Infectious diseases
A review

KARL G. NICHOLSON, MB, FRCP, MRCPath, Senior Lecturer in Infectious Diseases
MARTIN J. WISELKA, MB, MRCP, Wellcome Trust Fellow
Infectious and Tropical Diseases Unit, Groby Road Hospital, Leicester

Advances in the diagnosis, treatment and prevention of infections and developments in other branches of medicine have altered the spectrum of infections and their management. Diseases previously rare or unknown have assumed major importance, and opportunistic organisms, once regarded as lowly pathogens, have become increasingly prominent due to new surgical techniques, immunosuppression and the acquired immune deficiency syndrome. Advances in basic science have progressed rapidly leading to an increased understanding of microbial pathogenicity and exploitation of this knowledge will stimulate new methods of diagnosis, prevention and treatment.

Infectious diseases in Britain

The past

The entire pattern of infectious diseases in Britain has changed since the second world war. It is chilling to think that the antibiotic era only dates from 1940, well within the lifespan of many Fellows of the College, and that older colleagues recall vividly the hopelessness of bacterial endocarditis, the devastation of bacterial meningitis, and the toll of puerperal sepsis, syphilis, tuberculosis, pneumonia, typhoid fever, and many other bacterial infections. Until the 1950s, infectious patients often spent lengthy periods in isolation wards which were usually remote from the main hospitals.

Improved living standards, the introduction of the National Health Service and the rapid development of new antibiotics and vaccines greatly reduced the number of notified infectious diseases during the 1950s and 1960s. This decline coincided with new developments in other branches of medicine and, in comparison with these, the requirement for infectious disease physicians seemingly diminished.

The increasing choice and availability of antibiotics led many clinicians to the erroneous belief that infection could be managed readily by any doctor; instead their widespread indiscriminate use both in man and in animals has resulted in increasing antibiotic resistance. In most district general hospitals infection has been managed by general physicians and other clinicians, aided by on-site microbiologists. This situation has worked reasonably well for a number of years but several factors have led to the recognition that specialists in infection—as opposed to ‘infectious’ diseases—have a vital role.

The present

The increasing range and complexity of infection, together with the growing number of antibiotics, antifungals, antivirals, and antiprotozoal agents and the recent emphasis on clinical audit, has led to increasing ward consultations and referrals to the infectious diseases team.

The pattern of infection has altered in several ways:
1. There has been an enormous escalation in air travel and a concomitant increase in the number of imported infections such as chloroquine-resistant malaria, tuberculosis, typhoid, filariasis and schistosomiasis, acquired either during holidays to the Third World, business travel, or social travel by recent immigrants. Many imported infections are trivial, some require expert knowledge of infectious and tropical diseases, and others such as the haemorrhagic fevers have assumed major public health importance.

2. There has been a steady rise in the number of enteric infections, such as Salmonella enteritidis phage type 4, which can be related to changing eating habits, animal husbandry and food preparation. Several Salmonella and Legionella outbreaks have highlighted the importance of authorities having adequate arrangements for the prevention, detection and control of outbreaks.

3. As medical technology has advanced, multiplicity of invasive devices and therapeutic measures necessary to resuscitate and sustain life have, paradoxically, become the precipitating agents of subsequent serious infection. The average rate of nosocomial infections is 15–25% of all intensive care unit admissions. A survey of over 18,000 patients admitted to 43 hospitals showed 19% to be infected and of these half acquired their infection while in hospital. With the increasing number and complexity of surgical procedures the number of nosocomial infections will increase, not diminish. These infections are of particular importance in

Address for correspondence: Dr Karl Nicholson, Groby Road Hospital, Groby Road, Leicester LE3 9QE.

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certain groups of patients including the immuno-suppressed, neonates, those in intensive care units, those undergoing major surgery, and the elderly.

4. ‘New’ infections such as Lyme disease, pseudomembranous colitis, toxic shock syndrome, legionnaires’ disease, delta hepatitis, non-A non-B hepatitis, cryptosporidiosis, and the acquired immune deficiency syndrome are constantly emerging and posing new diagnostic and therapeutic problems. Infectious disease physicians now have a key role in the prevention and treatment of the various opportunistic infections which occur in patients with AIDS.

5. Widespread and uncritical use of antibiotics has resulted in increasing antibiotic resistance. The prevalence of methicillin resistant Staphylococcus aureus (MRSA), for example, has risen considerably in recent years, and clusters of MRSA infections have been responsible for ward and unit closures. Since antibiotic resistance can vary from one location to another, rational antibiotic therapy depends upon specialist training and continuing liaison with microbiologists.

Ongoing developments and future perspective

Public health

As a result of the Stanley Royd salmonella outbreak and the first and second reports of the Stafford legionnaires’ outbreak, the Department of Health has directed regional health authorities to review their access to public health advice and to ensure that each district health authority has in turn made arrangements for the surveillance, prevention, treatment and control of communicable diseases within its boundaries. Each Health Authority must now appoint a Regional or District Director of Public Health, who should ensure that appropriate services are provided to agreed standards of care. It is generally accepted that there is a shortfall of suitable people with training in public health, epidemiology and infectious diseases and that new training initiatives and resources are required.

‘Isolation’/‘infection’ units

The importance of having an infection unit in district general hospitals has been stressed by the Royal College of Physicians, by Dr David Tyrrell in his Rock Carling monograph [1], Professor Alasdair Geddes in this journal [2], and in a Lancet editorial [3]. The availability of such units, which could be an integral part of main hospital buildings, will encourage the appropriate isolation of patients without loss of day-to-day management by the admitting firm.

The integration of ‘infection beds’ into general hospitals provides additional benefits, especially with respect to teaching, training, and research. In at least one hospital the infectious diseases team and microbiologists have together organised a ward consultation rota for all patients having positive blood cultures or unusual pathogens. This should rationalise the use of antibiotics, improve patient care, and provide additional training for junior medical staff in diverse clinical specialties.

Proximity of infection wards to the microbiology department also facilitates combined ward rounds, seminars, and laboratory work by trainee infectious disease specialists, and ward work by junior microbiologists, as recommended by the Joint Working Party of the Royal College of Physicians and the Royal College of Pathologists [4]. Genito-urinary physicians see the infection unit as a facility where they can jointly manage AIDS patients and other patients, such as those with severe genital herpes, and where their junior staff can fulfil training requirements. Nursing management and control of infection sisters see a centralised infection unit as a focal point for the training of staff in the control of infection, thereby maintaining high standards in other hospital areas.

AIDS

A Department of Health Working Group has predicted that there will be between 10,000 and 30,000 AIDS cases diagnosed by the end of 1992 in England and Wales. The main burden of care of patients is being met initially in infection units, departments of genito-urinary medicine, haemophilia centres, and by clinicians with a specific interest, particularly those in chest medicine. This ensures that expertise and resources are concentrated in specific locations which can then be the focal points for the training of junior medical and nursing staff, paramedical staff, community nurses and the voluntary sector.

Laboratory diagnosis

Many of the current diagnostic methods are labour-intensive, time-consuming, and lack specificity. Conventional microbiology, for example, largely depends upon the ability to grow micro-organisms or detect antibody rises to known pathogens. Many bacterial infections can be diagnosed within several days, but others, such as Legionella and mycobacteria, are fastidious or grow only slowly in the laboratory. Bacteriologists see the need for improved methods for identifying the more fastidious and slow-growing micro-organisms and to obtain data more rapidly on antibiotic resistance. Additional problems are created by the prior administration of antibiotics.

Viruses

Viruses grow intracellularly and may cause a typical cytopathic effect or can be detected by immunofluorescence or haemadsorption, usually within several days of inoculation of suitable cell monolayers. The rewards of viral cultures are generally small and most viral diagnoses are based on serology with the results usually only available some weeks after the patient has
been discharged from hospital. Until recently viral infections could not be treated with drugs and it was therefore not essential to confirm the diagnosis. However, with the increasing number of candidate antiviral agents and the severity of viral infections in neonates, the elderly and the immunocompromised, it has become increasingly important to improve diagnostic virology.

Considerable progress has already been achieved. Cytomegalovirus, for example, can now be detected within 24 hours using the direct early antigen fluorescent focus (DEAFF) test, whereas the appearance of the typical cytopathic effects can take many days. Monoclonal antibodies have also been used successfully to detect other viruses, particularly those present in high titre.

Gene probes

The advantages of the use of gene probes in diagnosis include the early detection of organisms difficult or impossible to grow in vitro and the ability to analyse hundreds of specimens simultaneously.

Gene probes are highly specific and react only with a particular sequence of nucleic acid found in that organism, or group of organisms. The usual technique is to use a radioactive probe of RNA or DNA, whose hybridisation with the sequence or gene can be detected by autoradiography. Briefly, the unknown clinical specimen and appropriate controls are deposited onto a sheet of hybridising membrane which is then incubated with the radiolabelled probe, washed to remove unbound probe and exposed to X-ray film. Positive samples light up by autoradiography, and the intensity of the dot broadly corresponds with the amount of nucleic acid present. Although the assays are sensitive, specimens may need cultivating to increase the organism or virion count to readily detectable numbers. An extension to this technique is in situ hybridisation which localises specific sequences in pathological specimens.

Gene probes also represent a powerful research tool. For example, they can be used to search for genes coding for putative virulence factors in organisms from healthy carriers and patients with invasive disease. Unfortunately, radioactive probes can only be handled by skilled personnel under controlled conditions, and the entire process of labelling the probe, hybridising, and exposure can take several days. Non-radioactive enzyme-linked probes that give a colour reaction are being developed and evaluated. Although easier and safer to use, they appear to be less sensitive, particularly when the clinical material contains few organisms.

Polymerase chain reaction

The polymerase chain reaction (PCR) is an imaginative technique for the in vitro amplification of the RNA or DNA of an organism. It is so sensitive that it is possible to detect even one organism in a clinical speci-

Pathogenesis of infectious diseases

Since a number of potentially highly pathogenic micro-organisms are ubiquitous, it remains obscure why some people carry bacteria such as the meningococcus without symptoms, while others, apparently infected with the same organism, have invasive disease.

Advances in molecular and cellular biology and the development of animal models and their manipulation using methods such as transgenic technology (animals that gain new genetic information from the addition of foreign, eg human, DNA are described as transgenic) should now facilitate studies on the immunopathogenesis of infection at the molecular level.

A variety of approaches are being used. The variability of organisms—in terms of species distribution, geographic distribution, and virulence—can readily be studied with panels of monoclonal antibodies and by gene cloning and sequencing. The ability to clone the genes for each of a number of putative virulence factors, such as capsule production, adhesions, lipopolysaccharide, and various toxins allows the contribution
of each to be assessed, both in \textit{in vitro} assays and in animal models. At the clinical level, organisms obtained from patients can be studied for the presence or absence of putative virulence factors and these can then be correlated with carriage and the severity of infection. The engineering of mutants, deleted for or expressing modified putative virulence factors, will clarify further their pathophysiological role in \textit{in vitro} models and animal models, with increasing emphasis being given to transgenic technology. Thus, for example, the role of bacterial proteases on human immunoglobulins might be assessed in mice producing human immunoglobulin. Finally studies of the regulation of gene expression should provide new insights into the mechanisms controlling virulence.

\textbf{Vaccine development}

\textit{More vaccines required}

The ultimate goal of much contemporary research into infectious diseases is the production of new and more effective vaccines. Although vaccination has been extremely effective in controlling a number of infectious diseases and has seen the eradication of smallpox, vaccines composed of the purified polysaccharides of pneumococcal types responsible for the majority of paediatric infections have proved to be poorly immunogenic in the young. Similar vaccines for the prevention of infection with \textit{Haemophilus influenzae} type B and \textit{Neisseria meningitidis} group B have also been ineffective.

Control of malaria is badly needed. Estimates for the worldwide incidence of malaria range from 100 to 300 million cases of malaria and 1 to 2 million malaria-related deaths annually. Interest in vaccination against malaria is strong and several strategies are being investigated.

Upper respiratory tract infections are the most common type of infection. They cause considerable morbidity (which can be measured by the number of visits to medical practitioners each year, drug costs and days off work) and are responsible for a number of deaths, notably among high risk groups such as the very young, the elderly and those with chronic chest disease. Currently more than half a dozen viral agents are responsible for the majority of upper respiratory infections, but at least 30–40\% of respiratory infections go undiagnosed even when extensive laboratory tests are carried out. Of the known viral agents, rhinoviruses are implicated in 25–30\% of episodes, but more than 100 antigenic serotypes of rhinoviruses have been identified. Treatment remains only symptomatic and vaccination remains a long-term goal.

Possibly the greatest public health problem facing us is the emerging AIDS epidemic. No effective treatment for AIDS is available and azidothymidine, the only licensed drug against HIV, merely delays the progress of the condition and is poorly tolerated by many patients. Vaccines against HIV-1 and HIV-2 are obviously a priority but the major variation between strains of the same type presents a significant problem akin to the control of influenza.

\textbf{New vaccine development}

Progress during the last few years in molecular genetics and nucleic acid chemistry has led to exciting new prospects for immunisation against many diseases. The new technology is being applied in several ways. The most direct approach is by gene cloning and their expression in heterologous prokaryotic and eukaryotic systems, such as yeasts, bacteria, or viruses, to produce large quantities of the immunogen from organisms that are difficult or dangerous to grow. Recombinant DNA techniques have already been applied for expressing hepatitis B surface antigen and core antigen, and a surface antigen vaccine is available commercially.

Delivery of many existing vaccines must be improved but in many Third World countries public health officials already face severe financial and logistic problems. Thus the cynic might argue that there is little point in developing new vaccines, such as hepatitis B which is extremely costly. To be truly beneficial to those most in need, new vaccines must be inexpensive, easily administered, endow lifelong protection, and be free from serious adverse effects. Oral polio vaccine generally achieves these criteria (the risk of vaccine induced paralysis being 0.06 instances per million doses distributed and 0.14 per million doses in contacts); moreover, virus excretion from vaccinees and subsequent spread of infection ensures that many non-vaccinated children still become immune. A further application of the new technology is therefore to develop bacteria and viruses as carriers to deliver inserted antigenic components.

The use of vaccinia virus has attracted much attention since this virus is able to accept relatively large amounts of genetic material which can be fully expressed. Potential live vaccines using recombinant vaccinia viruses have been constructed for hepatitis B, and also for herpes, rabies, parainfluenza virus and other viruses. The advantages of this type of approach include low cost, ease of administration, vaccine stability, long shelf-life, and the possibility of inserting multiple antigens. However, the adverse effects of vaccinia virus are well recognised, and although the thymidine kinase deleted recombinants have reduced virulence in animal models, vaccinia remains an interesting experimental tool but a relatively poor prospect for immunogen delivery. The possibility of using other recombinant viruses as vectors is under study, including, for example, oral adenovirus vaccines, polio virus and genetically modified herpes simplex strains.

In the same way, considerable interest has focused on bacterial vectors, such as \textit{Salmonella typhi} mutants which are attenuated, are excellent cloning vehicles, and which provide the possibility for giving multiple antigens on one occasion. Moreover subsequent spread within the community would be beneficial. The possibilities are indeed exciting, but there still remain
serious concerns regarding the safety and effectiveness of this kind of approach.

Another development in new vaccine production stems from studies on the immunopathogenesis of disease and the precise identification of the important microbial epitopes. This makes possible the development of chemically synthesised polypeptide vaccines which offer many advantages, not least their freedom from quantities of irrelevant antigenic material. Short polypeptides are poorly immunogenic by themselves but when attached to a macromolecular carrier they can induce protective antibodies.

**Immune modulators**

Our understanding of the immune system has progressed in recent years and many of the factors mediating the immune system have been purified and cloned. This has brought many new therapeutic possibilities such as the use of interferon and the interleukins which are currently being investigated. In severe infections and septicaemia there is a large rise in these circulating lymphokines. Some of the actions of this group of substances may be counterproductive as in the hypotension and interstitial fluid leakage found in severe bacterial septicaemia and endotoxic shock which may be due to a rise in tumour necrosis factor (TNF). Shock may be averted or modified if the actions of TNF are blocked at an early stage in the infection.

**Conclusion**

Basic scientific research is leading towards a greater understanding of the interaction between pathogen and host and is opening up new possibilities for treatment and vaccination. The spectrum of infectious diseases, their investigation, management, and detailed study is constantly evolving and an increase in the number of infection physicians is required. The infection specialist of the future will not be isolated in old fever hospitals but will be part of a team approach to the management of hospital and community infection. The new scientific developments require evaluation in volunteers and patients by well trained clinicians. In order to specialise in the area of infection, the physician must have an appreciation of the principles of microbiology, immunology, epidemiology, pharmacology and molecular biology, for without this understanding it will be difficult to translate the important advances being made in the laboratory to changes in the care of patients with infection.

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