BACTERIA AND FUNGI PATHOGENIC TO MAN AND ANIMALS

M. A. Soltys

Preface

MANY pathogenic organisms can attack more than one host, with the result that many diseases caused by bacteria and fungi are common to both man and animals. In order to show this common pathogenic effect on man and animals an attempt has been made to make this book comparative in character. It is therefore hoped that it will be of value to both medical and veterinary clinical bacteriologists and pathologists and to others who wish to read a short authoritative account of comparative bacteriology.

Since medical and veterinary bacteriology is the study of host-parasite relationships, the book is concerned with those aspects of the structure and the properties of the organisms which play a part in their pathogenic behaviour and with the response of the invaded host to their constituents and products.

Following the short introductory chapters the book is devoted to detailed descriptions of pathogenic agents. The order in which the different bacteria are described has been adopted to illustrate the concept of similar reactions in the host, but fungi, dealt with in the third part, are described according to their significance and frequency of occurrence.

References included at the end of each chapter have been selected to provide the reader with a key to more detailed aspects of bacteriology. Recent monographs, reviews, articles and the most essential papers only have been considered. The appendix on Technical Methods deals with the most valuable and also with some recently introduced bacteriological techniques.

To the veterinary bacteriologist the book is a textbook containing not only descriptive accounts of all bacteria and fungi pathogenic to animals, but also information regarding those micro-organisms pathogenic to man only. The information regarding the latter is less complete than the former as there are many books dealing with the bacteria and fungi which affect man should fuller particulars be required.

To the medical bacteriologist the book will be a guide to the animal diseases that can be transmitted to man due to bacteria and fungi. It is not an exhaustive treatise, but sufficient information is provided to apprise the medical bacteriologist of the problems which affect the veterinary profession.

It is hoped not only that the medical and veterinary bacteriologists will find the book both of interest and practical value, but also that the veterinary student will be able to use it as a basic textbook for the study of the subject.

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Cambridge
May, 1963.

ACKNOWLEDGEMENTS

The author most gratefully acknowledges the debt he owes to all who helped him. Particular thanks are extended to Professor W. I. B. Beveridge, Dr. S. D. Elliott, Mr. A. R. Jennings, Dr. G. Lapage, Dr. P. Lamont, Dr. P. Whittlestone of the Department of Animal Pathology, University of Cambridge, to Dr. H. Walzl of Vienna, Dr. I. Zlotnik of Moredun Institute, Edinburgh, and to Professor A. van der Schaaf, Professor of Bacteriology, University of Utrecht, for their patience in reading portions of the manuscript and their helpful suggestions. The author wishes also to thank many of his students for their advice. Special thanks are due to Dr. A. C. Palmer to whose careful and critical perusal of the manuscript many improvements in the text are due. The author wishes also to express his deep appreciation of generous assistance received from Mr. M. S. Mitchell, laboratory assistant, Mr. J. Richardson, the artist, and Miss J. Minns, photographer, of the Veterinary School, University of Cambridge.

Finally the author wishes to thank Mrs. Phyllis Sharpe of Cambridge and Mrs. A. Kempers of Utrecht for their assistance in typing and retyping the manuscript, and to record special gratitude to his wife whose help in the preparation of the manuscript has made possible the completion of this book.

A special word of thanks is due to the publishers for their constant care in the preparation of this book.

M. A. S.

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HOST-PARASITE RELATIONSHIPS

1

Mechanism of Infection

WHILE bacteria are responsible for many diseases of man and animals, it is important to recognize that relatively few bacteria are capable of producing experimental disease. The majority are unable to multiply in the tissues unless some accessory factors change the state of health of the host. Miles (1955) defines pathogenicity as "an index of the behaviour of a microbe either within the tissues or on the surface of a given host in a certain agreed or defined state of health". This state of health of the host is therefore an important factor because it is in this specific state that the pathogen is able to interfere with the structure and metabolic process of the host. The division of bacteria into those able to produce disease (the pathogenic forms) and those without this capacity (the non-pathogenic forms) is only relative, as an absolute division into two such groups is impossible. It should be realized also that one bacterium is not infrequently pathogenic for one animal species and not for another, while many so-called non-pathogenic bacteria may produce pathological changes if sufficient numbers are introduced into the tissues and a suitable route of infection is used.

PATHOGENICITY

All the pathogenic species of bacteria that attack animals and man must possess three properties which determine their pathogenicity: (1) transmissibility, (2) infectivity, and (3) virulence.

Transmissibility

Transmissibility from one animal species to another depends on three factors: (*a*) the number of bacteria, (*b*) the ability to survive in susceptible subjects and (*c*) to survive outside the host. The number of bacteria is of considerable significance because the conditions necessary for survival in the new host are likely to be different and if the inoculum is large there is more chance for transmission.

The ability to survive in susceptible individuals and the development of a carrier state either among infected individuals not showing detectable lesions or symptoms, or among recovered individuals, is of greater importance in the transmission of the disease. In latent infections pathogens can persist in an active form in the tissues of a susceptible host without causing detectable lesions or symptoms during its lifetime. The parasite and the host tolerate each other until some kind of physiological disturbance occurs in the host. Then the parasite starts proliferating in an uncontrolled manner changing the latent infection into an open disease. The problem of latent infections acquires large

practical importance from the fact that many infectious diseases among animals are caused by micro-organisms which are widely distributed among normal healthy members of the livestock.

The ability of the pathogen to survive outside the animal body varies according to the organism. Some of them, like the syphilis organism, survive only a few minutes, while others, like *Bacillus anthracis*, which form spores, can survive in the soil for many years. Certain groups of micro-organisms, of which the plague organism is a good example, have the ability to survive and multiply in an intermediate host or vector. The plague bacillus causes natural diseases in many species of rodents in different parts of the world and it is transmitted to man through the bite of various species of fleas, which are ectoparasites of the rodents.

Infectivity

By infectivity we mean the ability of the pathogen to establish itself in the host. Increased infectivity may depend either on an adaptation to the nutritional environment provided by the host or on an increased resistance to the antibacterial properties of the host surfaces.

Virulence

Pathogens seeking to maintain themselves in a desirable host cause injury which is termed infection. The cells of the host then respond with physiological functions of their own defensive reactions to meet harmful influences of the pathogen; the latter produces some virulent factors, as a direct reaction to the defences of the host. Whatever the nature of the reactions through which provoking agents decrease the resistance of the host, either systemically or locally, one of their effects in all likelihood is to alter the physiochemical environment in the tissue involved. This in turn is bound to influence the severity of the disease since the multiplication and viability of micro-organisms as well as their toxic properties are conditioned by the composition of their surrounding environment. The metabolic activities and the nutritional requirements of bacteria are neither fixed nor stable; they depend for both on their enzyme content, which is capable of adaptation. Constitutive enzymes are always produced by a given organism whatever the medium in which it is growing. Many of the toxins and toxic substances of pathogens are adaptive enzymes and they appear in a host only when the bacterium is growing in specific tissues and under certain conditions. The fact that the virulence of an organism can frequently be increased by animal passage also implies that substances and processes connected with pathogenicity are produced *in vivo* to a greater extent than *in vitro*.

Virulence is a property that comes into play only after the pathogen has gained a foothold in the host. Unfortunately virulence and pathogenicity are often used synonymously. *Pathogenicity is usually defined as the ability of a parasite to cause disease either natural or experimental and is used in respect to species only, while virulence means the degree of pathogenicity and is used in respect to strains within a species; the severity of the produced injury is a measure of the virulence.* An armoury of products produced by individual bacteria *in vivo* are responsible for its virulence. In some organisms the activity of these virulent factors may be largely interdependent and the absence of one

component may result in a striking loss of virulence. In general the virulence of a pathogen depends either on toxigenicity or invasiveness, or on both. All pathogenic bacteria must, of course, be toxigenic, otherwise their growth in host tissues would not cause damage. There are a few highly toxigenic species which produce exotoxins; all the rest produce endotoxins which are liberated only after lysis of the bacteria. In the highly toxigenic bacteria such as *Corynebacterium diphtheriæ* or *Clostridium tetani* in which the potency of the toxin and the quantity produced per bacterial cell are high, the organisms do not spread from the local lesion. If the quantity and the potency are low, symptoms of disease will appear only after extensive invasion and multiplication of the bacteria.

Toxins

In the early days of work on bacterial toxins, the distinction between exotoxins and endotoxins was generally recognized. To-day the distinction is far less clear, and Oakley (1954) in his review of bacterial toxins proposes to replace the word toxin by "soluble bacterial antigen". It was believed that exotoxins were secreted by the organisms into the medium in which growth was occurring, while endotoxins which formed part of the body of the organism could be separated from it only by autolysis or other destructive procedures. Later it was shown that exotoxins of *Cl. botulinum* and *Cl. tetani* were synthesized within the bacterial cell and that the yield of toxin was greatly increased following autolysis. Exotoxins are characteristic of Gram positive bacteria and are produced by pathogenic species of the genus Clostridium or Corynebacterium. The clostridia produce far more toxins than any other genus. At least twenty toxins have been described besides a number of other active protein complexes. With increasing knowledge of the chemistry of proteins more interest is being shown in separating toxins from bacterial filtrates or extracts. The pure toxin of *Cl. botulinum* is the most active toxic substance known: it has a molecular weight of 900,000 and 7 oz. of it would be sufficient to kill the human population of the world (Van Heyningen, 1950). At the same time as botulinus toxin was isolated and crystallized, Pillemer *et al.* (1946) isolated tetanal toxin (spasmin) which contained 1-2 million mouse MLD/ml. Later other toxins such as diphtheria toxin, pestal toxin, staphylococcal toxin, toxin of *Hæmophilus pertussis* and many others were separated and purified. Chemical analysis of bacterial toxins has not yet found an explanation for their extreme toxicity. No unusual chemical groupings which can in any way account for their properties have been discovered. It appears that the toxicity is due to special configuration of amino-acids within the intact protein molecule. Any method which denatures or alters the protein of the toxin results in a simultaneous loss of toxicity.

A variety of reagents, including formaldehyde, ketones, iodine, diazo compounds, ascorbic acid, carbon disulphide and pepsin, may cause irreversible loss of toxicity without loss of antigenicity or power to combine with antitoxin. Formaldehyde is the most commonly used reagent. Toxin inactivated with dilute formalin (0·4-0·5 per cent.) at slightly alkaline pH is termed toxoid. Toxoids are now used on a large scale for active immunization of man and animals against infections resulting in toxæmia. The most characteristic features

of exotoxins are their heat lability, high antigenicity, easy formation of toxoid with formalin, and demonstration of the symptoms of the respective diseases. On the other hand endotoxins are relatively heat stable, weakly toxic and only few are able to reproduce some of the symptoms; the majority of endotoxins require the presence of additional factors. Although the endotoxin complex may be highly antigenic, the toxicity is not effectively neutralized by antibody. It seems very probable that in endotoxins which are composed of carbohydrate, lipid and protein, only the carbohydrate moiety of the complex is chiefly concerned with its antigenic property, while the protein portion is poorly antigenic but highly toxic. This seems to provide the answer to the mysterious inability of antisera to neutralize these toxins; the complex is a good enough antigen, but antibodies are not directed against that part of it which poisons animal tissue.

The susceptibility of different species of animals to a given exotoxin can vary considerably. For instance the dog, while sensitive to diphtheria toxin, is extremely resistant to the action of botulinus and tetanus toxins.

When the toxin is injected into the tissues it undergoes an irreversible reaction with the tissues within the first few minutes after the injection. This fact has an important bearing on the mode of action as well as implications regarding the use of antitoxin in treatment. For these reasons, antitoxic serum is an effective therapeutic agent only when inoculated before symptoms develop, or at very early stages of the disease. Literature concerning bacterial toxins has been reviewed by Pillemer and Robbins (1949), Burrows (1951), van Heyningen (1950) and Oakley (1954).

Invasiveness

Bacteria which produce powerful toxins scarcely need to grow in the host to produce disease. The infection remains strictly localized and the volume of invaded tissue is small. The disease is therefore almost entirely a toxæmia. The essential characters of the diseases caused by these toxigenic bacteria can be reproduced in susceptible animals by injection of the toxin itself. If bacteria do not produce exotoxins and the harmful effect of the individual organism is low, symptoms of disease will appear only after extensive invasion and multiplication of bacteria. By invasiveness we mean the ability to spread and multiply in the host tissues. The invasive forms seem to differ from the non-invasive ones in their ability to overthrow the normal host defences. Examples of invasive organisms are the anthrax bacillus, *Pasteurella septica, Erysipelothrix rhusiopathiæ*, streptococci and several other mainly Gram negative organisms. Invasiveness, like toxigenicity, is not necessarily an independent character of virulence. It has been demonstrated that damage to the epithelial wall of the intestinal canal brought about by toxic products of various pathogens may facilitate invasiveness. Invasive bacteria possess one or more surface components which render them relatively resistant to host defences. The surface component, generally referred to as a capsule, is a layer of viscous material which may be composed of highly polymerized polysaccharides as in the case of pneumococcus, an acidic polysaccharide, hyaluronic acid in the case of streptococci and poly-glutamic acid in the case of the anthrax bacillus. Possession of a capsule does not mean that organisms are virulent. In addition to the capsule

other factors are necessary to virulence. Rothbard (1948) has presented evidence which suggests that both the hyaluronic acid capsule and "M" antigen, which is the type specific protein of the pathogenic streptococci, contribute to virulence, but the "M" substance is of major importance. Encapsulated strains deficient in "M" substance were readily phagocytized, while strains containing "M" substance were resistant to phagocytosis. Other factors influencing the virulence of pathogens consist of various bacterial enzymes or aggressins. For example pyogenic staphylococci produce a coagulase which accelerates the clotting of blood plasma, by converting soluble fibrinogen to the insoluble substance fibrin. It has been suggested that the deposition of fibrin *in vivo* may have two consequences. First, a fibrin wall is caused to form around the site of infections, thus preventing dispersal of the bacteria: being thus localized, the pathogens produce effectively higher concentration of toxic substances. Second, it has been suggested that coagulase-producing staphylococci may cause a layer of fibrin to be deposited on their own cell surfaces, forming capsules that confer relative resistance to phagocytes. *Vibrio choleræ* produces an enzyme which destroys the mucous layer lining of the bowel and exposes the underlying cells to its toxic action.

Virulent streptococci produce an enzyme-activator called streptokinase or fibrinolysin, which helps to digest the fibrin in blood clots and this presumably enables the organisms to invade the local tissues. Many invasive bacteria secrete hyaluronidase, an enzyme that catalyses the breakdown of hyaluronic acid, a constituent of connective tissue. It has been believed that hyaluronidase facilitates the spread of bacteria through tissues, but no conclusive evidence has yet been demonstrated. Other enzymes that have been described as factors in invasiveness include collagenase, which breaks down collagen, a protein of fibrous tissue, leucocidin, which kills leucocytes, hæmolysin and lecithinase which help to destroy red blood cells. However, no one has convincingly demonstrated the participation of any of these enzymes alone in the process of invasion. Rammelkamp and Dingle (1948) reviewed the literature concerning various properties of the pathogenic streptococci and it appears from their review that an armoury of products produced by streptococci *in vivo* is responsible for their virulence. It is possible that the activity of these virulent factors may be largely interdependent and the absence of one component results in a striking loss of virulence although the other factors necessary for virulence are present. Any attempt to implicate any single factor as a central mechanism in the virulence phenomenon is over-simplification.

Agressins

Agressins, or auxiliary pathogenic factors, were first demonstrated by Bail and Weil (1911) in anthrax. It has been claimed that during growth in animal tissues, pathogenic bacteria produce special types of substances, the agressins, which are capable of enhancing virulence. Further studies on the pathogenesis of experimental anthrax demonstrated that the virulence of *Bacillus anthracis* is dependent on the production of two main factors, a capsule and the extracellular toxin (Smith *et al.*, 1956a, b). The capsule of *B. anthracis* has been shown to contain polyglutamic acid, which is an important agressin due to its antiphagocytic activity. The anthrax toxin has virulence-enhancing and anti-

phagocytic activity at low concentrations. Miles *et al.* (1957) described a quick and convenient method of making virulence-enhancing tests. After intradermal injection of the substance, the size of the subsequent lesions is a measure of the degree of virulence enhancement.

Enhancement of virulence

Enhancement of bacterial virulence usually takes place when organisms are passaged through animals. It seems probable that enhancement of virulence by animal passage is either the result of selection of virulent mutants which resist the defensive mechanism of the host, or the adaptation of the pathogen to new nutritional and environmental conditions. In fact, some virulent factors may well be produced as a direct reaction to the defences of the host. Whilst studying the development of neutralizing antibodies in animals infected with *Trypanosoma brucei*, Soltys (1957) observed that only a strain of *T. brucei* which was passaged through mice and not exposed to antibodies could be inactivated by antibodies *in vitro* and become non-infectious to mice. On the other hand, the same strain passaged through rabbits and exposed to antibodies for some time became antibody resistant so that neutralizing antibodies had no effect upon it. It was also noticed that antibody resistant strains were more virulent to rabbits and guinea pigs than antibody sensitive strains.

Virulence may also be increased by certain artificial methods, such as injecting bacteria suspended in mucin (Olitzki, 1948) or in adrenaline (Evans *et al.*, 1948). The former method acts by coating the bacteria and inhibiting their destruction by the natural defences of the host, while the latter protects the parasite by inhibiting their mobilization. Treatment of a host with cortisone may also influence the infection.

Many pathogens isolated from diseased tissues may lose their virulence by continued cultivation on artificial media. It seems probable that the artificial media are lacking in some growth factor present in animal tissue, which is required by the virulent organism, but is not required by the avirulent mutants. The virulent strains are not capable of readapting themselves to an environment very different from those provided by the host, so any mutant that chances to be present and that can grow faster than the parent type will be selected and will rapidly become predominant. It has been observed that micro-organisms recovered directly from infected tissues do not exhibit the same metabolic properties as their laboratory counterparts. More recent observations with tubercle bacilli washed directly from infected mouse lungs showed that such organisms differ from organisms of the same strain grown *in vitro* by various biochemical characteristics (Segal and Bloch, 1956). The population of bacteria may also be gradually shifted from the smooth and mucoid forms to the avirulent "R" (rough) forms. This particularly happens when the culture is grown under unfavourable conditions. The "R" (rough) variants are formed by the loss of the ability to produce a certain surface component. It must be realized, of course, that not all avirulent strains are "R" variants. Many attenuated vaccines like *Brucella abortus* S19, although in smooth forms, are avirulent or only slightly virulent. Morphological and chemical studies often failed to determine any significant change. Their difference can only be detected *in vivo*. Recently Burrows and Bacon (1956) in their study of *Pasteurella pestis* showed that

virulent and avirulent strains of *P. pestis*, which were indistinguishable by any test *in vitro*, could easily be recognized by their behaviour in the peritoneum of a mouse. The avirulent strains were phagocytized progressively until all the bacteria disappeared; while the virulent strain was phagocytized only for a very short period of time and within half an hour some organisms had become resistant to phagocytosis. The ability of *P. pestis* to become resistant to phagocytosis in the absence of visible capsulation is associated with the presence of various substances which can be detected only on gel diffusion plates. Many virulent factors have been produced *in vitro*, but there is little doubt that a whole armoury of factors is produced in the diseased animal. Therefore, when we want to know all the compounds and processes involved in pathogenicity, the pathogen must be considered as growing in the tissue of a host, where it reacts to the peculiar nutritional conditions and the host defence mechanism. Once we know all the compounds responsible for the disease symptoms it may be possible to find which of these factors are able to produce active immunity against the disease. We must realize that all virulent factors need not be immunogenic. For example, the virulence of *Bacillus anthracis* is dependent on the production of two main factors, a capsule and the extracellular toxin (Smith *et al.*, 1956b), but the toxin is the chief antigen for inducing immunity against anthrax. On the other hand immunity to plague appears to be due to the immunogenic factor present in the cell wall of *Pasteurella pestis* rather than to the toxin (Pollitzer, 1954). Recent investigations of pathogenicity in the tissue of a host opened a new approach to the study not only of the pathogenicity of bacteria, but also the role of the pathogenic factors both in human and animal immunization.

In closing this chapter the author hopes that in future many living vaccines will be replaced by effective chemical agents which may be able to control some of the infectious diseases in man and animals, as in the cases of diphtheria and tetanus.

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2

Non-Specific Resistance of the Host

THE response of the host to a parasite involves various reactions in order to maintain the physiological integrity of the host body. After nearly a century of pathology and bacteriology various responses to infectious agents have been described, but a great deal more knowledge is necessary before any claim to real understanding can be made. It has been customary to recognize two types of protection against infectious agents: (1) non-specific resistance, which includes genetic and physiological resistance, and (2) specific resistance which deals with specific antibodies. Recently Miles (1955) modified the old classification of resistance by discussing the subject in terms of the constitutive and adaptive mechanisms with which the host is endowed. According to Miles constitutive defences of the host are in full working order independently of the presence of an invader, while adaptive defences are produced only in response to certain stimuli. He then divides adaptive defences into non-specific, such as inflammation, and into specific, which includes antibody responses.

Before discussing advances in our knowledge of the resistance to infectious diseases it may be helpful to summarize in the form of a diagram the known factors which determine the resistance of an animal to pathogenic agents.

TABLE I

MECHANISM OF RESISTANCE OF A HOST TO A PARASITE

Non-specific constitutive and adaptive

Non-specific constitutive resistance Contributing factors		*Humoral and cellular defences*	*Specific adaptive resistance* Acquired immunity			
			Active		*Passive*	
Genetic	*Physiological*		*Natural*	*Artificial*	*Natural*	*Artificial*
Non-susceptibility among various species of animals and variations in susceptibility in the same species	Natural barriers, age, sex, nutrition, hormones and other factors	Complement, properdin, immunoconglutin, phagocytes and other defences	Recovery from the disease	Vaccines	Maternal antibodies placental and colostral	Serum therapy

The non-specific resistance to infectious agents is complicated not only by the variety of mechanisms involved, but also by the variety of agents to which the host is naturally resistant or susceptible. In addition to the local environmental

conditions at the various portals of entry, which have defensive functions, various constitutive mechanisms with which the host is endowed take part in protecting the host against pathogenic micro-organisms.

CONSTITUTIVE MECHANISMS

Genetic resistance

Constitutive mechanisms may be divided into genetic and physiological patterns. Genetic pattern is exemplified in racial or species resistance. This is illustrated by the fact that man or a dog is non-susceptible to spontaneous infection by a large number of parasites to which the cow or pig is susceptible. On the other hand these animals are resistant to measles, gonorrhœa, mumps and syphilis. This type of resistance is inherited to the same extent as any other species characteristics and is not dependent upon detectable antibodies.

Studies on susceptibility to various infectious agents among the same species have shown that species differences depend also on inheritance, but not the kind to which genetic methods can often be applied. The same disease in the same species of animals may range from a mild asymptomatic case, through various abortive ones to a severe and fatal infection. The scale of the effect may be set by the dose of the pathogen, its virulence and the resistance of the host; it frequently depends on constitutive defences of the host.

Earlier work on human tuberculosis resistance by family studies culminated in indicating that there was an exceptionally high degree of hereditary determination of both mortality and morbidity in this disease. Lurie (1941) observed differences in the survival value of families of rabbits: one family survived five months as compared with nine months for another. Reviews of the genetic differences in animals have been presented by Gowen (1948) and Russell (1955).

Physiological resistance

Various mechanical barriers aid in preventing the entrance of micro-organisms into susceptible tissues and also in localizing infections. These barriers include coverings such as hair, the epithelium of the skin, the epithelium of the respiratory tract, the mucosa of the gastro-intestinal and urogenital tract, the fascia in the deeper body structure, and the living cell itself. Body fluids such as nasal secretions, gastric juice, saliva, mammary gland secretions, genito-urinary tract secretions and many others, also exercise antimicrobial actions and do some service in defending the host.

It is now generally known that in any infective process, the microbe is only part of the story and not the most important part either; it is the reaction of the cell to the presence of the microbe which constitutes the condition we have to study. The rapid post-mortem invasion of organs by the intestinal flora suggests that the inhibitory effect of defence mechanisms that operate during life is suppressed by death of the host.

A mass of frogs' eggs will remain entirely resistant to bacteria of many varieties surrounding them. However, when by some accident such a mass of eggs is injured or killed, it is immediately invaded by the surrounding bacteria. The gastric juice enzymes do not act upon the healthy mucous membrane of the