Microbial Disease:

the use of the laboratory in diagnosis, therapy and control

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Preface

There are so many excellent books dealing with microbiology and with the role of infection in medicine and surgery that it may seem that there is no reason for us to have written yet another. However we think that this is a new sort of book for which there is a real need that has not previously been met, although we must leave it to the reader to decide whether the need has been correctly defined and adequately fulfilled.

We have all worked in different ways and in different parts of the world in a state of oscillation between the laboratory and the bedside. At times we have been clinicians with a keen interest in bacteriological and virological diagnostic tests, at others we have been laboratory workers visiting the wards to find out about the clinical situation in which a test was asked for or the results are to be applied. In these situations, which we might describe as the interface between laboratory and clinical medicine, we have had to draw on bits of information derived from conventional bacteriological texts, books on clinical medicine or control of infection, and others too. We felt that it would be a useful new venture to put together and write down the information that we had found useful, and the result is this book. The only details of bacteriological technique it covers are a selection of methods for collecting specimens and details of just a few laboratory methods that may not be widely used, while the clinical descriptions are mere thumbnail sketches; but we hope that a doctor who is presented with a clinical problem, perhaps a febrile patient who might have typhoid fever, will be able to open the book and quickly extract information on what tests to initiate and how, what results to expect and when and what they will mean, what other diagnoses to consider, what to do to limit the spread of infection, and what treatment might be suitable. We think that, in the past, microbiology has been taught too much as an isolated laboratory subject, and hope that this book will show that it is really an integral and very interesting and useful part of clinical practice.

At the end of most chapters we give references to the few publications that are mentioned in the text. Most of these are not the main or original works on the topic but report recent advances, and themselves carry reference to the important earlier work. For general information on microbial diseases we, like many microbiologists and infectious-diseases physicians, often refer particularly to the six books that are listed at the end of this preface. These books are mentioned in the lists at the end of

some chapters but provide a great fund of information that is relevant to all.

We are grateful to the many clinical and laboratory colleagues whose collaboration with us has led to the production of this book, to Mr Richard Bowlby for the photographs, and to others for their permission to reproduce or adapt illustrations and tables.

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Part I General principles

1

The principles of microbiological diagnosis

Like other aids to clinical practice, the microbiology laboratory is sometimes not used when it could give much help and is sometimes used inappropriately, by being asked for what it cannot give; and the results may be misunderstood or not put to good use. Although there is a great deal to be learned about each group of clinical situations and infecting microbes — and these are dealt with separately in later chapters — many and diverse problems can be approached confidently by application of the simple principles of microbiological diagnosis that follow in this chapter.

Classes of disease and diagnostic methods

Bacteria, viruses, and other parasites may establish themselves in a patient at the point of entry and around it by direct extension, or they may invade and spread throughout the body though commonly they then localize in a site of preference; however, they may persist at this site when they have been cleared from their route of invasion — such as the bloodstream.

After infection, whether or not there is invasion and whether or not it is accompanied by toxin production and disease, there is usually a host response. This may be relatively 'non-specific', for example leucocytosis and the changes of plasma proteins that are indicated by an increased erythrocyte sedimentation rate. The 'specific' immune response is firstly the production of antibodies that usually become detectable in the blood about a week after an effective antigenic stimulant has entered the body, though they may appear later after a first exposure or if the antigen is weak; secondly there may be a cell-mediated immunity such as the delayed hypersensitivity that is detected by the tuberculin-type skin tests.

Detection of infecting organism

The first principle of microbiological diagnosis is thus to detect the infecting organism. A range of methods is available. Direct microscopy of fresh material or of a stained smear of material such as pus or sputum is valuable. It may be possible to detect the antigens of the invading organism by immunological methods — examples of this are the identification of hepatitis B antigen in blood and meningococcal antigen in spinal fluid or blood. And the organism may be cultured by inoculation into culture media.

The clinician is partly responsible for the success of these tests because

no laboratory can detect a microbe that is not present in the specimen; this means first of all that one must think where the microbe might be, and then get as much of the potentially infected material as possible — an example would be to ensure that in a case of pneumonia a specimen of freshly expectorated sputum was collected rather than stale saliva or an almost dry throat swab. Sputum may also fail to yield a significant pathogen because it has been collected after the patient has been treated with a potent antibiotic. Likewise, even in untreated disease, a virus may disappear; there is little point in trying to isolate influenza virus a week after the disease began. Next, one must think what the microbe might be, because this may very much influence how the specimens are handled. A dry cotton-wool swab is lethal to some organisms; air kills some anaerobes; and cultures for some delicate organisms such as gonococci can be set up really successfully only in the clinic or the ward. There is so much to be gained from good specimen collection and so much scope for improvement that, in Appendix C, we have prepared some notes on the collection and transport of the types of specimen that are most often sent to departments of microbiology.

Secondly, the clinician, and those he deputes to collect specimens, need to remember that there are so many tests that could be applied to any specimen that without adequate clinical information it may easily happen that an appropriate test is not performed. Moreover, methods for the culture of some organisms are specialized and time consuming and if the laboratory is to employ its time and resources effectively, it will not perform them unless there is a good reason for doing so — an example might be making cultures for *Bordetella pertussis*.

The sighting or culture of an organism is often immediately meaningful if the specimen is from a fluid that is usually sterile, such as blood and spinal fluid, but other specimens, such as faeces and vaginal secretions, normally contain many bacteria and often other parasites, so that the organisms must be sorted out and identified; this may take days or weeks, and the laboratory may report to the clinician stage by stage as more information becomes available that may be useful in making a diagnosis or planning treatment. There will often be a report on a significant organism, giving its sensitivity to antibacterial drugs. At this stage, or earlier, a discussion between the clinical and laboratory workers may be helpful to both.

Antibody titrations

Antibody titrations by various techniques can be useful, but their limitations must be recognized. Antibody can be detected only if a corresponding antigen is available for laboratory use; and the presence of antibody indicates only that the patient has at some time been exposed to the antigen used, or to one related to it. The fact that antibody develops after the antigenic stimulus may help to make a late diagnosis possible, or to exclude a specific infection if the patient has been ill for some time; it also means that the absence of antibody early in the disease does not

exclude infection with the microbe used in the test. On the other hand if antibody is present it cannot be assumed that it has been evoked during the present illness unless supplementary tests are positive; the most important are examination of a later specimen to determine whether there has been an increasing titre of antibody ('paired sera'), and to test for the type of antibody — IgM suggests that the antibody production is recent.

It has to be remembered that artificial immunization stimulates the production of antibodies, and laboratories should always be given information about this when they are asked to do serological tests.

Drawing conclusions

The limits of accuracy of laboratory work must be borne in mind. Many laboratories now participate in national and other quality-control schemes that help to maintain the reliability of their internal work, but some procedures are inherently more precise than others; for example, most modern methods of microbial culture and identification are specific and reliable but rapid diagnostic methods, such as examination of a stained smear, may be less precise.

Even if the laboratory work is accurate, the limitations on its significance must be recognized. Cultures of what should be sterile fluids, such as blood or spinal fluid, may yield growth only because the specimen was contaminated during collection. Positive cultures from areas with a normal flora or from which specimens are often contaminated also require careful evaluation — a heavy growth is more likely to be of significance than a few organisms. For example, it is now standard practice to indicate whether urine contains more or fewer than 10^5 organisms per ml; fewer organisms than this may indicate only that the microbe is a contaminant. In cases of doubt it may be helpful to know whether there has been an antibody response to the organism.

Negative results may also be difficult to evaluate. Pathogens may be present intermittently so that, for example, blood or faeces may need to be cultured repeatedly. The specimen may have been badly collected or handled, as mentioned earlier, or the laboratory test may be insensitive and, for virus isolation, this is often for ill-understood reasons. But the most common cause of failure to recover an organism in what is eventually shown to be a bacterial disease is failure to collect a suitable specimen.

Even when a pathogenic organism has been isolated from a localized lesion, such as a discharging sinus, it may not be the primary cause, which may be *Mycobacterium* or an anaerobe that is much more difficult to recover. In deeper seated disease the specimen collected may not represent the diseased tissue adequately — thus sputum or a throat swab may contain streptococci or pneumococci when a lung infection is actually due to a virus.

In most instances it is impossible to prove that the organism detected

has caused the patient's disease, because the presence of most pathogenic organisms does not always indicate a clinically significant infection. In the diagnostic process we see a combination of symptoms and signs that point to a particular infection or group of infections; this is why we ask the laboratory to search for them. If one is found it does not prove that the disease is due to it, but only indicates the probability. We may then predict that the patient will respond to a certain drug and if he recovers on that treatment we may be tempted to believe that the presence of the infection is proved because this prediction has been fulfilled; but again the proof is not complete because the patient may have got better spontaneously at that time.

In these diagnostic processes we are drawing on our experience and the experience of others that a certain clinical picture is often associated with a particular microbe; and although these may be very firmly established facts for the population as a whole, they may or may not be true for the individual patient. The difficulties become even greater when what may be rarer forms or complications of the disease occur — a patient may have influenza and proven influenza-virus infection, but his encephalitis might be due to an unrecognized syphilitic infection.

The only wise course is to use every scrap of information available, to check the plausibility of laboratory findings against previous clinical experience and *vice versa* and, until the patient's discharge and after, to 'think it possible that you may be mistaken'.

Uses, abuses, and failures

The value of microbiological tests has already been indicated and they can greatly increase the precision of diagnosis by identifying the probable cause; by relating his clinical diagnosis to the results of laboratory tests a clinician learns to recognize infections more accurately and can take more confident action in the future.

Some abuses of the laboratory have been mentioned already but others include the collection of unnecessary specimens 'for completeness'; the collection of unnecessary specimens sometimes leads to the error of treating the laboratory report instead of the patient. An error opposite to this is the collection of appropriate specimens and then deliberately or carelessly ignoring the results of tests done on them.

A major reason for failing to get help from the microbiologist is failure of communication; for example, clinical information may not be supplied or the laboratory may fail to act on it; the microbiologist and clinician may not get in touch personally to exchange details and background information that they have about a difficult case and which should be combined and fully discussed if the patient is to receive the full benefit of what is available for him.

2

Antimicrobial drugs

The purpose of this chapter is to describe antibacterial agents mainly in terms of their antibacterial and pharmacological properties. We confine ourselves to agents that are, or are to be, commercially available. A full discussion of the mode of action of antibacterial drugs is beyond the scope of this book, but will be found in a book by Gale *et al.* (1972). Essential reading for those interested in antimicrobial chemotherapy is *Antibiotic and chemotherapy* (Garrod, Lambert and O'Grady, 1973).

For the clinician, antibacterial agents are perhaps most usefully classified in terms of their spectrum of antibacterial activity. They fall into seven broad groups. Group 1 consists of agents active only against Gram-positive organisms and Gram-negative cocci, Group 2 of those acting mainly on Gram-negative bacilli, except the anaerobes which are acted on by Group 3. Group 4 is a large group of agents with broad-spectrum antibacterial activity, Groups 5–7 consist of agents active on mycobacteria, fungi, and viruses. Agents active against the protozoa are discussed in Chapter 20. It must be emphasized that not all antibiotics in each group are active against all organisms in it. Some organisms are intrinsically resistant to some agents and others may acquire resistance.

Group 1. Agents active mainly against Gram-positive organisms and Gram-negative cocci

The organisms that are sensitive to the members of this Group may perhaps best be defined as all bacteria that are not aerobic Gram-negative bacilli. Thus apart from the organisms implied by the Group heading —

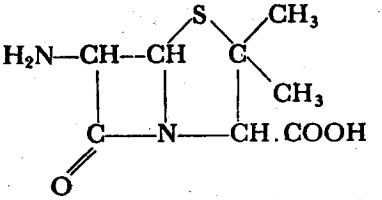
Table 2.1 GROUP 1. Important antibacterial agents active against Gram-positive organisms and Gram-negative cocci

Penicillins	Macrolides and similar agents	Peptides	Miscellaneous
Sensitive to staphylococcal penicillinase			
Benzylpenicillin	Erythromycin	Tyrocidine	Vancomycin
Phenoxymethylpenicillin	Lincomycin	Gramicidin	Spectinomycin
Phenethicillin	Clindamycin	Bacitracin	Fusidic acid
Resistant to staphylococcal penicillinase			
Methicillin			
Cloxacillin			
Flucloxacillin			

Staphylococcus, Streptococcus, Bacillus, Corynebacterium, Actinomyces, Clostridium, and *Neisseria* — it is also convenient to include the spiral organisms. Table 2.1 lists the useful agents.

Penicillins

All penicillins act by inhibition of bacterial cell-wall synthesis. They are derivatives of 6-aminopenicillanic acid:



Penicillins are non-toxic drugs, except when injected directly into the cerebrospinal fluid or given in vast doses of 50–100 megaunits per day to patients with renal failure so that concentrations in spinal fluid rise to toxic levels. Rarely, benzylpenicillin — and methicillin — may cause nephritis. In contrast, hypersensitivity to penicillins is common, its manifestation ranging from acute anaphylaxis — fortunately rare — angioneurotic oedema, and serum sickness to skin rashes and drug fevers. About 5 per cent of patients given a penicillin develop a skin rash.

Group-1 penicillins fall into two subgroups. The first comprises benzylpenicillin, phenoxymethylpenicillin, and phenethicillin. These are susceptible to staphylococcal β-lactamase (penicillinase); production of this enzyme is the most common mechanism of penicillin resistance among staphylococci. Benzylpenicillin is also destroyed by acid, and is therefore usually given by injection, but the phenoxypenicillins are acid stable and can thus be given orally. Phenethicillin is the better absorbed, but is more highly bound to protein. Like all penicillins these drugs are widely distributed, but they do not cross uninflamed meninges. They are rapidly excreted in the urine and to a much smaller extent in the bile. Urinary excretion is blocked by probenecid.

The second subgroup of Group-1 penicillins consists of methicillin, and a series of isoxazolyl penicillins, including cloxacillin, flucloxacillin, and oxacillin, specifically developed because of their resistance to staphylococcal β-lactamase and, thus, their activity on penicillin-resistant staphylococci. However, staphylococci may be resistant to these, and to all other penicillins, by a non-enzymic intrinsic mechanism. Other compounds such as nafcillin, diphenicillin, and quinacillin are also penicillinase resistant and have had limited trials. Methicillin need no longer be used because it is not very active and can be given only by injection; the rest can be given orally. Flucloxacillin is considered by many to be the drug of choice in this group because of its better absorption. In terms of distribution, excretion and toxicity, the agents in this subgroup are typical penicillins.

Macrolides

Antibiotics in this large group all have a macrocyclic lactone ring attached to various sugars. All inhibit protein synthesis on the ribosomes by preventing translocation of peptide chains. Three, oleandomycin, spiramycin, and erythromycin have reached the market but the last, being more active, is the only one that has had considerable use. Spiramycin, however, is used for the treatment of toxoplasmosis. Erythromycin has broad activity within Group 1, but resistance emerges among staphylococci and streptococci if the drug is extensively used in an institution. Erythromycin base is acid labile, and it is thus given orally as a stearate, ethyl succinate, or estolate. The stearate dissociates in the intestine, liberating the base; the ethyl succinate is hydrolysed to erythromycin base after absorption, and the estolate dissociates to the propionyl ester which is absorbed and then hydrolysed to active drug. These factors affect the dosage needed to produce effective blood concentrations, but if these are achieved all seem to be clinically effective. For parenteral use, the glucoheptonate and lactobionate of erythromycin are available but intramuscular injections are painful and should be avoided if possible; intravenous administration causes phlebitis. The drug is well distributed but does not gain access to the cerebrospinal fluid. It is, however, concentrated in the prostate, an unusual and useful property. The drug is excreted in urine and bile, and it is also probably metabolized. Erythromycin itself is remarkably non-toxic, but the estolate is hepatotoxic, especially after prolonged use, and if this form has to be given, courses of more than 14 days should be avoided.

Lincomycins

The two available drugs, lincomycin itself and clindamycin, are chemically unrelated to other antibiotics. The activity on Group-1 organisms is broad, with the exception of neisseriae which are relatively resistant. Lincomycins inhibit protein synthesis on the ribosomes by preventing translocation of peptide chains. Of numerous derivatives, only lincomycin itself and clindamycin are well absorbed orally and although food diminishes the absorption of the former it does not appear to affect the latter. Both drugs can be given parenterally, clindamycin as its phosphate, and both are widely distributed in the body, except to the cerebrospinal fluid, and achieve significant concentrations in bone. They are largely excreted via the bile. Although diarrhoea is common, the only significant toxic effect of the lincomycin group appears to be pseudomembraneous enterocolitis which varies in severity and is sometimes fatal, particularly in the elderly. This condition is associated with a variety of antibiotics, but in some parts of the world the lincomycins appear to induce it relatively frequently.

Peptides

Various peptides, particularly tyrocidine, gramicidin, and bacitracin, are active against Gram-positive organisms. All these drugs are too toxic for parenteral use and are therefore used in topical preparations.

Miscellaneous

Vancomycin

Vancomycin, which is unrelated to other antibiotics and which has activity only on Gram-positive organisms, acts by inhibiting bacterial cell-wall synthesis. It is not absorbed from the gut and, because of its irritant properties, has to be given by intravenous injection. The drug is excreted almost entirely by the kidney, and single doses of 500–1000 mg in anephric patients produce effective serum concentrations for about a week because it is not removed by dialysis. Thrombophlebitis is common after repeated injections, but the most serious toxic effect is deafness, associated with serum levels in excess of about 40 mg per litre (μg per ml).

Spectinomycin

Spectinomycin is an aminocyclitol which is in fact broad spectrum but this is limited by the fact that resistance emerges rapidly during treatment for most organisms except gonococci. It is not absorbed from the gut and is thus given by intramuscular injection. Because it has largely been used for the single-dose treatment of gonorrhoea little is known about its pharmacokinetic properties, but it appears to be remarkably non-toxic.

Fusidic acid

Fusidic acid is a steroid-like antibiotic that is active mainly on staphylococci. Unfortunately resistance emerges rapidly, and the drug is thus usually used in combination with another agent. Like macrolides and lincomycins it prevents translocation of peptide chains on ribosomes. It is well absorbed after oral administration, and well distributed except to the cerebrospinal fluid. It is extensively metabolized, and the metabolites are excreted in the bile. Apart from gastrointestinal upset the drug has no common toxic effects. Rapid administration of the intravenous preparation may lead to haemolysis.

Choice of antibiotic from Group 1

Because of their lack of toxicity, penicillins are the drugs of choice for the treatment of infections due to Gram-positive organisms and Gram-negative cocci, with the exception of those in hypersensitive patients, those due to insensitive strains, and those in which the particular pharmacological or antibacterial properties of other drugs may offer an advantage.