Microbes, Man and Animals

The Natural History of Microbial Interactions

Alan H. Linton

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Foreword

This book grew out of a course on Pathogenicity and Epidemiology taught to Honours Microbiology students at Bristol by the late Dr Anna Mayr-Harting and myself. Until recently very few texts brought these subjects together in a form readily available to students, and the need prompted us to consider publishing a joint work. Sadly, Dr Harting did not survive long enough to contribute more than a few notes and, in consequence, it has taken much longer to complete than was originally anticipated. The book is now presented in the hope that it will fill a gap in the student literature.

In order to widen the coverage of the subject a number of colleagues have kindly contributed specialist articles. In spite of this the text does not claim to be comprehensive but rather a collection of subjects selected to illustrate principles and the author's own interests. 'I have gathered a bouquet of flowers from other men's gardens: naught but the string is my own' (Montaigne).

The book is aimed at science microbiology undergraduates but since examples are taken from the medical and veterinary fields, both undergraduate and post-graduate students of these professions should also find it useful.

ALAN H. LINTON
1982

Introduction

> Infection must be considered as a struggle between two organisms . . . the parasite and its host. This brings about adaptations on both sides.
>
> METCHNIKOFF, 1891

Micro-organisms are ubiquitous but one of their major habitats is in association with other living organisms. Animals raised conventionally are exposed to micro-organisms from the time they leave the sterility of the uterus or egg. Most of these contaminants are rapidly eliminated from the animal's body but some are able to colonize the young animal or chick and persist for part or the whole of its life. These associations are not solely a matter of contamination, i.e. one of mutual indifference, but involve specific interactions creating the so-called host–parasite relationship.

Both animals, and the micro-organisms that colonize them, are dynamic systems capable of independent existence. Gnotobiotic animals (Chapter 2), for instance, removed aseptically from the uterus of the dam in the late stages of pregnancy, can be raised independent of micro-organisms. Similarly gnotoxenic chicks can be raised after hatching under sterile conditions. These 'sterile' animals can survive for long periods of time and grow; a few species have even been successfully bred under aseptic conditions. They exhibit only minor differences in physiological function from those raised conventionally.

Micro-organisms, too, can follow an independent existence. The majority of micro-organisms able to colonize the animal body can be propagated in pure culture, i.e. axenic culture, on inanimate media, and this can continue indefinitely under artificial conditions.

It is therefore not unexpected that when the two independent biological systems live in association with each other they will interact to a greater or lesser degree. The degree of interaction will vary according to the nature and biological status of each. At one end of the spectrum are those associations in which only minor adaptations are experienced by each partner and this results in an ideal state of parasitism; at the other extreme are associations which damage or even kill one or other of the partners.

Micro-organisms which damage the host in the course of their association are recognized as pathogens. Microbial disease is the consequence of damage to the host resulting from the interaction and a wide range of clinical response is experienced. The level of the interaction and the extent of the resultant damage

depends on both the virulence of the pathogen and the host's defences. From the standpoint of the pathogen, its ability to colonize and damage the host depends, at least in part, on how well it can adapt its physiology to the host's environment. Adaptations are necessary to overcome, or to come to terms with, the anatomical structures and physiology of the defence mechanisms of the host. If the pathogen can overcome the host defences, the host will be damaged and may not survive; if, on the other hand, the defences overcome the pathogen, the micro-organism may fail to establish itself in the host and die. The sequence of events occurring throughout the interaction is the subject of pathogenesis; the ensuing clinical manifestations constitute the disease syndrome.

A study of pathogenesis therefore must take into account the intrinsic biological properties of both host and parasite, and their responses to each other during interaction. Ideally, since each adapts to the sequence of modifications consequent upon their interaction, a study of the two in association must be attempted (Chapter 3). This approach is more difficult than studying the host and parasite independently but the *in vivo* approach, developed over the last 25 years, has been richly rewarding. It has been possible to identify virulence factors which arise only *in vivo*, to unravel the biochemical basis of certain specific mechanisms and other aspects of the host–parasite interaction.

Most texts are written either from the medical or veterinary standpoints. This book is an attempt to present an integrated account of our knowledge at the present time bringing together information and examples from the medical and veterinary fields. The text is divided into three parts.

Part I is concerned with interactions between the individual host and the parasite. The emphasis throughout the book is on the parasite but it is not possible to treat this in isolation and frequent reference is made to the host's contribution to the interaction. The first chapter considers some of the factors essentially dictated by the host. It includes a brief description of the various host defences and responses to infection, together with a brief consideration of differences in susceptibility of various animal hosts (host-specificity), differences in susceptibility between individuals of the same animal species, and reasons why certain host tissues become preferentially colonized by pathogenic organisms during the course of an infection (tissue-specificity).

It is against this background that the role of the micro-organism is considered *in extenso*. Most micro-organisms are harmless to animals and man: indeed many are highly beneficial, if not essential, to the host or in the natural cycles of nature. The autotrophic micro-organisms which utilize inorganic chemicals as sources of energy and nutrients are completely independent of organic molecules and, therefore, of living hosts for survival, and are never pathogenic. The heterotrophic micro-organisms, in contrast, require organic nutrients of differing degrees of complexity and, among these organisms, all levels of host–parasite interaction are found ranging from complete independence to total dependence upon a living host. This large group of organisms is responsible for degrading dead organic

materials in the various cycles of nature. Parasitic micro-organisms, in contrast, have become adapted to grow in association with the living animal or plant and depend to a greater or lesser degree on the living host for essential nutrients. They include non-pathogens or commensals and organisms regularly associated with disease.

Under normal circumstances the healthy animal is in delicate balance with the micro-organisms of its environment, particularly with those which make immediate contact with the exposed surfaces of the body. Usually the two co-exist in equilibrium without causing apparent adverse effects to each other, and possibly benefit one another. Micro-organisms regularly found at the same body site are termed the 'normal' or 'indigenous flora' (Chapter 2). In the healthy individual, by virtue of its defence mechanisms, commensal organisms of the indigenous flora are confined to the external surfaces of the body.

Comparatively few of the large number of parasitic heterotrophs are regularly pathogenic. Parasitism *per se* is not therefore an indication of pathogenicity but the converse is usually true; that is, pathogenic micro-organisms are usually parasitic. Microbial pathogens have unique properties or virulence factors by which they overcome the body defences and actively damage host tissues. The means by which the virulence factors of microbial pathogens can be investigated and quantified are considered in Chapter 3.

Bacterial virulence factors, determined by both *in vitro* and *in vivo* studies, are the subject of Chapter 4. These are considered in the sequence characteristic of an infective process. Those factors which help the organism to establish a primary lodgment in the host are treated first. This is followed by factors which affect the multiplication of the pathogen and its invasion of the tissues leading to the development of overt disease.

In many bacterial diseases the greatest damage to the host is due to the activity of bacterial toxins. The protein toxins (exotoxins) are considered in Chapter 5 and examples of diseases in which exotoxins play an important role are included; bacterial lipopolysaccharide toxins (endotoxins) are the subject of Chapter 6. Part I is concluded by a chapter on viral pathogenicity in which differences between bacterial and viral pathogenicity are emphasized (Chapter 7).

Individuals usually live in groups, herds, or communities of smaller or greater size. This leads to a further level of interaction between infected and susceptible individuals in contact with each other. These community aspects are considered in Part II.

The perpetuation of a microbial species depends upon its ability to move from one individual to another without dying out in the process. Microbes which kill their host run the greater risk unless they can escape from the dead or dying host, survive outside the host, and later gain a foothold in another susceptible one. The manner in which infection is perpetuated in a community and the build-up of reservoirs of infection are considered in Chapter 8. Already differences in susceptibility between individuals have been considered (Chapter 1) but this

assumes even greater importance within the community. Apart from differences in immune status, individuals will vary in the degree of exposure to a community infection (the contact probability); in the size of the dose of infection to which they are exposed, in the genetic constitution both of themselves and of the community and various environmental factors which also play an important role.

Outbreaks of infectious disease within a community lead to illness with its accompanying suffering or handicaps and considerable economic losses. Their control is therefore of first importance. Three lines of approach are generally followed: attempts are made to control or eradicate the sources of infection and to limit the spread of infection within the community (Chapter 9), to protect susceptible individuals against infection by artificial immunization (Chapter 10), and prophylactic treatment (Chapter 11). The special case of controlling cross-infections in hospitals is considered in Chapter 12.

Part III is concerned with the subject of 'epidemiology'. From a microbiologist's point of view epidemiology is much wider than the statistical evaluation of morbidity and mortality rates. It embraces the ecology of the microbial pathogen, its natural history, and the effects produced by the outbreak at local, national, or international levels. In order to bring these various aspects together examples have been selected on the basis of their current interest, their value in illustrating important principles of epidemiological investigation or control, and the way they represent different pathways of infection. A general treatment of human diseases of animal origin—the zoonoses—is first considered (Chapter 13). This is followed by chapters on the epidemiology of foodborne, waterborne, airborne, contact, vectorborne, and wound infections respectively (Chapters 14, 16, 17, 18, 19, and 20). Other subjects of current interest include brucellosis (Chapter 15), and the epidemiology of mycological diseases (Chapter 21).

Contents

Part III Selected studies in epidemiology, based on various routes of transmission of infection and topics of special interest

PART I

INTERACTIONS BETWEEN THE HOST AND THE PARASITE

Chapter 1

Host defences and responses to micro-organisms

Man and animals are in continuous contact with the micro-organisms of their environment but only certain species are able to colonize the various body sites and, of these, only comparatively few cause overt disease. There are many reasons for these various degrees of interaction. Some are essentially linked with the host; these play a significant role in deciding the nature and extent of the interaction. A summary of the host's contribution to the host–parasite interaction is the subject of this chapter. Others are inherent in the micro-organisms themselves; the contribution made by micro-organisms to the host–parasite interaction is the major theme of the rest of the book.

Different animal species show marked differences in susceptibility to a particular microbial pathogen. Some species succumb to attack while others are partially or totally resistant to the same pathogen. Even within the same animal species individuals may exhibit differences in the degree of response to a pathogen. There are many reasons for these differences, some of which will be considered first.

The healthy animal actively defends itself against microbial attack at different stages in the process of infection. The *non-specific defences* are common to all healthy animals and provide general protection against contamination or assault by micro-organisms. The *specific defences* or *immune responses* are stimulated by the particular pathogen causing the infection; this is a highly efficient host defence. Both types of defence are briefly described.

A. DIFFERENCES IN SUSCEPTIBILITY OF ANIMAL HOSTS TO MICROBIAL PATHOGENS

1. Host-specificity to microbial pathogens

Apart from differences in host response to micro-organisms (see below) the various animal species display either a *natural susceptibility* or an *innate resistance* to the same pathogen; this may be absolute or relative. Certain pathogens exclusively affect man; others affect only animals. Lower animals do

not naturally contract syphilis, gonorrhoea, diphtheria, leprosy, typhoid fever, poliomyelitis or measles—infections common to man. Man, on the other hand, is not naturally susceptible to Johne's disease, vibrionic abortion or distemper—diseases found only in various species of animals. These are examples of absolute resistance. In contrast, many pathogens show only relative or very low host-specificity, being able to infect a wide range of animals species; these include the microbial pathogens causing brucellosis, leptospirosis, tuberculosis, anthrax, salmonellosis, tetanus, listeriosis, and psittacosis. Because they are often transmitted from animals to man, these are referred to as zoonoses (Chapter 13).

At present, only limited knowledge is available to explain differences in host-specificity. It may be directly related to the ability of the organism to grow at the body temperature of the host. The avian variety of *Mycobacterium tuberculosis*, unlike the mammalian varieties, is able to grow at the higher body temperature of birds. On the other hand, the anthrax bacillus, not being able to grow at the higher body temperature of birds, does not normally cause infection unless the birds are artificially cooled, e.g. by standing in cold water.

Other host-specificities may be linked with exacting nutritional requirements of certain pathogens. This would appear to be the explanation of purine-dependent strains of *Salmonella typhi*, which can only grow in hosts supplying purines. In mice and guinea pigs, which lack this growth factor, purine-requiring strains of *Salm. typhi* are avirulent for these rodents. By injecting purines into these animals in quantities sufficient to satisfy the nutritional requirements of the strains, the organisms prove to be virulent. Naturally occurring purine-dependent mutants of *Salm. typhi*, and of other bacterial species, have been reported (Chapter 4); other examples of host-specificity due to nutrients are considered later.

Another basis of host-susceptibility lies in the ability of the microbe or its products to damage the host. For an animal to be susceptible to a pathogen it must possess a target site for the microbe to attack. For example, injection of the exotoxin of the diphtheria bacillus into rats fails to kill the animal. The unchanged toxin is excreted in the rat's urine, and if a sample of the urine is injected into a guinea pig, the animal dies and lesions typical of those caused by diphtheria toxin (Chapter 5) are produced. This indicates that a sensitive target site is absent from the rat but present in the guinea pig, and also that the toxin excreted by the rat is chemically unmodified.

2. Differences in susceptibility of individuals within the same animal species

Healthy individuals are more likely to resist infection than those suffering with disease, injury or undergoing certain forms of treatment. An attempt is made in Table 1.1 to evaluate the order of host defence efficiency based on the health status of the individual. This is a reasonable ranking order but should not be interpreted too literally.

Apart from health status, individuals within a community vary in their response

Table 1.1 The efficiency of host defences in relation to health

Host state	Host defence efficiency
Healthy adult	High
Adults with local defence impairment, e.g. wounds, especially with tissue damage, skin diseases, foreign body (e.g. obstructed bladder)	↑
Uncontrolled diabetes	↑
Newborn infant	↑
The elderly	↑
General impairment, e.g. malignant disease of reticuloendothelial cells, leukaemia, etc., and by immunosuppressive drugs and corticosteroids	↓ Low

to the same infectious agent. In those diseases in which a well-balanced host–parasite relationship has been established the majority of individuals will be infected subclinically and exhibit no symptoms of illness. Of those which do fall ill most will exhibit the normal range of clinical illness characteristic of the infecting agent. Mild clinical symptoms may indicate greater resistance to infection and, in most instances, this will be due to immunity, or differences in the virulence of the organism (Chapter 3). By prior exposure to the same infective agent, or as a consequence of artificial immunization, active immunity will have been stimulated, thereby providing subsequent protection (Chapter 10).

There are many reasons why individuals of the same animals species may exhibit greater susceptibility than the majority to the same infective agent. In the normal, healthy animal this may be linked with age, sex, or both. Where the individual's health is impaired this is often accompanied by reduced resistance to infection, frequently due to deficiency in the host defences. Many factors can bring this about such as injury (accidental, surgical, or due to insidious damage as may be caused by smoking which leads to chronic bronchitis), malnutrition, environmental stress, organic disease, and various drugs used in therapy. Their effects on host defences are summarized in Table 1.2. Host resistance may be reduced, not only to regular pathogens, but also to organisms not normally pathogenic, and infections by these 'opportunist' organisms are being encountered with increasing frequency (Chapter 2). Selected factors which influence host resistance will be considered.

(a) *Age as a factor in disease*

Infectious diseases are often more severe at the extremes of life, in the very young, and in the elderly (Table 1.3). The newborn animal is particularly prone to infection, especially if it has not received protective passive immunity from its mother. Many neonatal diseases are alimentary in nature. In the early days of life the gut,

Table 1.2 Normal host defences and factors predisposing to opportunist infections (modified from Klainer and Beisel, 1969, and reproduced by permission)

Altered host defence	Predisposing factors	Possible mechanism
Protection afforded by normal flora	1. Burns, trauma, other infection	May alter normal skin flora by changing skin ecology and physiochemical properties
	2. Surgery	Preoperative or prophylactic antibiotics may alter normal flora
	3. Hospitalization	May colonize host with new or resistant organisms
	4. Antiobiotics	See Table 1.4
Anatomic barriers and secretions	1. Burns, trauma, bites, surgery, other infection, inflammatory diseases	See above; also direct penetration or other disruption of integrity provide new portals of entry for micro-organisms
	2. Extremes of age	May alter physiological defences, e.g. loss of gastric acidity as a protective mechanism against ingested organisms or toxins; depressed cough reflex, deficient ciliary action in respiratory tract, defective clearing mechanism in lung predispose to pulmonary infection
	3. Foreign body, prostheses	May act as nidus for infection, provide new entry portals, or cause obstruction with stasis and infection
	4. Diagnostic procedures	May provide new portals of entry for micro-organisms
	5. Urinary tract and intravenous catheters	May provide new portals of entry; may result in obstruction, stasis; or may act as nidus for infection
	6. Antimetabolites, irradiation	See Table 1.4
	7. Local ischaemia	May alter permeability of skin or mucous membranes to produce new portals of entry
Inflammatory response	1. Diabetes mellitus, renal failure	Accompanying acidosis results in sluggish polymorphonuclear response of reduced intensity, defective leucocyte function, ineffective phagocytosis and lack of fibroblastic proliferation
	2. Diseases of hematopoietic system	Infiltration of bone marrow may result in deficient and defective granulocytic pool
	3. Antimetabolites, irradiation, corticosteroids, other drugs	See Table 1.4