the presence of obstruction. The possibility of an underlying tuberculous infection should also be considered.

It is not sufficiently realized that specimens of urine, whether mid-stream or catheter, are very frequently contaminated with the types of organisms which cause infection. and that multiplication of organisms occurs in stale specimens. Hence, reports on urine cultures should be treated with reserve and assessed with regard to the presence of pus and to the patient's clinical condition. Repeated cultures on specimens collected with extra care are sometimes helpful.

INFECTIONS OF THE BOWEL

The Examination of Fæces

Fresh specimens of fæces are required for the cultivation of *Salmonella* and *Shigella* species. If specimens are more than two hours old the percentage of successful isolations is greatly reduced, but if delay is inevitable the investigation should be done. The collection of specimens in a solution of 30% glycerine in phosphate buffer promotes the viability of the organisms.

Rectal swabs may be used, but *Salmonella* and *Shigella* species die rapidly on plain swabs. It is better to use serum-treated swabs moistened with tap water and kept moist in transit (49).

Certain types of *Bacterium coli*, called alpha (or D433) and beta, and certain types of paracolon bacilli have been associated with infectious diarrhœa. Special serological tests are required for their identification.

Food poisoning may be caused by the consumption of food containing the enterotoxins of certain strains of *Staphylococcus aureus* or of *Clostridium welchii* or rarely of *Clostridium botulinum*,

but these organisms are not found unless specially looked for. There is no specific chemotherapy.

Severe staphylococcal enteritis has been described in patients receiving preoperative treatment of the bowel with sulphaguanidine, streptomycin or one of the broad spectrum antibiotics (59). Staphylococci should be looked for in smears and cultures of fresh fæces, and if present in large numbers they may be significant. They may be expected to be resistant to the drugs used, and treatment with erythromycin may be necessary. It should be borne in mind, however, that many persons in apparent health excrete staphylococci in fæces.

Fresh specimens of fæces, preferably containing mucus, are required for examination for *Endamœba histolytica*. Cysts may be detected in other specimens. Rectal swabs are not satisfactory.

SEROLOGICAL TESTS IN DIAGNOSIS*

Isolation of the causative organism is usually the most reliable method of diagnosis. When this cannot be achieved serological tests are often helpful, but they are subject to misinterpretation and may be misleading. Collaboration between clinician and bacteriologist is therefore desirable.

Antibodies are often present in low titre and occasionally in high titre in normal sera, owing either to previous unrecognized contact with infection or to vaccination. Hence, no arbitrary titre can be accepted as diagnostic of active infection.

I. Certain serological tests are routine procedures in most laboratories. These are :

(1) Wassermann (complement fixation) and other tests for syphilis.

(2) Agglutination tests with bacterial suspensions :
  (*a*) *Salmonella typhi* and *Salmonella* species endemic in the area.
  (*b*) *Brucella* species.
  (*c*) Certain strains of *Proteus* used in the diagnosis of typhus.

(3) Agglutination tests with sheep's red cells to demonstrate heterophile antibodies in glandular fever (Paul-Bunnell test).

(4) Agglutination tests with human Group O red cells to demonstrate cold agglutinins in atypical pneumonia (rarely required).

(5) Antistreptolysin tests for the detection of infections with hæmolytic streptococci.

II. Other serological tests require special antigens and are at present carried out only in laboratories engaged in related research work. These are :

(1) Agglutination tests for leptospiræ according to the endemic species, e.g. *L. pomona*, *L. mitis* and *L. icterohæmorrhagiæ* in Victoria.

* The reader is referred to an excellent recent review by Price (46) on tests for venereal disease, and to another by Spooner (53) on serological tests in general.

(2) Agglutination or complement fixation tests with rickettsial suspensions for the diagnosis of typhus or "Q" fevers.

(3) Complement fixation tests or tests demonstrating the inhibition of hæmagglutination in certain virus infections, e.g. mumps, dengue fever, certain encephalitides, psittacosis and *lymphogranuloma venereum*, influenza, poliomyelitis.

I. The tests in Group 1 may be considered briefly.

(1) *Syphilis*

The value of Wassermann and other tests in diagnosis is well known.

The use of penicillin in the treatment of gonorrhœa and its simultaneous effect on spirochætes, if present, has made it imperative that patients suffering from gonorrhœa should be followed for several months with serological tests, in order to be sure that they are not suffering from syphilis.

Treatment with penicillin for one day is sometimes sufficient to suppress the appearance of a primary lesion or to prolong the period before it appears. When a surface lesion is present, treatment for one day can cause the permanent disappearance of spirochætes from it. However, penicillin does not appear to affect the appearance of the first serological reaction if due allowance is made for the variability of the time of its appearance in untreated patients.

Florey (22) states that in patients treated for gonorrhœa, if no other examination suggests syphilis, regular serological tests between 4 weeks and 4 months after exposure to infection should reveal its presence.

(2*a*) *Enteric Fever*

It is usually stated (53) that in a pyrexial patient *with no history of inoculation or of previous enteric infection*, a titre of 1 in 50 for H agglutinins and of 1 in 100 for O agglutinins observed during the first 10 days of illness may be regarded as strong presumptive evidence of enteric infection. In such a patient treatment would not be withheld but confirmation would be sought first by initiating cultures from blood, urine and fæces and the agglutination test would be repeated after a few days to look for a rising titre.

Titres lower than those cited may at times be significant when found in the first 10 days of illness, and the institution of chemotherapy depends on due consideration of the clinical and laboratory findings. A rise in agglutinin titre may be expected in a true infection and confirmation by cultural methods may be obtained. A low titre found in the third week of illness with no subsequent rise is not evidence of infection.

In investigating pyrexia of unknown origin it is suggested that a sample of blood for agglutination tests be collected at the same time as the first blood culture. The titre of the serum can then serve as a base-line for the detection of a subsequent significant (at least fourfold) rise.

In inoculated persons or in those with a previous history of enteric fever, diagnosis by serology may be difficult. H agglutinins are nearly always found, occasionally in high titre. O agglutinins

are less persistent, and a titre of 1 in 100 is usually regarded as suspicious, particularly if a rise in titre can be demonstrated. However, in certain patients a rise in titre (particularly of H agglutinins) can occur during the course of a non-enteric pyrexial illness. Persistent efforts should be made to culture the organism responsible for the infection and the clinical condition should be carefully evaluated.

(2*b*) *Brucellosis*

Healthy persons may develop agglutinins to *Brucella*, particularly if they are repeatedly exposed to infection. Thus in Victoria 10·4% of abattoir workers were shown by the direct agglutination method to have agglutinins varying in titre between 1 in 40 and 1 in 2560 (19). When the modified Coombs' method of agglutination (60) was used, agglutinins were demonstrated in 47·8%. In a control series drawn from sera submitted for Wassermann test no agglutinins at 1 in 40 or higher dilutions were detected by the direct method, but 4·5% showed agglutinins by the anti-globulin technique.

These observations, together with the fact that brucellosis is often a vague chronic illness, emphasize the difficulty of establishing a diagnosis. A rising titre is likely to be significant and a very high titre such as 1 in 20,000 (direct method) cannot be ignored. The clinical significance of antibodies detected by the antiglobulin technique is unknown. Each case must be considered on its merits in both clinical and bacteriological aspects.

(2*c*) *Typhus Fever*

In typhus fever the strains of Proteus used in diagnostic agglutination tests are *Proteus* OX19 (murine typhus), *Proteus* OXK (scrub typhus) and *Proteus* OX2 (North Queensland tick typhus); see page 67.

A rising agglutinin titre may be significant, but single titres are of doubtful value and the test should be interpreted strictly in relation to the clinical findings.

(3) *Glandular Fever* (*Infectious Mononucleosis*).

The diagnosis of glandular fever may be aided by (*a*) the examination of blood films, and (*b*) the Paul-Bunnell test. The characteristic blood picture may be found early in the illness, but the time of its appearance is variable and it is often transient, so that it may be missed.

In the mild type of infectious mononucleosis the Paul-Bunnell test may be positive by the end of the first week, but in the more severe types of the disease the development of agglutinins may be related to the end of the disease rather than to the beginning, or at times may not occur. A positive Paul-Bunnell test may be accepted as diagnostic, but a negative reaction is of little value.

A titre of 1 in 128 in the direct test is suggestive and a titre of 1 in 256 is usually accepted as positive. A rising titre may be demonstrated. The test is more reliable if absorption tests are carried out with ox red cells and with an emulsion of guinea-pig kidney. In

infectious mononucleosis, the heterophile antibodies are absorbed by ox red cells, but not by guinea-pig kidney. Using the absorption technique, a titre of 1 in 28 may be significant (40).

There is no evidence that chemotherapy is of any value.

(4) *Atypical Pneumonia*

Atypical pneumonia is thought to be of virus origin, and the demonstration of " cold agglutinins " with a rising titre is considered to be of diagnostic significance, although there is no satisfactory explanation for their development.

(5) *Hæmolytic Streptococcal Infections*

Streptolysin O is a hæmolysin elaborated by most strains of the hæmolytic streptococcus Group A, and by some strains of Group C and Group G. It reacts *in vitro* with anti-streptolysin O, an antibody found in the sera of patients infected with such streptococci.

In recording the anti-streptolysin titre the figure is an inversion of the dilution of patient's serum. It is usual to read a figure under 100 as negative, between 100 and 200 as doubtful and above 200 as evidence of a " fairly recent " infection. As in other serological tests, a rising titre is more significant than a single reading and is good evidence of recent infection. A stationary moderately high titre over a period of several weeks may merely reflect a previous infection months before. It may be quite unrelated to a patient's current illness and may be seriously misleading if other investigations are overlooked.

II. In patients with pyrexia of unknown origin the tests in Group II would not be considered until other investigations had been carried out, except in areas where the infections were endemic. In all these tests it is particularly important to discuss with the bacteriologist concerned the significance of his serological findings.

PUERPERAL AND ABORTIONAL INFECTIONS

The Examination of Smears and Swabs

By H. M. Butler

Puerperal Infections

Specimens required are :

(1) Two vaginal smears made at the bedside.

(2) One or two vaginal swabs for culture. If practicable, cultures should be made at the bedside. Alternatively swabs (preferably serum-treated) should be despatched to a laboratory without delay. All vaginal swabs should be taken at the same time and from the same area.

(3) A catheter specimen of urine for micro and, if necessary, cultural examination, to exclude pyelitis.

(4) A blood culture if indicated, e.g. in a patient gravely ill or with a sustained high temperature.

Vaginal cultures alone are of little value except in infections with *Staphylococcus aureus* and *Streptococcus pyogenes*, but these together account for less than 10% of today's infections, the great majority of which are due to mixtures of the non-sporing anaerobes, usually anaerobic cocci and anaerobic Gram-negative bacilli (*Bacteroides*). In many of the latter cases, and in most cases of infection due to either coliform bacilli or *Streptococcus fæcalis* (Group D streptococcus), several types of bacteria are present in cultures made from the genital tract. In such cases direct smears are essential to determine which bacterial type or combination of types is responsible for the infection. Direct smears also indicate the presence or absence of genital tract infection.

Vaginal Smears

In experienced hands the examination of direct smears yields rapid and accurate information regarding the nature and probable severity of the infection (11). Each particular type of infection has a characteristic direct smear pattern based on the number and morphology of the bacteria present and the number and condition of the leucocytes. Hence it is desirable to send specimens to bacteriologists known to be experienced in these types of infection. However, a bacteriologist with a general training may often give effective aid to the clinician provided that he is aware of the following points :

(*a*) A good binocular microscope with adequate illumination is essential.

(*b*) In the uninfected patient whose labour and delivery have been normal, only a few pus cells are present in direct smears during the first three days of the puerperium, and at no stage of the lying-in period will there be many ; bacteria, if present, are usually Döderlein's and diphtheroid bacilli.

(*c*) An appreciable number of pus cells, especially early in the puerperium, indicates a genital tract infection, unless considerable trauma has occurred during delivery.

(*d*) In general, there are more pus cells, more bacteria and more intense phagocytosis to be seen in direct smears in anaerobic infections than in those caused by aerobic bacteria. Also, in anaerobic infections there are usually two or more distinct bacterial types in the direct smear, while in aerobic infections it is more common to see only one type.

(*e*) Many strains of anaerobic cocci are smaller and more pleomorphic than either the aerobic streptococci or staphylococci. *Bacteroides* are smaller than coliform bacilli. Approximately 70% of *Streptococcus pyogenes* strains show capsules in direct smears stained with 0·5% Leishman stain in methyl alcohol (10).

Vaginal Cultures

It is essential to make anaerobic as well as aerobic cultures. Cultures are necessary both to confirm the direct smear findings and to enable sensitivity tests to be carried out if indicated. With the slow-growing anaerobes sensitivity tests may be delayed, but this is not a serious problem provided that an accurate bacteriological diagnosis has been made, as it may safely be assumed that all strains

of anaerobic cocci are reasonably sensitive to penicillin and the majority of strains of *Bacteroides* to sulphonamides. Failure of clinical response to penicillin and sulphonamides is most likely to be due either to failure to correct an associated anæmia with adequate blood transfusion, or to the development during treatment of a secondary infection caused by *Streptococcus fæcalis* or a sulphonamide-resistant coliform bacillus. In such cases and in the rare instance in which a *Bacteroides* infection persists after the anaerobic cocci have been controlled, one of the tetracycline drugs should be used.

It is in infections with *Staphylococcus aureus* and coliform bacilli, and sometimes in infections with *Streptococcus fæcalis*, that sensitivity tests are most needed. Strains of *Streptococcus pyogenes* can still be regarded as invariably sensitive to penicillin.

Blood Cultures

It is necessary to make anaerobic as well as aerobic cultures, and it is desirable, if some strains of anaerobic streptococci are not to be missed, that the anaerobic medium contain free trypsin.

Abortional Infections

The bacteriology of abortional infections resembles that of puerperal infections with one important exception. This is the prevalence of *Clostridium welchii* infections which are the commonest cause of death in abortional infections in certain communities such as Melbourne.

Cervical smears are more reliable than vaginal smears, and should be made at the bedside. When the Gram stain reveals the presence of organisms resembling *Clostridium welchii* a second smear should be stained by Muir's method to demonstrate capsulation and the state of the leucocytes. Heavily capsulated bacilli are more invasive than slightly capsulated organisms, and strains which cause rapid destruction of the leucocytes are highly toxigenic. The strains which cause rapidly fatal infections almost invariably display both attributes (9).

Aerobic and anaerobic cultures should be made from a cervical swab taken at the same time as that from which the direct smears were made. Sensitivity tests are unnecessary as penicillin is undoubtedly the antibiotic of choice.

SUNDRY PYOGENIC INFECTIONS

The Examination of Pus

Any collection of pus or similar fluid is investigated by the examination of direct smears (to indicate the types and relative numbers of organisms present), and of cultures. However, the examination of direct wet preparations is essential for the proper estimation of the cell-content of fluids such as pleural effusions.

It is important to obtain good specimens collected preferably in sterile test-tubes, or if only small quantities are available, on serum-treated swab sticks. If the results of bacteriological investigation appear unsatisfactory, a second specimen should be obtained.

Smears and cultures for gonococci (made prior to micturition) should be taken directly from the patient because these organisms do not survive on swab sticks. A medium for the preservation of gonococci in transit can be prepared.

Smears and cultures from the eye or from any other situation where the discharge is usually slight should likewise be made directly from the patient.

In most investigations it is desirable to include anaerobic methods of culture as a routine, especially in wounds, abscesses and peritoneal effusions.

If no pyogenic bacteria can be demonstrated in pus from a patient who has not had chemotherapy or in whom chemotherapy has failed, the possibility of a tuberculous or fungal infection should be considered.

It should be recognized that any lesion which has a serous discharge such as a burn or an ulcer of the skin readily becomes contaminated with pathogenic organisms, particularly in hospital. Such contamination does not necessarily constitute infection, and chemotherapy is often not indicated. However, it may be desirable to be informed as to the kinds of bacteria present in case infection develops.

PYREXIA OF UNKNOWN ORIGIN

Various Laboratory Tests

In attempting to elucidate pyrexia of unknown origin, the nature of the investigations and the order in which they are carried out depend mainly on the history, the signs and symptoms presented, and the severity of the illness. A knowledge of the fevers endemic in a particular area (as in Queensland) is essential.

It is important first to try to diagnose or exclude serious acute infections which require immediate treatment with a specific drug, such as meningitis (not always clinically evident in children), typhoid fever or septicæmia caused by various bacteria. The examination of cerebro-spinal fluid and of blood cultures should therefore be considered.

Blood examination and micro examination of urine should then have priority. They are easily and rapidly carried out, and often yield helpful information.

The most common and likely diseases should be sought before the rare ones, and it should be remembered that repeated tests may be necessary for the diagnosis of certain infections such as tuberculosis.

Serological tests have been reviewed above. They require careful interpretation, because the findings may not be related to the current illness.

If any laboratory result does not appear to fit in with the clinical picture, it should be discussed with the pathologist or bacteriologist concerned so that its significance can be determined.

It is very important to try to make an accurate diagnosis before instituting chemotherapy, but it is a matter for clinical judgment whether chemotherapy can be withheld. In any case, suitable specimens for investigation should be collected *first* because chemotherapy often masks the bacteriology and thus delays the diagnosis.

A list of some laboratory methods which may be considered in the elucidation of pyrexia of unknown origin is appended.

Examination of the blood should always be carried out. The order of and necessity for the other tests listed should be determined by a frequent review of the clinical findings. They should never be mere routine procedures, but the significance of the results should be carefully assessed as the investigations proceed.

(1) *Blood examination.* Total and differential leucocyte count. Also consider malaria, infectious mononucleosis, etc., and rarely, L.E. cells in systemic *lupus erythematosus.*

(2) *Urine micro examination.*

(3) *Urine culture* if micro examination shows pus cells.

(4) *Blood cultures.*

(5) *C.S.F. examinations.*

(6) *Throat swabs and antistreptolysin tests.*

(7) *Agglutination tests* for typhoid and other *Salmonella* infections, brucellosis, glandular fever (infectious mononucleosis), typhus fevers and Q fever, and leptospiral infections.

(8) *Tests for tuberculosis.*

- (i) Mantoux tests.
- (ii) Sputum or gastric contents, or pleural effusion (if present) : smear, culture and guinea-pig inoculation.
- (iii) Urine, if micro shows pus cells or erythrocytes : smear, culture and guinea-pig inoculation.
- (iv) Biopsy and culture of lymph-glands in relation to possibly tuberculous joints.

(9) *Wassermann tests.*

(10) *Tests for hydatid.*

- (i) Casoni skin test.
- (ii) Complement fixation test.

(11) *Tissue biopsy*, e.g. gland in Hodgkin's disease.

(12) *Examination of bone marrow.*

- (i) Film and section (tuberculosis, sarcoid, etc.).
- (ii) Culture for *Brucella abortus*, *Salmonella typhi*, etc.

(13) *Investigations for virus infections.*

- (i) Complement fixation tests or tests demonstrating the inhibition of hæmagglutination.
- (ii) Frei test (skin test with virus grown in yolk sac of chick embryo, and killed) for *lymphogranuloma venereum.*
- (iii) Demonstration of cold hæmagglutinins in primary atypical pneumonia.
- (iv) Liver function tests in infective hepatitis.
- (v) Tissue culture.

SENSITIVITY TESTS

If sensitivity tests are to be of practical value, results must be available as soon as possible. It is better to test some organisms unnecessarily than to be unable to supply information when it is required. More reliable results are obtained if the tests are done regularly and on a number of organisms simultaneously.

Sensitivity tests employ one or other of two principles :

(1) Diffusion methods.

(2) Dilution methods.

The more common variations of these are :

(1*a*) The whole surface of a blood agar plate is inoculated with the organism to be tested. Antibiotics are applied to localized areas on the plate, from whence they diffuse to a surrounding zone. Absence of growth in such a zone implies sensitivity of the organism to a certain concentration of antibiotic, but any attempt to define this quantity entails a good deal of exact work and the largest zone does not necessarily indicate the greatest sensitivity. The concentration of antibiotic applied is therefore chosen to give a rough empirical relation to successful or unsuccessful treatment with the usual dosage given to the patient.

The antibiotic may be applied :

- (1) in discs of paper or pellets of other inert substance, which may be purchased,
- (2) in discs of filter paper impregnated with a measured quantity of antibiotic from stock solutions in the laboratory and applied wet, or made beforehand in batches, dried and kept in a desiccator in the refrigerator,
- (3) in holes cut in the medium and refilled with antibiotic mixed with agar or as solutions of antibiotic placed in cups inserted in the medium.

In all these variations there is no check on the result given by an individual disc.

(1*b*) Discs, etc., are placed on the medium and each is surrounded, not by a continuous area of inoculation of one organism, but by radiating streaks of inoculation of several organisms, including organisms of known sensitivity.

(2*a*) Dilutions of antibiotic are made in broth and inoculated with a definite quantity of culture of the organism to be tested. An organism of known sensitivity is tested in parallel. The point at which no growth or a specified reduction in growth occurs may be determined by turbidity, or various devices such as the addition of a fermentable sugar and an indicator may be used. The method can readily be made to give exact results, but is laborious.

None of these three methods show automatically the production of penicillinase by staphylococci, though they may all be modified to do so. If desired a separate test for its presence may be included (5).

(2*b*) Dilutions of antibiotics are made in blood agar plates as the plates are being poured. The organisms to be tested and organisms of known sensitivity are inoculated on the surface in a series of short streaks and also on the surface of control plates which do not contain antibiotic. The important concentrations of antibiotics are those which approximate the concentration reached in the blood of the patient on the usual dosage. The size of the inoculum is controlled. Heavy inocula are used in the case of *Staphylococcus aureus* being tested against penicillin, in order to disclose the presence of penicillinase. Light inocula, intended to produce discrete colonies, are used in all other cases. Spreading organisms such as *Proteus vulgaris* are segregated by means of ditches cut through the medium. Stock concentrated solutions of antibiotics may be kept in the refrigerator for a month. Dilutions of these for incorporation in the plates are made weekly. Lysed blood is added to plates containing sulphonamides to annul the effect of sulphonamide inhibitors in the medium (25).

This method, which is used at the Alfred Hospital, enables large numbers of cultures to be tested with little expenditure of time and material. Twenty-four cultures can be tested on a 9 centimetre plate. The concentrations recommended are :

Penicilliu	..	0·01, 0·1, 1·0 units per millilitre.
Sulphadiazine	..	2·5, 10, 20 milligrams *per centum*.
Streptomycin	..	1, 10, 20 micrograms per millilitre.
Aureomycin	..	1, 5, 10 micrograms per millilitre.
Terramycin	..	1, 5, 10 micrograms per millilitre.
Tetracycline	..	1, 5, 10 micrograms per millilitre.
Chloramphenicol	..	2, 10, 20 micrograms per millilitre.
Erythromycin	..	0·1, 1, 10 micrograms per millilitre.
Bacitracin ..	..	0·1, 1, 10 micrograms per millilitre.
Polymyxin	..	5, 10 micrograms per millilitre.
Sulphamar	..	2·5, 25 and 250 milligrams *per centum*.

Colonies are picked from the original platings of specimens whenever possible, and inoculated into 2 millilitre quantities of tryptic broth. After about 6 hours' incubation the sensitivity plates are inoculated from a dilution of one 2 millimetre loopful of culture in 5 millilitres of saline except in the case of *Staphylococcus aureus* and penicillin in which the undiluted culture is used. Urgent specimens may be put directly on the plates, and even if the growth is mixed useful information may be gained. In each case, organisms resistant to the highest concentration listed above are assumed not to be amenable to treatment ; organisms sensitive to the highest concentration but resistant to the next highest concentration may respond to large dosage, but if another drug can be used it is to be preferred, while organisms sensitive to the second highest concentration or less are thought to be of such sensitivity that treatment will be efficacious if other factors are not adverse.

Mycobacterium tuberculosis is usually tested, in parallel with the standard strain H37Rv, by methods of the type of (2*b*), on slopes of the usual media (Lowenstein, Petragnani or Herrold) in which the drug is incorporated. However, when only occasional tests are done it is more convenient to add the drug to semi-synthetic liquid media such as Dubos' base containing albumin but without Tween 80, or Youmans' modification of Proskauer and Beck's medium with albumin added, as in (2*a*).

The concentrations of drugs recommended are :

Streptomycin	.. ..	1, 10, 50 micrograms per millilitre.
Para-amino-salicylic acid	..	1, 10, 100 micrograms per millilitre.
Isonicotinic acid hydrazide		0·2, 1, 5 micrograms per millilitre.

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