THE PATHOGENESIS OF INFECTIOUS DISEASE

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Introduction

For the physician or veterinarian of course, the important thing about microorganisms is that they infect and cause diseases. Most textbooks of medical microbiology deal with the subject either microbe by microbe, or disease by disease. There are usually a few general chapters on the properties of microorganisms, natural and acquired resistance to infection etc., and then the student reads separately about each microbe and each infectious disease. It is my conviction that the centrally significant aspect of the subject is the mechanism of microbial infection and pathogenicity, and that the principles are the same, whatever the infectious agent. When we consider the entry of microorganisms into the body, their spread through tissues, the role of immune responses, toxins and phagocytes, the general features are the same for viruses, rickettsiae, bacteria, fungi and protozoa. This book deals with infection and pathogenicity from this point of view. All microorganisms are considered together as each part of the subject is dealt with. There are no systematic accounts of individual diseases, their diagnosis or their treatment, but the principal microorganisms and diseases are included in a series of tables and a figure at the end of the book.

Just as the virologist has needed to study not only the virus itself but also the cell and its responses to infection, so the student of infectious diseases must understand the body's response to infection as well as the properties of the infecting microorganism. It is hoped that this approach will give the reader an attitude towards infection and pathogenicity that will be relevant whatever the nature of the infectious agent and whatever the type of infectious disease. Most of the examples concern infections of man, but because the principles apply to all infections, the book may also prove of value for the student of veterinary or general science.

C. A. MIMS

Acknowledgement

I would like to express my gratitude to my secretary Terry Stewart, who deciphered my hieroglyphics and prepared the manuscript with intelligence and precision.

For creatures your size I offer
  a free choice of habitat,
so settle yourselves in the zone
  that suits you best, in the pools
of my pores or the tropical
  forests of arm-pit and crotch,
in the deserts of my fore-arms,
  or the cool woods of my scalp

Build colonies: I will supply
  adequate warmth and moisture,
the sebum and lipids you need,
  on condition you never
do me annoy with your presence,
  but behave as good guests should
not rioting into acne
  or athlete's-foot or a boil.

From: "A New Year Greeting" by W. H. Auden. (Epistle to a Godson and other poems. Published by Faber and Faber (U.K.) and Random House, Inc. (U.S.A.))

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1

General Principles

In general biological terms, the type of association between two different organisms can be classified as parasitic, where one benefits at the expense of the other, or symbiotic (mutualistic), where both benefit. There is an intermediate category called commensalism, where only one organism derives benefit, living near the other organism or on its surface without doing any damage. It is often difficult to use this category with confidence, because an apparently commensal association often proves on closer examination to be really parasitic, or symbiotic, or it may at times become parasitic or symbiotic.

The same classification can be applied to the association between micro-organisms and vertebrates. Generalized infections such as measles, tuberculosis or typhoid are clearly examples of parasitism. On the other hand, the microflora inhabiting the rumen of cows or the caecum of rabbits, enjoying food and shelter and at the same time supplying the host with food derived from the utilization of cellulose, are clearly symbiotic. Symbiotic associations perhaps also occur between man and his microbes, but they are less obvious. For instance, the bacteria that inhabit the human intestinal tract might theoretically be useful by supplying certain vitamins, but there is no evidence that they are important under normal circumstances. In malnourished individuals, however, vitamins derived from intestinal bacteria may be significant, and it has been recorded that in individuals with subclinical vitamin B_2 (thiamine) deficiency, clinioal beri-beri can be precipitated after treatment with oral antibiotics. Presumably the antibiotics act on the intestinal bacteria that synthesize thiamine.

The bacteria that live on human skin and are specifically adapted to this habitat might at first sight be considered as commensals. They enjoy shelter and food (sebum, sweat etc.) but are normally harmless. If the skin surface is examined by the scanning electron microscope, the bacteria, such as *Staphylococcus epidermidis* and *Corynebacterium acne,* are seen in small colonies scattered over a moon-like landscape. The colonies contain several hundred individuals* and tend to get smeared over the surface. Skin bacteria adhere to the epithelial squames that form the cornified skin surface, and

*The average size of these colonies is determined by counting the total number of bacteria recovered by scrubbing and comparing this with the number of foci of bacterial growth obtained from velvet pad replicas. The sterile pad is applied firmly to the skin, then removed and applied to the bacterial growth plate.

extend between the squames and down the mouths of the hair follicles and glands opening onto the skin surface. They can be reduced in numbers, but never eliminated, by scrubbing and washing. The secretions of apocrine sweat glands are metabolized by these bacteria and odoriferous substances are produced, giving the body a smell that modern man, at least, finds offensive. Deodorants, containing aluminium salts to inhibit sweating, and often antiseptics to inhibit bacterial growth, are therefore applied to the apocrine gland areas in the axillae. But for other mammals, and perhaps primitive man, body smells have been of great significance in social and sexual life. Not all body smells are produced by bacteria, and skin glands may secrete substances that are themselves odoriferous. Skin bacteria nevertheless contribute to body smells and could for this reason be classified as symbiotic rather than parasitic. There is also evidence that the harmless skin bacteria, by their very presence, inhibit the growth of more pathogenic bacteria*, again indicating benefit to the host and a symbiotic classification for these bacteria.

A microbe's ability to multiply is obviously of paramount importance; indeed, we call a microbe dead or nonviable if it cannot replicate**. The ability to spread from host to host is of equal importance. Spread can be horizontal in a species, one individual infecting another by contact, via insect vectors, and so on (Fig. 1). Alternatively spread can be "vertical" in a species, parents infecting offspring via sperm, ovum, the placenta, the milk, or by contact. Clearly if a microbe does not spread from individual to individual it will die with the individual, and cannot persist in nature. The crucial significance of the ability of a microbe to spread can be illustrated by comparing the horizontal spread of respiratory and venereal infections. An infected individual can transmit influenza or the common cold to a score of others in the course of an innocent hour in a crowded room. A venereal infection also, must spread progressively from person to person if it is to maintain itself in nature, but it would be a formidable task to transmit a venereal infection on such a scale. A chain of horizontal infection in this case, however, requires a chain of venery (sexual relations) between individuals. If those infected at a given time never had sexual relations with more than one member of the opposite sex, the total incidence could double in a lifetime, and when the infected people died the causative microbe would be eliminated. In other words, venereal infections must be transmitted to more than one member of the opposite sex if they are to persist and flourish. The greater the degree of sexual promiscuity, the greater the number of sex partners, the more successful such infections can be.

*For instance, pathogenic strains of *Staphylococcus aureus* are responsible for outbreaks of infection in nurseries, and outbreaks have been successfully terminated by colonizing infants with a nonpathogenic strain (502 A). The nonpathogenic strain interferes with growth and colonization by the pathogenic strain.

**Sterilization is the killing of all forms of microbial life, and appropriately the word means making barren, or devoid of offspring.

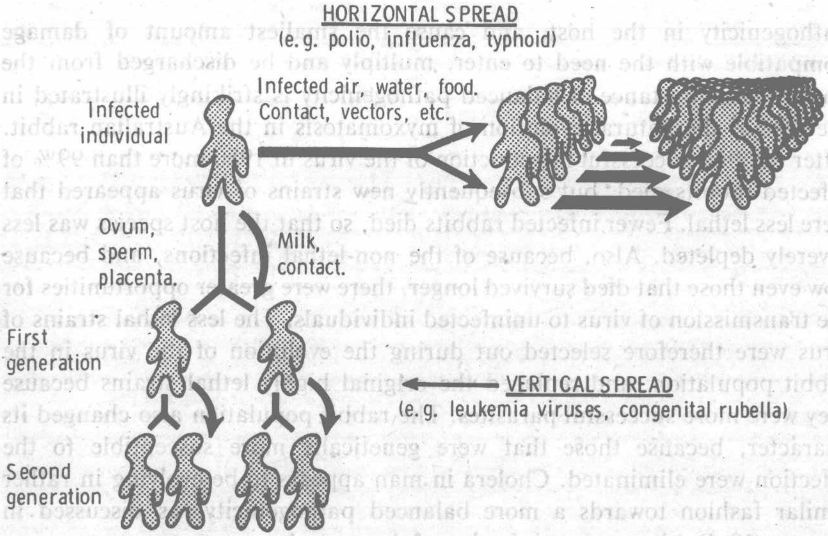

Fig. 1. Vertical and horizontal transmission of infection.

Only a small proportion of the microorganisms associated with man give rise to pathological changes or cause disease. Vast numbers of bacteria live harmlessly in his mouth and intestines, on his teeth and skin, and most of the 150 or so viruses that infect man cause no detectable illness in most infected individuals, in spite of cell and tissue invasion. From an evolutionary point of view, successful microbes must avoid extinction, persist in the world, multiply, and leave descendants. A successful parasitic microbe lives on or in the individual host, multiplies, spreads to fresh individuals, and thus maintains itself in nature.

A successful parasitic microbe, like all successful parasites, tends to get what it can from the infected host without causing too much damage. If an infection is too often crippling or lethal, there will be a reduction in numbers of the host species and thus in the numbers of the microorganism. Thus, although a few microorganisms cause disease in a majority of those infected, it is to be expected that most are comparatively harmless, causing either no disease, or disease in only a small proportion of those infected. Polioviruses, for instance, are transmitted by the faecal-oral route, and cause a subclinical intestinal infection under normal circumstances. But in an occasional host the virus invades the central nervous system, often causing meningitis, sometimes paralysis, and very occasionally death. This particular site of multiplication is irrelevant from the virus point of view, because growth in the central nervous system is quite unnecessary for transmission to the next host. If it occurred too frequently, in fact, the host species would be reduced in numbers and the success of the virus jeopardized. Well established infectious agents have therefore generally reached a state of balanced pathogenicity in the host, and cause the smallest amount of damage compatible with the need to enter, multiply and be discharged from the body. The importance of balanced pathogenicity is strikingly illustrated in the case of the natural evolution of myxomatosis in the Australian rabbit. After the first successful introduction of the virus in 1950 more than 99% of infected rabbits died, but subsequently new strains of virus appeared that were less lethal. Fewer infected rabbits died, so that the host species was less severely depleted. Also, because of the non-lethal infections, and because now even those that died survived longer, there were greater opportunities for the transmission of virus to uninfected individuals. The less lethal strains of virus were therefore selected out during the evolution of the virus in the rabbit population, and replaced the original highly lethal strains because they were more successful parasites. The rabbit population also changed its character, because those that were genetically more susceptible to the infection were eliminated. Cholera in man appears to be evolving in rather similar fashion towards a more balanced pathogenicity, as discussed in Chapter 10. Rabies, a virus infection of the central nervous system, seems to contradict but in fact exemplifies this principle. Infection is classically acquired from the bite of a rabid animal and the disease in man is almost always fatal, but the virus has shown no signs of becoming less virulent. Man, however, is an unnatural host for rabies virus, and it is maintained in a less pathogenic fashion in animals such as vampire bats and skunks. In these animals there is a relatively harmless infection and virus is shed for long periods in the saliva, which is the vehicle of transmission from individual to individual. Rabies is thus maintained in the natural host species without serious consequences. But bites can infect the individuals of other species, "accidentally" from the virus point of view, and the infection is a serious and lethal one in these unnatural hosts.

Although successful parasites cannot afford to become too pathogenic, some degree of tissue damage may be necessary for the effective shedding of microorganisms to the exterior, as for instance in the flow of infected fluids from the nose in the common cold or from the alimentary canal in infectious diarrhoea. Otherwise there is ideally very little tissue damage, a minimal inflammatory or immune response, and a few microbial parasites achieve the supreme success of causing zero damage and failing to be recognized as parasites by the host (see Chapter 7). Different microbes show varying degrees of attainment of this ideal state of parasitism.

The concept of balanced pathogenicity is helpful in understanding infectious diseases, but many infections have not yet had time to reach this ideal state. In the first place, as each microorganism evolves, occasional virulent variants emerge and cause extensive disease and death before disappearing after all susceptible individuals have been infected, or before settling down to a more balanced pathogenicity. Secondly, some of the microbes responsible for serious human diseases had appeared originally in one part of the world, where there had been a weeding out of genetically susceptible individuals and a move in the direction of a more balanced pathogenicity. Subsequent spread of the microorganism to a new continent has resulted in the infection of a different human population in whom the disease is much more severe because of greater genetic susceptibility. Examples include tuberculosis spreading from resistant Europeans to susceptible Africans, and yellow fever spreading from Africans to Europeans. Finally, there are a number of microorganisms that have not evolved towards a less pathogenic form in man because the human host is clearly irrelevant for the survival of the microorganism. Microorganisms of this sort, such as those causing rabies (see above), scrub typhus, plague, leptospirosis and psittacosis, have some other regular host species which is responsible, often together with an arthropod vector, for their maintenance in nature*. The pathogenicity for man is of no consequence to the microorganism. Several human infections that are spillovers from animals domesticated by man also come into this category, including brucellosis, Q fever and anthrax. As man colonizes every corner of the earth, he encounters an occasional microbe from an exotic animal that causes, quite "accidentally" from the point of view of the microorganism, a serious or lethal human disease. Recent examples are Lassa fever and Marburg disease from African rodents and monkeys respectively**.

Microorganisms multiply exceedingly rapidly in comparison with their vertebrate hosts. The generation time of an average bacterium is an hour or less, as compared with about 20 years for the human host. Consequently microorganisms evolve with extraordinary speed in comparison with their vertebrate hosts. Vertebrates, throughout their hundreds of millions of years of evolution, have been continuously exposed to microbial infections. They have developed highly efficient recognition (early warning) systems for foreign invaders, and effective inflammatory and immune responses to restrain their growth and spread, and eliminate them from the body (see Chapter 9). If these responses were completely effective microbial infections would be few in number and all would be terminated rapidly; microorganisms would not be allowed to persist in the body for long periods. But microorganisms, faced with the antimicrobial defences of the host species, have evolved and developed a variety of characteristics that enable them to bypass or overcome these defences. The defences are not infallible, and the rapid rate of evolution of microorganisms ensures that they are always many

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*These infections are called *zoonoses* (see p. 27).

**Lassa fever is a highly lethal infection of man caused by an arenavirus (see Table 28). The virus is maintained in certain rodents in West Africa as a harmless persistent infection, and man is only very occasionally infected. Another serious infectious disease occurred in 1967, in a small number of laboratory workers in Marburg, Germany, who had handled tissues from vervet monkeys recently imported from Africa. The Marburg agent appears to be a virus, but nothing is known of its natural history.

steps ahead. If there are possible ways round the established defences, microorganisms are likely to have discovered and taken advantage of them. Successful microorganisms, indeed, owe their success to this ability to adapt and evolve, exploiting weak points in the host defences. The ways in which the phagocytic and immune defences are overcome are described in Chapters 4 and 7.

It is the virulence and pathogenicity of microorganisms, their ability to kill and damage the host, that makes them important to the physician or veterinarian. If none of the microorganisms associated with man did any damage, and none were notably beneficial, they would be interesting but relatively unimportant objects. In fact, they have been responsible for the great pestilences of history, have at times determined the course of history, and continue today, in spite of vaccines and antibiotics, as important causes of disease. Also, because of their rapid rate of evolution and the constantly changing circumstances of human life, they continue to present threats of future pestilences. It is the purpose of this book to describe and discuss the mechanisms of infection and the things that make microorganisms pathogenic. As will be seen, little is known about this aspect of microbiology, but it is the central significant core of microbiology as applied to medicine, and our understanding is now steadily increasing as modern biochemical and immunological techniques are brought to bear on the problems.

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2

Entry of Microorganisms into the Body

INTRODUCTION

Figure 2 shows a simplified diagram of the mammalian host. In essence, the body is traversed by a tube, the alimentary canal, with the respiratory and urinogenital tracts as blind diverticula from the alimentary canal or from the region near the anus. The body surface is covered by skin, with a relatively impermeable dry, horny outer layer, and usually fur. This gives a degree of insulation from the outside world, and the structure of skin illustrates the compromise between the need to protect the body, yet at the same time maintain sensory communication with the outside world, give mechanical mobility, and, especially in man, act as an important thermoregulatory organ.

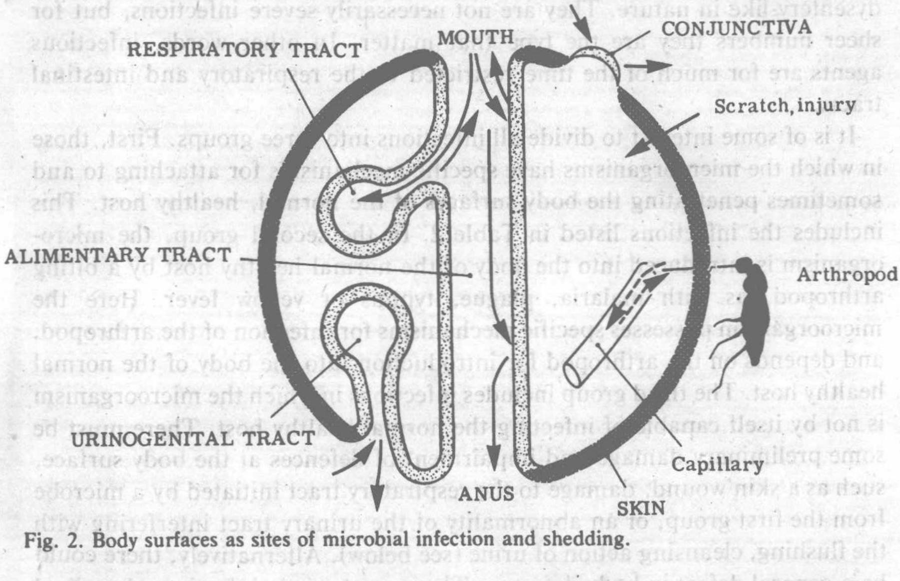

Fig. 2. Body surfaces as sites of microbial infection and shedding.

The dry, protective skin cannot cover all body surfaces. At the site of the eye it must be replaced by a transparent layer of living cells, the conjunctiva. Food must be ingested, digested and the products of digestion absorbed, and in the alimentary canal therefore, where contact with the outside world must be facilitated, the lining consists of one or more layers of living cells. Also in the lungs the gaseous exchanges that take place require contact with the outside world across a layer of living cells. There must be yet another discontinuity in the insulating outer layer of skin in the urinogenital tract, where urine and sexual products are secreted and released to the exterior. The cells on all these surfaces are covered by a fluid film. In the alimentary canal the lining cells are inevitably exposed to mechanical damage by food and they are continuously shed and replaced. Shedding and replacement is less pronounced in respiratory and urinogenital tracts, but it is an important phenomenon in the skin, the average person shedding about 5×10^8 skin squames per day.

The conjunctiva and the alimentary, respiratory and urinogenital tracts offer pathways for infection by microorganisms. Penetration of these surfaces is more easily accomplished than in the case of the intact outer skin. A number of antimicrobial devices have been developed in evolution to deal with this danger, and also special cleansing systems to keep the conjunctiva and respiratory tract clean enough to carry out their particular function. In order to colonize or penetrate these bodily surfaces, microorganisms must first become attached, and there are many examples of specific attachments that will be referred to (Table 2). One striking feature of acute infectious illnesses all over the world, is that most of them are either respiratory or dysentery-like in nature. They are not necessarily severe infections, but for sheer numbers they are the type that matter. In other words, infectious agents are for much of the time restricted to the respiratory and intestinal tracts.

It is of some interest to divide all infections into three groups. First, those in which the microorganisms have specific mechanisms for attaching to and sometimes penetrating the body surfaces of the normal, healthy host. This includes the infections listed in Table 2. In the second group, the microorganism is introduced into the body of the normal healthy host by a biting arthropod, as with malaria, plague, typhus or yellow fever. Here the microorganism possesses specific mechanisms for infection of the arthropod, and depends on the arthropod for introduction into the body of the normal healthy host. The third group includes infections in which the microorganism is not by itself capable of infecting the normal healthy host. There must be some preliminary damage and impairment of defences at the body surface, such as a skin wound, damage to the respiratory tract initiated by a microbe from the first group, or an abnormality of the urinary tract interfering with the flushing, cleansing action of urine (see below). Alternatively, there could be a general defect in body defences. The opportunistic infections described later in this chapter come into this third group, and further examples are given in Chapter 11.

Although microorganisms only reach the tissues of the body by penetrating body surfaces, some are capable of causing disease without doing this. Certain intestinal bacteria, for instance, secrete toxic substances that act locally to cause disease, as in the case of cholera. The bacteria exert their