INFECTIOUS DISEASES

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and
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With a Foreword by

J. W. HOWIE

SECOND EDITION

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FOREWORD

A generation ago, a period of full-time service on the staff of a hospital for infectious diseases was rated a valuable training for young general physicians, for apprentice Medical Officers of Health, and for laboratory workers in training. Those who accepted this discipline learned a great deal about the clinical side of acute medicine, about epidemiology, and about medical microbiology. Unfortunately, there was then no specific chemotherapy; and much the most important part of the treatment of patients was devoted and skilled nursing.

Now there is chemotherapy. Clinical and laboratory methods of diagnosis and treatment have flourished and diversified. The outlook for the patient is certainly brighter than it was. But this improved position is not a miraculous gift to be taken for granted. Patients will die who should have lived unless there is accurate diagnosis, and unless chemotherapy is properly controlled by sound interpretation of well judged tests adequately performed. Reliable information about and actual experience of the management of infectious diseases are now even more important than they were before chemotherapy. In other words, our present feeling that we are mastering infectious diseases will be justified only in so far as specialists in infectious diseases are well enough informed by reading and experience to make proper use of the resources now available.

I gladly commend INFECTIOUS DISEASES by Dr. Ramsay and Dr. Emond as a volume well fitted to its purpose of giving to students of all grades of seniority, including graduate students, exactly what they need to know for their own and their patients' good.

J. W. HOWIE

PREFACE TO FIRST EDITION

History reveals a constant ebb and flow in the pattern of infections and the emergence of new diseases. Plague was predominant in England for three centuries, then unaccountably disappeared. Smallpox held the stage for a century or more, but gradually fell away. Last century was notable for outbreaks of cholera and typhoid fever while this century has so far produced two pandemics of influenza and the most extensive epidemics of poliomyelitis ever recorded. We are now in the age of viruses; their number is legion and new methods of identification unfold an ever-expanding field for research. As yet there is no effective anti-viral agent while the scope of chemotherapy in bacterial infections is seriously limited by organisms which develop resistance and individuals who become sensitised to drugs which are much too frequently administered. The vision of a world free from infection is already a chimera and it becomes apparent that a sound training in the investigation and management of infections is essential for future generations of doctors. For the specialist the field demands a thorough grounding in general medicine as well as special training in infectious disease and familiarity with laboratory techniques. Close collaboration between clinicians, microbiologists and epidemiologists is necessary if the full value of modern techniques is to be realised. This book purports to furnish the basic facts regarding the common infections encountered in the British Isles and so affords a basis for training of undergraduate and postgraduate alike. No claim is made that it is comprehensive and it is hoped that its brevity may enhance its usefulness.

A.M.R.
R.T.D.E.

London, January 1967

PREFACE TO SECOND EDITION

Compilation of a second edition provides an opportunity to rectify inadequacies and omissions in the first and to take advantage of constructive criticisms. In this respect we were particularly fortunate in the suggestions made on initial publication. Chapters on malaria, tuberculosis, cytomegalic inclusion disease and rabies have now been added. The striking increase in the number of cases of malaria introduced as a result of air travel and the imminent threat posed by the relentless spread of rabies in western Europe make their inclusion essential in a modern treatise on infectious disease. The continued expansion in our knowledge of viruses, notably those of herpes simplex, rubella, infectious mononucleosis and hepatitis has made it necessary to expand and to a large extent re-write the chapters on these infections. This applies also to the chapter on meningitis.

The addition of a considerable number of monochrome illustrations should prove interesting and useful to the reader. We trust that the book will be valuable not only to clinicians but also to epidemiologists, microbiologists and community physicians whose work is intimately connected with the many problems in this field of acute medicine.

A.M.R.
R.T.D.E.

London, 1977

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LIST OF COLOURED PLATES

CHAPTER I

THE HOST-PARASITE RELATIONSHIP

The great epidemics of the past create a picture of vast armies of parasites, red in tooth and claw, competing with man for survival, a battle described in emotional terms of invasion and conquest. This concept, however, is far removed from the usual relationship between host and parasite which is one of peaceful coexistence. A few parasites and hosts, unfortunately, are not so well adapted and maintain a state of uneasy truce or even open war. With long contact, a balance is reached so that infection rarely results in disease. In fact, some parasites live in symbiosis producing metabolites essential for the nutrition of the host while others appear to protect against invasion by more virulent organisms.

In man, many organisms will live peacefully on the surface of the body obtaining food and growing without harm to the host. Only when the balance is disturbed does the parasite invade and react with its host causing disease. The staphylococcus on the skin, the *Streptococcus viridans* in the nasopharynx and the coliform organisms in the bowel have reached this happy state. Other organisms, after a period of conflict, reach equilibrium with their hosts and are tolerated, herpes simplex virus in the skin, adenovirus in the tonsils, the typhoid bacillus in the gall-bladder and the gonococcus in the genital tract, to mention but a few.

A parasite infecting man may undergo a stage of development in another host, for example, *Taenia solium* in the pig. Sometimes, man becomes involved with cycles of infection in animals, examples of such epizootic diseases being yellow fever in monkeys, plague in rodents, virus encephalitis in horses, anthrax in ungulates and salmonella enteritis in farm animals. In these circumstances, the host-parasite relationship is complex and readily disturbed. Arthropod vectors play an important part in the spread of many infectious diseases, particularly in tropical countries. The infection may be transferred passively on the surface of the vector, as in yaws, or the vector may be actively infected and spread the organism by biting the host, for example dengue and plague. In some infections, the parasite must undergo development within the arthropod before it can be transmitted, e.g. malaria and kala azar.

Factors Influencing Infection

Infection is a complex interaction of two different species, the host and the parasite, and the qualities of both may affect the issue.

A. Parasite Factors

(1) *Pathogenicity* is the ability to produce disease and varies not only from one species to another but also between different strains of the same species. The virus of chickenpox usually causes a mild illness whereas that of variola major is associated with severe disease. Within a species, pathogenicity may depend on some special factor such as the capsule of the pneumococcus and the enzyme coagulase of *Staphylococcus aureus*.

(2) *Infectivity* is the ability of an organism to spread readily from one host to another. With some organisms a large inoculum is required before a foothold can be gained in the host, as in paratyphoid fever where the bacillus must multiply in food before it is dangerous to man. Sonne dysentery on the other hand can be spread by small numbers

of bacteria that do not require an intermediate stage of growth. Virus diseases, likewise, vary greatly in infectivity. Some, like smallpox virus, are believed to cause disease with a single virus particle, while others, such as mumps, are only moderately infective. High infectivity is not necessarily associated with severe disease, chickenpox being a good example.

(3) *Invasiveness* is the ability of an organism to spread within the host. At one extreme is *Clostridium tetani* whose growth is limited to the site of injury and at the other *Treponema pallidum* which disseminates rapidly throughout the body. Most viruses and many protozoa produce generalised infections.

(4) *Virulence* is the ability to produce severe disease. The property may be fixed as in variola major virus or may be variable as in influenza in which epidemic strains are usually highly invasive and virulent.

(5) *Dosage*. The size of the infecting dose may be extremely important in determining the outcome. A large number of organisms invading the host may overwhelm the defences whereas a small number may be suppressed or tolerated. A mixed infection may produce more serious effects than separate invasion by the components. This is particularly noticeable in combined infection with viruses and bacteria as seen in measles or influenza complicated by staphylococcal pneumonia.

B. Host Factors

(1) **Constitution**

a. *Age*. Many virus diseases produce much less disturbance in the young, for example, chickenpox and mumps. Sometimes, however, the converse is true and the young suffer more severely, a good illustration being the susceptibility of new-born mice to Coxsackie virus infection and the high resistance of adults.

b. *Sex*. The two sexes may react differently to infection. Gonorrhoea is a mild disease in women and is readily overlooked, but in man the infection causes a severe reaction with an acute urethritis whereas the converse is true in infections with *Herpesvirus hominis* type 2. Pregnant women are particularly vulnerable to infectious disease and may suffer a high mortality rate, for example in outbreaks of infectious hepatitis.

c. *Hormones*. Cortisone and its deriyatives greatly influence the host's response to infection. The therapeutic administration of corticosteroids may be harmful, lowering the host's resistance to infection and occasionally causing spread from quiescent lesions. In animals, steroids are used to induce experimental infections, for example, Coxsackie infection in adult mice and poliomyelitis in monkeys. Sometimes, corticosteroids are of value in controlling the extent of the host reaction to infection and occasionally they are life-saving by tiding the host over the period of circulatory collapse that occurs in some severe septicaemias, or relieving respiratory obstruction from inflammatory oedema. Sex hormones also influence the reaction of the tissues to infection. Oestrogens render the vaginal epithelium much more resistant to bacterial invasion while testosterone sensitises the testes to mumps virus.

d. *Genetic Factors*. In man, resistance to malaria and tuberculosis may be genetically determined through natural selection (see defence reactions). The same processes are seen in outbreaks of myxomatosis in rabbits. The death rate in the initial epidemic may be as high as 99 per cent. but with the destruction of the most susceptible individuals, the survivors and their descendants have a higher immunity, consequently the death rate in subsequent epidemics falls.

(2) **Environment**

a. *Atmosphere.* The humidity and the temperature of the air play an important part in the spread of infection by the effects they have on the host and parasite. Influenza epidemics occur in the winter and poliomyelitis in the summer. Changes in humidity and temperature may both alter the habits of the host or the state of the respiratory mucosa. Atmospheric changes may also affect the survival of the parasite prior to invasion. Irritant gases and smoke reduce the resistance of the respiratory tract to infection and increase the incidence of pneumonia.

b. *Nutrition.* The three scourges of man, famine, pestilence and war, are traditionally linked together. Infection in the under-nourished host generally results in severe disease with a high death rate, well illustrated by outbreaks of measles and infectious hepatitis in poverty-stricken communities. More debatable is the apparent increase in the severity of poliomyelitis in affluent societies for this may be influenced by standards of hygiene and the age groups involved. Lack of protein in the diet may interfere with the development of cell-mediated immunity and deficiencies of vitamin A lower the resistance of epithelial surfaces.

c. *Water and Sanitation.* The standard of hygiene in a community influences the incidence of infection and the age at which it occurs. This may lead to a high infant mortality rate but the survivors will have a strong immunity to intestinal infection, and disease in the adults will be less frequent and less severe.

d. *Contact with other Species.* People coming in contact with animals and their products are prone to certain diseases, veterinary surgeons to brucellosis, hide porters to anthrax and bird fanciers to ornithosis.

(3) **Previous Immunological Experience**

The immunity generated from the primary encounter with an infection will alter the host reaction to subsequent exposures. This process will be discussed more fully in the section dealing with immunity.

Defence Mechanism of Host

The defences of the host restrict the growth of micro-organisms to the surfaces of the body and prevent invasion of the tissues. Should this first line of defence fail and invasion result, the reactions of the host are focused on preventing further spread and eradicating the parasite. As a rule, the invader is destroyed and the barrier restored. Occasionally, when the host is unsuccessful, death may ensue but, more often, the two species come to terms and a state of equilibrium is reached. These defence reations are complex and not fully understood.

A. Local Defence

Control of Surface Organisms by Competition: The growth of micro-organisms on the skin, in the respiratory passages and in the bowel is governed by the interaction of one parasite with another and with their host. If the balance of the flora is disturbed, for example by antibiotics, one species may proliferate with harmful results. Monilial stomatitis and staphylococcal enteritis are notorious complications of antibiotic treatment. Viruses, too, may compete in a manner beneficial to the host. Before a virus can multiply, it must enter the host's cells and in doing so may block invasion by other viruses—a phenomenon known as interference. Use is made of this property in controlling outbreaks of poliomyelitis by infecting man with a living but harmless polio virus to prevent later invasion by a virulent strain.

Prevention of Invasion

(1) *Mechanical.* The intact skin and mucous membrane present an effective barrier to invasion by many organisms. A few such as the tetanus bacillus can cause disease only when the host has been injured while others, for example the malarial parasite and the virus of yellow fever, must be injected by the bites of insects. Flushing with tears and saliva helps to keep the membranes of the eyes and mouth healthy and in the urinary tract the free flow of urine is important in preventing infection. Airborne bacteria are unable to reach the alveoli of the lung before being trapped in the mucus of the respiratory passages and swept upwards by the cilia. When this ciliary action is impaired by virus infections or irritant gases bacteria readily spread to the lung.

(2) *Physico-chemical.* Lysozyme, an enzyme present in tears, saliva and other body fluids, destroys some bacteria as do fatty acids in the skin. Many ingested bacteria are killed by the acid secretion of the stomach and, though some survive, the upper bowel is remarkably free of organisms.

(3) *Surface Antigen-Antibody Reactions.* IgA antibodies are present in seromucous secretions and probably prevent binding of micro-organisms to host cells. These antibodies are synthetised by local plasma cells and are stabilised against proteolysis by combination with a protein secreted by local epithelial cells. Antibodies against influenza virus may be detected in nasal secretions of people immune to influenza and neutralising antibodies may be found in the bowel contents of individuals immune to poliomyelitis.

(4) *Inflammatory Reaction.* Should a bacterium succeed in penetrating the skin or mucous membrane it provokes an inflammatory reaction with increased permeability of capillary vessels, infiltration by polymorphomuclear and mononuclear cells, and transudation of bactericidal factors. When the outcome is favourable the bacterium is destroyed or walled-off by fibrin and collagen.

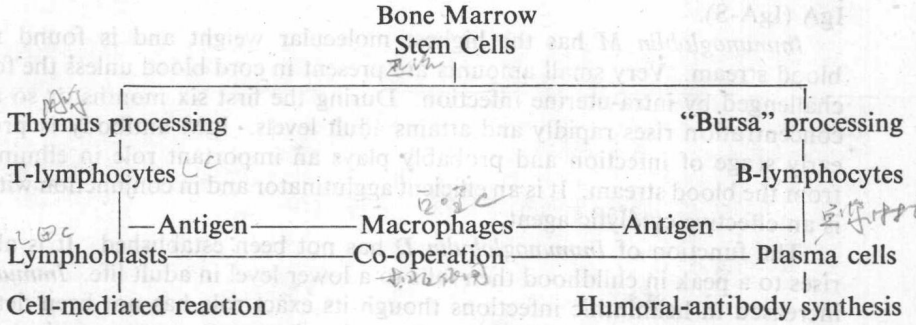
B. Disposal of Invader in Body Fluids

Once an invader has entered the body it may spread and multiply in the extra-cellular fluids or replicate within cells. There are three complementary processes for dealing with the organism, namely phagocytosis, cell-mediated immunity and antibody-dependent or humoral immunity.

(1) *Phagocytosis.* In the non-immune host the main defence is phagocytosis by polymorphonuclear cells and macrophages of the reticulo-endothelial system. Opsonisation of bacterial cells by antibody and complement facilitates adherence to the surface of macrophages where there are specific receptors with a high affinity for IgG and the C3 component of complement. Binding may also be enhanced by cytophilic antibody on the surface of macrophages. Once engulfed the micro-organism is destroyed by hydrolytic enzymes including lysozyme and by bactericidal basic polypeptides. The resultant antigenic fragments are presented to lymphocytes, stimulating the production of cell-mediated and humoral immunity.

(2) *Cell-mediated Immunity.* Non-specific defence mechanisms acting alone provide inadequate protection and the development of specific immunity is essential for survival. This is determined by two different populations of small lymphocytes, namely T-cells and B-cells, which in conjunction with phagocytes remove and destroy invading micro-organisms. Both are derived from the same stem cells in the bone marrow but T-lymphocytes are dependent on the thymus and are primarily responsible for cell-mediated immunity whereas B-lymphocytes are independent of the thymus and concerned with antibody synthesis. When stimulated by antigen T-cells are transformed into lymphoblasts with a cytoplasm rich in ribosomes but lacking antibody; similarly B-cells are

transformed into plasma cells with a well-developed, rough-surfaced endoplasmic reticulum characteristic of cells actively synthesising and secreting protein. A second stimulus is generally necessary for B-cell proliferation and is probably provided by T-cells though a few antigens may directly stimulate B-cells. Once programmed a proportion of lymphocytes act as memory cells and respond rapidly to further challenge by the same antigen. A highly sophisticated system of self-regulation has been evolved to prevent over-reaction and safeguard tissues against self-destruction by these powerful immune mechanisms. When T-cells are stimulated they form active lymphoblasts capable of destroying cells with a foreign antigenic structure and also give rise to suppressor cells with the ability to inhibit B-cells and sometimes T-cells. The level of circulating IgG appears to influence the production of further IgG antibody.



(3) *Antibody-dependent Immunity*. An antigen is a protein molecule or complex of proteins differing in structure from these present in the healthy animal. Homologous proteins are not antigenic but may become so after conjugation with foreign non-protein molecules. Drugs such as penicillin may unite with serum proteins to become antigenic and this combination is responsible for allergy. Micro-organisms are complex structures possessing many antigens, some of which play an important part in stimulating specific immunity. An antibody is formed in response to stimulation by an antigen. Following the initial stimulus there is a latent period of 2 to 10 days before antibody appears. Subsequently antibody levels increase steadily for 2 to 10 weeks then gradually decline. Further stimulation by the same antigen produces a more rapid response with a shorter latent period and a higher and more persistent antibody level. It should be noted that there is marked variation in the individual response and that the foetus and young baby respond poorly. The presence of antibody may bear little relationship to immunity against infection, for example, streptolysin O antibodies against streptococci, *Salmonella typhi* H antibodies in typhoid and the heterophil antibodies that appear in infectious mononucleosis and syphilis.

Antibodies are produced by plasma cells and belong to the group of proteins known as immunoglobulins of which there are five main structural types: IgG, IgA, IgM, IgD and IgE. The main environmental factor determining antibody production is antigenic challenge but individual variation in response is genetically determined by immune-response ('I-R') genes.

Immunoglobulin G is the most abundant and diffuses readily into the extravascular compartment of the body where it plays a dominant role in neutralising bacterial toxins and coating micro-organisms to facilitate phagocytosis. It readily crosses the placenta and provides major protection against infection during the first few weeks of life.

Transfer of IgG from the mother to the foetus takes place during the final trimester so premature infants tend to have low levels and are especially prone to infection. Serum IgG at birth is entirely derived from the mother and falls over a period of 3 to 6 months to one-third of the birth level. Thereafter it rises steadily as the infant produces its own IgG and reaches 80 per cent. of adult levels by the close of the second year of life.

Immunoglobulin A is not detectable at birth and adult levels in serum are not achieved until puberty. IgA is found predominantly in the external secretions of the respiratory and alimentary tracts where it protects the surface membranes against invasion by micro-organisms, probably by interfering with the binding of the organism to host cells. It does not fix complement but may act in conjunction with lysozyme and complement to destroy certain coliform organisms. IgA is protected against proteolysis by union with a protein secreted by surface epithelial cells, the combination being known as secretory IgA (IgA-S).

Immunogloblin M has the highest molecular weight and is found mainly in the blood stream. Very small amounts are present in cord blood unless the foetus has been challenged by intra-uterine infection. During the first six months or so after birth the concentration rises rapidly and attains adult levels. IgM antibody is produced in the early stage of infection and probably plays an important role in eliminating bacteria from the blood stream. It is an efficient agglutinator and in conjunction with complement is an effective cytolytic agent.

The function of *Immunoglobulin D* has not been established. It is absent at birth, rises to a peak in childhood then falls to a lower level in adult life. *Immunoglobulin E* is increased in helminthic infections though its exact role has not been determined. IgE antibodies bind firmly to mast cells and subsequent contact with antigen releases vasoactive amines, a process associated with hayfever and extrinsic asthma.

Complement plays an important part in the destruction of foreign cells or cells with an altered antigenic structure. It consists of a series of nine protein components. Activation of the complement system is usually triggered by binding of the first stage to a complex formed by the union of an antigen with IgG or IgM antibody but may be initiated by bacterial endotoxin acting through an alternate pathway independent of antibody. Subsequently each stage activates and amplifies the next so that one molecule may ultimately give rise to thousands of active components. Activity is regulated by a complex system of inhibitors. The final product damages the target-cell wall, possibly by the action of a phospholipase. In the case of bacteria this exposes the underlying plasma membrane to lysozyme, which destroys the mucopeptide layer with resultant bacteriolysis. A combination of antibody with complement can effectively neutralise viruses. Fragments produced during the consumption of complement have the additional effect of augmenting the inflammatory response by attracting phagocytic polymorphonuclear cells and by increasing vascular permeability. Complement fixation is used extensively in the laboratory to demonstrate the presence of antigen or antibody.

C. Intra-cellular Defences

Intra-cellular immunity appears to play an important part in resistance to infection, especially by viruses. The processes involved are incompletely understood but are dependent to some extent upon the formation of interferon, a non-specific antiviral protein produced by cells in response to living or inactivated virus. Interferon is capable of blocking virus replication in the absence of antibody and of bringing infection to an end. Viral interference, in which infection by one virus prevents superinfection by another, is probably mediated through interferon. Interferon production appears to be dependent in some way on cell-mediated immune mechanisms.

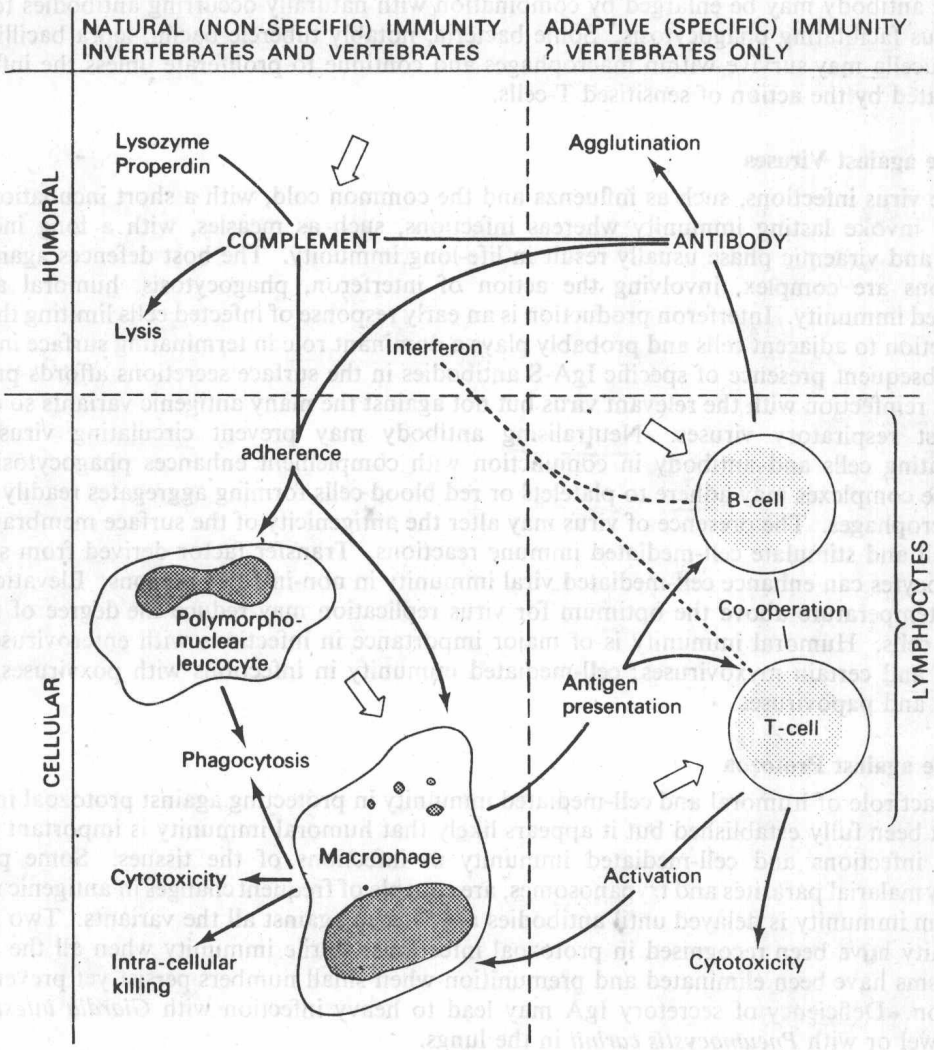


FIG. 1. Simplified scheme of the immune response to emphasise the distinction between natural and specific, and between cellular and humoral immunity.

Defence against Bacteria

Once a bacterium has penetrated the chemical, antibody and physical barriers on the surface membranes of the body and invaded the blood stream it is contained and eliminated by humoral and cellular defences. Phagocytosis by polymorphonuclear cells or by wandering and fixed macrophages of the reticulo-endothelial system is enhanced by opsonisation or by the presence of cytophilic antibody on the surface of macrophages. In the case of gram-negative bacteria the combined action of antibody and complement damages the cell wall and exposes the lining membrane to the action of lysozyme with resultant bacteriolysis. Complexes of toxin neutralised