An Outline of
BACTERIOLOGY AND IMMUNITY

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INTRODUCTION

SINCE the turn of the century, the laboratory has played a progressively more important part in the investigation of disease processes, until it is now an essential part of hospital practice. Such integration has a great deal to recommend it. But it has its obvious dangers in that there is always a possibility that the more obviously utilitarian side of the laboratory procedures may be over-emphasized to students, not only at the bedside but also in the lecture room.

To some extent this has occurred in the case of bacteriology, where there has always been, and indeed still is, a tendency on the part of both clinician and the hospital bacteriologist to stress the importance of the part played by the laboratory in the diagnosis of disease. This, in turn, is reflected in the teaching of bacteriology which generally lays such emphasis on the methods used for the isolation and identification of the larger organisms that important subjects such as virus diseases, immunity and epidemiology are either omitted altogether or relegated to the background.

For many years, so one-sided an approach was perhaps justifiable. Knowledge of other aspects of the subject was rapidly accumulating it is true, but much of it was controversial and unsystematized. But within the past ten years two events in particular have occurred which make it doubtful whether so narrow an outlook is now permissible: the introduction of modern chemotherapy, with all its many implications, and the spectacular advance that has been made in our knowledge of viruses. In addition, much has been learned of the sources and methods of transmission of respiratory and wound infections, of the behaviour of micro-organisms in the community, of the part played by bacterial antigens in infection and immunity, and of mass immunization.

These and many other advances constitute a body of knowledge far removed from the comparatively narrow confines of diagnostic bacteriology, which is of equal, if not greater, importance to a student of disease. Without it he cannot hope to arrive at an understanding of the genesis of bacterial and virus infection, nor can he institute methods for their prevention or apply the new chemotherapy with its many necessary safeguards. But quite apart from its direct application to the prevention and cure of disease at the present time, such a background will be essential if the student is to assess and apply any advances that may come in the future.

The greater part of this book—which is based on the course of lectures given to clinical students at St. Thomas's Hospital—attempts to impart this wider view of bacteriology and immunity. It is therefore, in essence, an exposition of the relationship of micro-organisms to man in both health and disease; where, it should be added, the viruses are accorded equal status with the bacteria. But in order to impress on the student that much of this is of practical importance, appendices dealing with this aspect have been added to many of the chapters. Systematic and diagnostic bacteriology is purposely relegated to a separate and distinct section in which only information likely to be of use to a practitioner is given, and as shortly and concisely as possible. This procedure has been adopted because these subjects can only be learnt by prolonged experience in a routine laboratory, and it is quite impossible for medical students to acquire more than a very superficial knowledge of these matters in the limited time at their disposal for laboratory work. For the same reason, no attempt has been made to describe the more elaborate technical procedures employed in bacteriological laboratories. Accordingly, much that is of interest and importance to the practising bacteriologist has been omitted.

While the book was being prepared, two important changes were suggested by the International Committee on Bacteriological Nomenclature The first concerns the name *Bacterium* hitherto employed by most English writers to denote a genus which includes three distinct organisms, *Bact. coli*, *Bact. friedländeri* and *Bact. aerogenes*. The use of the term *Bacterium* to denote a genus has, however, been declared invalid and the suggestion put forward that one genus, *Escherichia*, should comprise organisms formerly known as *Bact. coli* and another genus, *Klebsiella*, should include the remaining two organisms.

The second change concerns the genus *Haemophilus*. The type species is *H. influenzae* and *H. pertussis*, the organism associated with whooping cough, has generally been placed in this genus. This organism does not require either the V or X growth factors and if this requirement is retained as the hall-mark of *Haemophilus*, the creation of a new genus to include *H. pertussis* is obviously a necessity. *Bordetella* has been suggested for this purpose.

The new taxonomy may be unfamiliar to many English bacteriologists but because it is essentially more reasonable and in better accord with the facts than the old, it will almost certainly be adopted in the future. For these and other reasons it has been employed in this work.

It would be foolish to pretend that, when dealing with so enormous a subject as modern bacteriology and immunity, any one person can have personal acquaintance with more than a very small part of it. For this

reason I have had to draw heavily on the knowledge of others, but particularly Topley and Wilson's *Principles of Bacteriology and Immunity*, Dubos's *Bacterial and Mycotic diseases*, River's *Virus and Rickettsial infections of Man*, and Bedson, Downie, MacCallum and Stuart-Harris's *Virus and Rickettsial diseases*. My debt to these authors is very great and no one is more conscious of it than myself.

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CONTENTS

Chapter One

THE CLASSIFICATION AND MORPHOLOGY OF MICRO-ORGANISMS

DURING the latter half of the seventeenth century a Dutchman, Antony van Leeuwenhoek, employed primitive microscopes of his own design and manufacture to examine such fluids as rainwater which had been allowed to stand in an earthenware pot, or water in which peppercorns had been steeped. In some of them he could see minute bodies which were quite invisible to the naked eye. They were actively motile and, for this reason, van Leeuwenhoek concluded that they were alive. For many years little notice seems to have been taken of these observations, but when compound microscopes were first produced during the 1830's, it began to be realized that large numbers of living particles of this description are, in fact, constantly present in the atmosphere, the soil, water containing decaying vegetable matter, and in putrefying carcasses.[1]

Most of these particles are minute, unicellular forms of life varying greatly in shape and size, for which the all-embracing term "micro-organism" is frequently employed. Their true significance was not appreciated until about a century ago when Louis Pasteur began to study the mechanism of fermentation, that is, the conversion of the sugar in barley or grapes into alcohol in the manufacture of beer and wine. Hitherto it had been assumed that this was a purely chemical reaction but Pasteur showed clearly that it was due to the formation of enzymes by micro-organisms in the course of growth and multiplication.[2]

This entirely new interpretation provoked a great deal of opposition and it accordingly became necessary for Pasteur to embark on a long series of experiments to identify the source of the micro-organisms which are responsible. As a result it was proved conclusively that they are frequently present in the materials that subsequently undergo fermentation, in the water added to them, or even in the atmosphere of the brewery or still-room. Micro-organisms, therefore, never arise spontaneously; they are

[1] DOBELL, C. 1932 *Antony van Leeuwenhoek and His Little Animals.* Staples Press, London.

[2] PASTEUR, L. 1879. *Studies on Fermentation.* Trans. F. Faulkner and D. C. Robb. Macmillan, London.

living forms to which the Lamarckian doctrine of the continuity of the germ plasm applies as much as to larger animals.

While these studies were in progress, large square-ended micro-organisms were seen by Davaine and others in the circulating blood of sheep suffering from anthrax. For a long time there was doubt whether they were the cause or the consequence of the disease and it was left to Robert Koch to demonstrate clearly that these organisms are, in fact, the responsible agents. Soon afterwards, in 1881, Koch turned his attention to tuberculosis in man and in the course of only a few months not only identified the organism which causes this disease, but cultivated it and produced experimental tuberculosis in laboratory animals.[1]

This was the first human infection clearly shown to be due to micro-organisms and so momentous a discovery naturally attracted a great deal of attention. Before very long, others attempted to prove that micro-organisms are responsible for many different pathological conditions. Difficulties were quickly encountered because micro-organisms are extremely widespread, so that they might not only be present in the lesions without necessarily being responsible for them, but several different species might be found at the same time. To prove that a particular micro-organism found in a pathological condition is its cause and not an opportunist invader which has taken advantage of local alterations in the tissues to settle there is not always easy. Criteria had therefore to be evolved which organisms must fulfil before being accepted as the causative agents of disease processes in which they are found. Such criteria had actually been laid down by Jakob Henle long before the part played by micro-organisms in disease had been established, but they were adopted by Robert Koch and are usually referred to as Koch's postulates. They are three in number:

(1) The organism must be found in all cases of the disease under discussion and its distribution in the body should be in accordance with the lesions observed.

(2) The organism should be cultivated outside the body of the host in pure culture for several generations.

(3) The organism isolated in this way should reproduce the disease in other susceptible animals.

Before the turn of the century, micro-organisms responsible for many human and animal diseases had not only been described but had been clearly shown to fulfil Koch's postulates.

While these advances were being made, study of soil, air and the water of lakes and streams showed that they all contain many different species of micro-organisms some of which, particularly those in the soil, are of

[1] KOCH, R. 1882. Berlin klin. Wschr., **19**, 221.

very considerable economic importance. All of them obtain their foodstuffs from the substances present in the situations in which they are normally found, and are usually referred to as free-living organisms. For many reasons, most free-living species cannot survive or multiply in human or animal tissues. They are therefore harmless and of little direct importance in medicine.

Nevertheless, some at least of the free-living species resemble closely those capable of survival and multiplication in mammalian tissues and it is extremely probable that the latter have, in the course of evolution, been derived from the former. In the process they have lost the ability to reproduce themselves in soil, water, etc., and have become parasites, completely dependent on a much larger form of life usually referred to as the host. This property is best defined as *infectivity*. But survival and multiplication in the tissues need not produce disease, for many species may parasitize the skin or the mucous membranes of man and animals for very long periods of time without causing any changes indicative of their presence; such organisms are generally referred to as *commensals* although some authors describe them as *saprophytes*.

The organisms which produce disease are able to do so because they possess certain attributes of which commensals and free-living species are devoid. What these attributes may be, and the particular way in which they assist the organisms to produce disease, are discussed later, but organisms possessing them are usually described as *pathogens*. But they exhibit wide variations in ability to produce so severe an infection as to cause death of the host. This variation is best described in terms of *virulence*. Highly virulent organisms produce marked symptoms and frequently death of the host, whereas those of low virulence may be incapable of causing more than a fleeting illness.

CLASSIFICATION AND NOMENCLATURE OF MICRO-ORGANISMS

Micro-organisms capable of survival as parasites in human or animal tissues vary greatly in size, appearance, mode of reproduction and biochemical activities, but bacteriology concerns itself only with the smaller and simpler forms of life. They fall into three main subdivisions.

Fungi are branching filaments. The true fungi may possess a rudimentary sexual apparatus but those of medical importance are *fungi imperfecta*, which reproduce themselves by a completely asexual process described in more detail in this chapter. Fungi can all multiply readily in artificial media provided they contain the necessary raw materials.

Bacteria are unicellular organisms which show no signs of sexual conjugation and multiply by division or, as it is usually called, binary fission. They are all sufficiently large to be visible with the higher powers

of the optical microscope. Like the fungi, the great majority can be cultivated away from the tissues of the host in artificial media, that is to say, in solutions of protein, carbohydrate, etc.

Viruses and rickettsiae are much smaller, the majority being too small for resolution by the optical microscope. Their mode of reproduction differs in a number of respects from that of bacteria and fungi. But their chief characteristic is their extreme degree of parasitization. They can only multiply in living cells because they are quite unable to utilize the foodstuffs of artificial media.

Bacteriology also concerns itself with **Bacteriophages**. These are parasites but their hosts are bacteria. When added to organisms in culture, they bring about disruption of the bacterial cells. At one time referred to as the Twort d'Herelle phenomenon, there was, for a time, acute controversy as to what is responsible, but there is no doubt that it is due to the growth of viruses in bacterial cells.[1]

Nomenclature. The bacteria and fungi can be classified into families, genera and species on the basis of their morphology, staining reactions and behaviour towards chemical compounds. They have, accordingly acquired binomials based on the Linnaean system of nomenclature in which the first name denotes the genus and the second the species. The rickettsiae have also been given Linnaean names, most of which have obtained general approval. But although such a system of nomenclature has been proposed for the viruses, it shows little sign of adoption, and most authors adopt the expedient of naming each virus according to the disease for which it is responsible.

The organisms which are pathogenic for man, and to which reference is made in this book, are listed in Table 1.1, using the Linnaean names generally employed in this country. Other names by which they are sometimes known are also given. The larger organisms are grouped according to their morphology and Gram reaction, a test referred to in detail later in this chapter. Each group corresponds to one or other of Chapters 15–23 and further details such as the geographical distribution of the organisms, their ability to produce disease, and the methods employed to isolate and identify them will also be found in these chapters.

THE MORPHOLOGY AND MODE OF REPRODUCTION OF MICRO-ORGANISMS

In all the higher forms of life the demarcation of genera and species depends almost entirely on morphology. Because they are all large enough for study under the higher powers of the optical microscope, this also

[1] TWORT, F. W. 1915. Lancet, **2**, 1241; D'HERELLE, F. 1917. Compt. rend. Acad. Sci., **165**, 373.

TABLE 1.1

Names and synonyms of the commoner human pathogenic and commensal organisms

Linnaean name employed in this book	*Other names frequently used in practice*	*Names sometimes employed*	*Diseases for which the organisms are responsible*
	Gram-positive cocci		
Staphylococcus			
Staph. aureus	*Staph. pyogenes*		Pyogenic infections Food poisoning
Staph. albus			
Staph. citreus			
Streptococcus			
Strep. pyogenes	Group A of Lancefield	*Beta* haemolytic streptococci	Tonsillitis and scarlet fever
		Streptococcus haemolyticus	Pyogenic infections
		Strep. longus	Erysipelas
Strep. agalactiae	Group B		Bovine mastitis
Strep. equi	Group C		Strangles of horse
Strep. faecalis	Group D Groups E, F, G, H, K, L, M.	Enterococci	
Strep. lactis *Strep. cremoris*	Group N		
Strep. viridans		*Alpha* haemolytic streptococci	Subacute bacterial endocarditis
		Strep. brevis	
		Strep. salivarius	
?	Non-haeomolytic streptococci	*Gamma* haemolytic streptococci	
Strep. putridus	Anaerobic streptococci		Puerperal and wound infections
Pneumococcus	*Strep. pneumoniae*	*Diplococcus pneumoniae*	Lobar pneumonia
	Gram-negative cocci		
Neisseria			
N. gonorrhoeae	Gonococcus		Gonorrhoea
N. meningitidis	Meningococcus	*Diplococcus intracellularis meningitidis*	Cerebrospinal meningitis
N. flavescens			Cerebrospinal meningitis
N. catarrhalis			
N. pharyngis sicca			
N. flava			
Veillonella			
V. alkalescens			
V. parvula			

Linnaean name employed in this book	*Other names frequently used in practice*	*Names sometimes employed*	*Diseases for which the organisms are responsible*
	Gram-positive bacilli		
Clostridium			
Cl. botulinum			Botulism
Cl. tetani	*B. tetani*	Tetanus bacillus	Tetanus
Cl. welchii	*Cl. perfringens*	Welch's bacillus	Gas gangrene Food poisoning
Cl. septicum		Vibrion septique	Gas gangrene
		B. odedematiens maligni	Gas gangrene
Cl. oedematiens		*B. oedematis sporogenes*	
+ other species			
Bacillus			
B. anthracis		Milzbrand bacillus	Anthrax, wool-sorters' disease
B. subtilis			Food poisoning
+ other species			
Corynebacterium			
C. diphtheriae	*B. diphtheriae*	Klebs Loeffler bacillus	Diphtheria
C. xerosis		Diphtheroids	
C. hofmanni		Diphtheroids	
C. acnes			Found in acne
C. ovis	Preisz Nocard bacillus		Chronic suppuration in horses
C. pyogenes			Chronic suppuration in cattle, sheep, goats, etc.
C. equi			Infection of foals
Mycobacterium			
Myco. leprae	*B. leprae*		Leprosy
Myco. tuberculosis	*B. tuberculosis*	Koch's bacillus	Tuberculosis
Myco. smegmatis		Smegma bacillus	
Myco. phlei		Timothy grass bacillus	
Myco. stercoris		Mist bacillus	
Myco. johnei			Johnes disease of cattle
Lactobacillus			
L. acidophilus	Döderlein's bacillus		
L. odontolyticus			? Caries of teeth
L. bifidus			
Fusiformis			
F. fusiformis			Vincent's angina
F. necrophorus			Infections of intestinal tract

Linnaean name employed in this book	*Other names frequently used in practice*	*Names sometimes employed*	*Diseases for which the organisms are responsible*
	Gram-negative bacilli		
Proteus			
Proteus vulgaris			Wound and kidney infections
Proteus morgani			Diarrhoea and urinary infections
Escherichia			
E. coli	*Bact. coli*	*B. coli*	Urinary tract infections Gastro-enteritis in children
Klebsiella			
K. pneumoniae	*Bact. friedländeri*	Friedländer's bacillus *B. mucosus capsulatus* *Pneumobacillus*	Occasionally in pneumonia
K. aerogenes	*Bact. aerogenes*	*Aerobacter. B. lactis aerogenes*	
Salmonella			
Salm. typhi	*Eberthella typhi*	*B. typhosus*	Typhoid fever
Salm. paratyphi A also *B*			Paratyphoid fever
Salm. typhi-murium		*B. aertrycke*	Food infection
Salm. enteritidis + many other species		Gaertner's bacillus	Food infection
Shigella			
Sh. shigae	*Sh. dysenteriae*	*B. dysenteriae*	Dysentery
Sh. flexneri		*B. dysenteriae*	Dysentery
Sh. boydi			Dysentery
Sh. sonnei			Dysentery
Sh. schmitzi			Dysentery
Pseudomonas			
Ps. pyocyanea	*Ps. aeruginosa*	*B. pyocyaneus*	Wound infection
Pfeifferella			
Pf. mallei			Glanders in horse and man
Pf. whitmori		*B. pseudomallei* *B. whitmori*	Melioidosis
Pasteurella			
Past. pestis		*B. pestis*	Plague
Past. septica			Haemorrhagic septicaemia of cattle
Past. pseudotuberculosis			Infection of rabbits and guinea-pigs
Haemophilus			
H. influenzae		*B. influenzae* Pfeiffer's bacillus	Meningitis

Linnaean name employed in this book	*Other names frequently used in practice*	*Names sometimes employed*	*Diseases for which the organisms are responsible*
H. aegypticus		Koch Weeks bacillus	Eye infections
H. influenza suis			Swine influenza
H. ducreyi		Ducrey's bacillus	Soft sore
Bordetella			
Bord. pertussis	*H. pertussis*		Whooping cough
Bord. bronchisepticum			Respiratory infection in animals
Brucella			
Br. melitensis		*M. melitensis*	Malta fever
Br. abortus		*B. abortus*	Undulant fever
Br. suis			Undulant fever
Br. tularensis			Tularemia
Bartonella			
Bartonella bacilliformis			Oroya fever Verruga peruana
Moraxella			
M. lacunata		Morax-Axenfeld bacillus	Angular conjunctivitis
	Vibrios		
Vibrio			
V. cholerae		Comma bacillus	Cholera
	Branching filaments and fungi		
Actinomyces			
Actino. israeli		Ray fungus	Actinomycosis
Actino. bovis			Actinomycosis of cattle
Actino. madurae	*Streptothrix madurae*		Madura foot
Actino. muris	*Streptothrix muris ratti*	*Streptobacillus moniliformis*	Rat-bite fever
Actino. gypsoides			Bronchopneumonia
Erysipelothrix			
Ery. rhusiopathiae		*Ery. erysipeloides* *B. rhusiopathiae* *Erysipelothrix porci* *B. erysipelatis suis*	Erysipeloid of Rosenbach
Microsporum			
M. audouini			
M. canis			
Trichophyton			Ringworm
Tr. interdigitale			
Tr. rubrum			
Tr. mentagrophytes			Ringworm and tinea pedis
Tr. discoides			
Epidermophyton			
E. floccosum			Dhobie itch

Linnaean name employed in this book	*Other names frequently used in practice*	*Names sometimes employed*	*Diseases for which the organisms are responsible*
Sporotrichum Sp. schenki			Skin infections
Candida albicans	*Monilia*		Infections of mouth
Cryptococcus neoformans			Meningitis (torulosis)
Blastomyces dermatitidis			Granuloma of skin and lungs
Histoplasma capsulatum			Histoplasmosis
Coccidioides immitis			Coccidioidomycosis San Joachin fever
	Spirochaetes		
Borrelia			
Borrelia vincenti			Vincent's angina
Borrelia recurrentis			Relapsing fever
Borrelia duttoni + other species			Relapsing fever
Treponema			
Tr. pallidum	*Spirochaeta pallida*		Syphilis
Tr. pertenue			Yaws
Tr. pinta			Pinta or Mal de los pintos
Leptospira			
L. icterohaemorrhagiae	*Spirochaeta icterogenes*		Weil's disease } Leptospirosis
L. canicola			Spirochaetal jaundice
L. grippotyphosa + other species			
Rickettsia	**Rickettsiae**		
R. prowazeki			Epidemic typhus
R. mooseri			Endemic typhus
R. tsutsugamushi			Scrub typhus
R. rickettsi	*R. typhi*		Rocky Mountain spotted fever
R. quintana			Trench fever
R. burneti			Q fever
Group 1	**Viruses**		
Psittacosis (ornithosis)			Psittacosis
Trachoma			Trachoma
Inclusion blepharitis			Inclusion blepharitis
Lymphogranuloma inguinale			Lymphogranuloma

Linnaean name employed in this book	*Other names frequently used in practice*	*Names sometimes employed*	*Diseases for which the organisms are responsible*
Group 2			
Smallpox	Variola		Smallpox
Alastrim			Alastrim
Chickenpox	Varicella		Chickenpox
Herpes zoster			Herpes zoster
Cowpox	Vaccinia		Cowpox
+ other pox diseases			
Group 3			
Influenza A			Influenza
Influenza B			Influenza
Influenza C			Influenza
Mumps			Mumps
Newcastle disease of fowls			
Group 4			
St. Louis encephalitis			Encephalitis
Japanese B encephalitis			
Equine encephalomyelitis			
Russian spring-summer encephalitis			
Lymphocytic choriomeningitis			Benign lymphocytic choriomeningitis
Bwamba encephalitis			Encephalitis
Mengo encephalitis			
Ilheus encephalitis			
Murray valley encephalitis			
+ other varieties			
Group 5			
Yellow fever			Yellow fever
Rift Valley fever			Rift Valley fever
Dengue			Dengue
Sandfly fever			Sandfly fever
Group 6			
Poliomyelitis			Poliomyelitis
Coxsackie virus			Bornholm disease
			Epidemic herpangina
			Aseptic meningitis
Others			
Infective hepatitis			Infective hepatitis
Serum hepatitis			Serum hepatitis
Measles			Measles

Linnaean name employed in this book	*Other names frequently used in practice*	*Names sometimes employed*	*Diseases for which the organisms are responsible*
German measles	Rubella		German measles
Common cold			Common cold
Rabies			Rabies or hydrophobia
Primary atypical pneumonia			Primary atypical pneumonia
Herpes simplex			Herpes
Molluscum contagiosum			Molluscum contagiosum
Warts			Warts
Adenoidal-pharyngeal-conjunctival viruses			Infections of respiratory tract and eyes
Gastro-enteritis			Gastro-enteritis

applies to a very large extent to the bacteria and fungi. But classification of the viruses and rickettsiae by such methods has not yet progressed very far because extremely little was known of their size, shape or mode of reproduction until the invention of the electron microscope quite recently. Nevertheless, morphology of micro-organisms is a matter of considerable importance in bacteriology.

The Structure and Reproduction of Bacteria

Much may be learned about the morphology of bacteria from preparations in which they are fixed to the surface of microscope slides and stained by a simple watery stain, such as methylene blue. It is, of course, necessary to use the higher powers of the optical microscope. A unit of measurement is also advisable in order to facilitate comparison between different species. That which is generally employed in bacteriology is one thousandth of a millimetre and is known as one micron or 1·0μ. This may be further subdivided into 1000 millimicrons.

Bacteria are of varying shapes and sizes. The *cocci* are spherical, generally about 0·8–1·0μ in diameter, although some species may be oval with rather pointed ends. The *bacilli* are elongated, cylindrical forms, varying in length according to species, from about 1μ–8μ. Their width may also vary considerably. They may be straight or slightly curved, while the ends may be square, rounded or pointed. *Vibrios* are bacilli with a much more pronounced curvature so that they resemble commas. *Spirochaetes* are spiral organisms superficially resembling corkscrews.[1]

The simple cylinders or spheres which constitute the bacteria consist

[1] Low, R. C. & Dodds, T. C. 1947. *Atlas of Bacteriology*. Livingstone, Edinburgh.