Reviews in Medicine

Infection and infectious diseases

P.D. Welsby

Department of Infectious Diseases, City Hospital, 51 Greenbank Drive, Edinburgh EH10 5SB, UK.

Introduction

Even in a somewhat selective personal view of recent developments in infection and infectious diseases one has to take a historical view.

The 1970s were a quiescent period for most infectious diseases. There were small outbreaks of traditional infections such as Salmonella but overall there was little to cause public alarm. Lassa fever was (incorrectly as it turned out) perceived to be a highly infectious disease that could sweep through western societies such that draconian measures were necessary to protect the community at large – in fact the use of the Trexler Isolator, a ventilated negative pressure polythene bag into which the suspect was invited to enter was to protect the medical and nursing attendants rather than the community. Later there was a worry that we were all about to be engulfed in an epidemic of genital herpes but, despite several paperback books, life continued as before with dramatic statements by doctors receiving much transitory media attention. The general public and the government became immunised by failed prophecies of impending doom. Articles which prophesied that there would always be new infections to keep us busy, 'New Plagues for Old', were not treated seriously. In the late 1970s many 'realistic physicians,' including myself, thought that the specialty of infectious diseases was in a slow decline, because nothing obvious was happening. But a lot was happening covertly. Infection with the human immunodeficiency virus (HIV) was spreading widely in the late 1970s but, because of the long incubation period before the, now well-recognized, clinical consequences ensued, and because of the continual (although variable) infectivity, and because it was spreading by an almost universal human activity (sexual contact), by the time it was obvious that the 'homosexual harbinger groups' in the United States had a clinical problem, up to 25% were infected. Despite much accusation by homosexually biased writers the medical profession was not malicious in its neglect of this new disease: it was unfortunately but understandably slow to realize the implications, and even slower to take action. Indeed the first published report of the acquired immunodeficiency syndrome (AIDS) took second place to an article on Dengue virus type 4 in the Carribean – and who now knows about the problem that Dengue virus caused?

This review will reveal the increasingly appreciated role of infection as a factor, if not necessarily the factor, in many conditions ranging from dandruff to peptic ulceration.

AIDS

AIDS is now such a familiar topic of medical concern that every weekly journal always has at least one mention. Annual reviews, to reflect current interests, cannot fail to devote a major section to AIDS.

Despite the subsection heading, 'AIDS' is regarded by some as being an obsolete term because HIV is a progressive disease and the diagnosis of full-blown AIDS often reflects not a pathological or immunological judgement but rather a clinical diagnosis dependent on the somewhat serendipitous development of various complications of HIV infection. What is needed is some easily measurable index or assessment of HIV-related immunodeficiency such that prognosis and response to new treatments of HIV (and associated opportunistic infections and neoplasms) can be discerned.

Three patterns of HIV infections can be identified. In the usual pattern (pattern 1) there is prolific replication of the virus within 3 to 6 weeks after exposure and antibodies develop and, in general, persist. In the very rare pattern (pattern 2) a prolonged seropositive state is followed by loss of antiviral antibodies but with viral DNA still detectable by complex tests. The loss of antiviral antibodies probably reflects the cessation, or severe restriction, of production or release of the virus. In
pattern 3 there is prolonged asymptomatic 'silent' infection without the production of (conventionally detectable) antiviral antibodies. Pattern 3 is a very mixed blessing. It suggests that replication of HIV may be spontaneously suppressed by combination of cellular, viral and other immune mechanisms – and this has implications for the likely success of vaccination (as does the fact that some highly exposed sexual partners of HIV patients do not develop conventional evidence of infection). Less favourably we do not know if such patients are infectious to others, either by sexual contact or blood transfusion. We also do not know if such patients will eventually seroconvert and go on to develop classical HIV manifestations.

The major question for the HIV infected and their medical advisors is the likely progression of the infection. Will every HIV infected individual eventually develop HIV-related disease (as is suggested by the approximately constant rate of accumulation of AIDS patients in the HIV infected with the passage of time), or will there be some individuals who will achieve a state of symbiosis?

Some predictors are available which can assist the doctor in giving advice. A 3-year study from San Francisco showed a progression of 22% to AIDS with a further 19% developing AIDS-related conditions, with β2 microglobulin concentration, packed cell volume, HIV p24 antigenemia, and the proportion and number of T4 lymphocytes each independently predicting progression to AIDS, the β2 microglobulin being the most powerful predictor. It was predicted that half the men who were HIV-positive will develop AIDS by 6 years and that no less than three quarters will ultimately develop AIDS or an AIDS-related condition. Other predictors include the age of the patients (the older the patient the more rapid the progression to AIDS) which was well shown in a series of haemophilia patients.

It seems logical to predict that such predictors will assume increased importance in determining which patients will be most likely to benefit from early zidovudine treatment. However, some studies have found a remarkably poor prognosis in patients with generalized lymphadenopathy or AIDS-related complex irrespective of initial clinical, immunological, and serological findings and the authors suggest that almost all such patients may be candidates for antiviral therapy irrespective of predictor status.

Three important papers have described the quantity of virus present in the plasma or cells of those infected with HIV9-11 and a useful editorial summarises the important aspects.12

Many, possibly all, HIV-infected patients have circulating virus that can be cultured in their (cell free) plasma. Patients with more advanced disease have higher levels of circulating virus. Most cell-associated HIV in the blood is contained within the CD4 + T cells (although other cells may be important reservoirs). Despite the numerical decline in the absolute numbers of CD4 + cells, the proportion of those cells infected increases with the progression of the disease. The extent of plasma viraemia shows a much better correlation to the clinical stage of disease than tests for HIV p24 (HIV core) antigen and may act as an accurate prognostic sign for disease progression. Treatment with zidovudine reduces the quantity of plasma virus but, in the first 4 weeks of treatment at least, has little effect on cell-associated virus levels.

Paediatric AIDS also is a cause for concern. An Italian multicentre study reported that perinatal infection occurred in 32.6% of children born to HIV-positive mothers with a higher transmission rate in those born vaginally and then breast fed. A European multicentre study reported an estimated vertical transmission rate of 25%, which was probably an underestimate because of the insensitivity of testing. In this study no child became HIV seronegative and then reverted to positivity, but 5 antibody-negative children were positive on virus culture or antigen testing: these children were well and did not have endstage AIDS in which antibody may be lost. Such observations give rise to disquiet and will need to be confirmed as detection of antibody is the major screening test for infection. An editorial discusses these two papers in depth.

The extent to which HIV may become a common 'standard heterosexually transmitted disease' in the developed world is still debated (in the developing world, especially Africa, there is no debate – it is). Although the answer to the question in the developed world will have to await the future there are remarkable instances of heterosexual spread. A heterosexual man was shown to have been associated with HIV infection in 11 (out of 19) female contacts. So there is no room for complacency. Despite the small numbers of people known at present to have been infected heterosexually in Britain there is no doubt in my mind that the government is correct to treat HIV infection as a problem for the whole community and not just the initially recognized at-risk groups.

Early detection of complicating infections is an important feature of management of AIDS patients. In a study of patients with proven Pneumocystis carinii pneumonia 94% of those with a low resting PaO2 desaturated on exercise, as did 80% of those with a normal PaO2 at rest. Only 10% of patients with other chest disorders did this. Although a laboratory study, there are important clinical implications: HIV-positive individuals ought be warned to present for early 'HIV-orientated medical attention' if they become breathless on exertion.

Where should patients present themselves – to
specialist centres or to local facilities? A paper described the results of treatment of 257 patients with Pneumocystis carinii pneumonia in 15 Californian hospitals. Not surprisingly, but important to have confirmed, patients treated in specialist centres did better.

Pneumocystis pneumonia has, by virtue of its novelty, received much publicity. This fact has tended to obscure the increased incidence of 'standard' bacterial pneumonias that can occur in HIV infection. A study of bacterial pneumonia in HIV-positive intravenous drug abusers revealed an increased incidence of Strep. pneumoniae and Haemophilus influenzae pneumonias in patients who did not fulfil the criteria for full-blown AIDS.

A study of haemophilic patients showed a 'substantial burden' of fatal disease among patients positive for HIV who had not been formally diagnosed as having AIDS. This increased morbidity in pre-AIDS HIV-positive patients will provide extra work which will not usually be attributed to HIV infection. This increased incidence is not surprising given the HIV-induced polyclonal stimulation of antibody production with associated failures to respond appropriately to challenge with certain organisms.

Pneumocystis carinii is of course well known to be a protozoal infection but it seems that it may be a fungus! Using sophisticated RNA base sequence analysis it was found that Pneumocystis carinii had sequences very similar to those occurring in certain fungi, but not in other protozoa.

Life-threatening infection with Cytomegalovirus occurs in 7.4% or more of AIDS patients: retinitis, colitis, oesophagitis, and gastritis are the commonest manifestations. Because relapse is common, life-long prophylactic treatment is usually required. The two major treatments are with ganciclovir and foscarnet (the latter does not cause myelosuppression which may limit treatment with ganciclovir – especially in patients on zidovudine).

Homosexual activity and intravenous drug abuse are risk factors for both hepatitis B and HIV infection: it is thus not surprising that hepatitis B carriage and HIV infection may occur together. A report based on HIV-positive homosexual hepatitis B carriers suggested that chronic hepatitis B may be less severe when accompanied by HIV infection – but viral replication may make hepatitis B more transmissible and resistant to antiviral treatment.

The risks of caring for HIV-infected patients are always a subject for concern. Despite the theoretical risks, the evidence is accumulating that the practical risks are small. There have only been 11 cases reported in British or United States scientific literature in which HIV is thought to have been transmitted in a health care setting and two of the health carers were non-professional. Nevertheless there are estimates of needlestick transmission of less than 1% and approximately 0.35%. Zidovudine should be considered for all known needlestick injuries involving HIV-positive blood but given the low seroconversion rates it will be difficult to confirm its efficacy in this situation.

Botulism

Over a 2-week period in mid-1989 in the north of England 26 people developed botulism after eating yoghurt which contained 'intoxicated' hazelnut purée. As is usual the patients were scattered, and before it was realized that the individual illnesses were the result of a shared exposure (because of unusual clustering of some patients), the diagnosis of individual patients remained obscure or another diagnosis (usually Guillain-Barré syndrome) was suspected.

The causative organism, Clostridium botulinum, may cause classical botulism 'food poisoning,' wound botulism, or infant botulism. Clostridium botulinum is an anaerobic Gram-positive bacillus that survives by forming spores that germinate under appropriate conditions, with the liberation of one of eight possible neurotoxins during growth. Botulinum toxin is probably the most potent poison known: for obvious reasons the relevant studies have not been performed. The toxin prevents release of acetylcholine at peripheral cholinergic synapses.

Patients typically complain (if they are not found dead) of a symmetrical descending weakness with progressive respiratory paralysis 12–36 hours after eating the toxin-containing food. Failure of cholinergic innervation produces profound lack of salivation, ileus, and urinary retention. Diplopia, dilated unreactive pupils, blurred vision, ptosis and photophobia may result, as may a bulbar palsy picture and postural hypotension. Symptoms of gastroenteritis are usually notable by their absence, as is fever – there is no tissue inflammation and thus no febrile reaction. Patients are not infectious; they are intoxicated and it is the relevant food that is 'infectious' in that the food will transmit the illness to others (indeed it is a matter of urgency to ensure that no one eats any remaining food that the patient might have ingested).

A physician who sees only one patient may not be able to make a confident clinical diagnosis of botulism. Helpful features in differential diagnosis include the finding of a normal cerebrospinal fluid in botulism, whereas in Guillain-Barré syndrome the cerebrospinal fluid may show an increased protein with no increase in the cellular elements. Patients with myasthenia gravis respond dramatically to edrophonium (Tensilon) whereas patients with botulism respond poorly, if at all. Polio is a febrile illness with asymmetrical paralysis and...
cerebrospinal fluid abnormalities. Botulism is confirmed by finding toxin in the patient's blood, gastric contents, or in the food concerned.

Treatment is urgent administration of antitoxin and intensive care, usually with prolonged ventilation. Some physicians give penicillin to eliminate gut carriage of the organism, and others give enemas for the same reason. The mortality rate is usually about 25%.

Bovine spongiform encephalopathy

Bovine spongiform encephalopathy, known to the farming population as 'mad cow disease' is a disease that affects the brains of cows and there may be a risk that infection may spread from cow to human brains by the ingestion of infected foods (in much the same fashion that Kuru was transmitted by the eating of the brains of deceased relatives in the Fore tribe in Papua New Guinea – this infection being halted by government health warnings that eating the brains of relatives was harmful to health). By December 1988 there had been 2160 known cases in cows, with about 100 new cases each week. A government report (Report of the Working Party on Bovine Spongiform Encephalopathy) blamed unnatural feeding practices in that concentrated cattle feeds often include meat and bonemeal which might include material from sheep infected with scrapie, a similar disease of sheep. There is currently no evidence to link BSE with human encephalopathies including Creutzfeld-Jacob disease. Such unnatural feeding practices also have caused Salmonella contamination of eggs. The banned ofal is now apparently being fed to pigs. Whatever next?

Cat-scratch disease

After at least one false identification, the organism responsible for cat-scratch disease (CSD) has been identified.39

CSD is usually a regional lymphadenitis of nodes that drain the site of the cat scratch but rarely more severe illness may result including encephalitis, retinitis, osteomyelitis, arthritis, hepatitis, splenitis, or pleurisy. The causative organism is a Gram-negative bacterium (or its cell wall defective variants) which was isolated from 10 patients with CSD. Koch's criteria were all fulfilled: the organism was not isolated from patients with other disease, it was morphologically identical to forms seen in human lesions, patients with recent CSD had elevated or fourfold rises in CSD antibody titres, antibody to CSD bacterium reacted with known CSD bacilli in human tissues, and caused skin lesions in armadillos which were identical to human lesions, and the bacterium was reisolated from such lesions.

Many bacteria can attack the immunosuppressed and there is no reason to exclude cat scratch bacteria from consideration. Skin lesions superficially resembling Kaposi's sarcoma, having on microscopy a distinct haemangiomatous appearance, have been described in seven AIDS patients. Early diagnosis is important because treatment with antibiotics or surgery produces a complete cure.30

Chronic fatigue syndrome

The best name for this syndrome is still disputed. Chronic fatigue syndrome, Royal Free disease, post viral syndrome and benign myalgic encephalomyelitis are but four examples. Fortunately there are several clear statements concerning the aetiology; unfortunately many of these are mutually exclusive.

Is it hysteria? Analysis by two psychiatrists of 100 Royal Free nurses and 100 matched controls contended that the outbreak was hysterical.31 It certainly wasn't hysteria. Fever was found in 89%, lymphadenopathy in 79%, ocular palsy in 43% and facial palsy in 19%.32 Is it hyperventilation? 'All the patients (a total of 68) previously diagnosed by physicians and then referred to us have turned out to have effort syndrome (exhaustion and hyperventilation).33 Is it a metabolic disorder? Yes, probably caused by persistent virus infection and associated with defective immunoregulation.34

Is it caused by chronic enteroviral infection? Enteroviruses were found in the stools of 17 out of 76 patients (22%) but only in two controls. One year later 5 patients were still excreting the same virus. An enteroviral group-specific antigen was detected in 44 of 87 sera and in 42 IgM circulating complexes were found.35 A recent uncontrolled study involving a large number of patients suggests an enteroviral factor in the aetiology of the disorder.36 The Postgraduate Medical Journal in the same issue carried an editorial on the subject.37

Part of the problem lies with epidemiological studies based on selected patients with poor control groups, and poor definition of what constitutes a confirmed case. Working definitions have been proposed but until someone develops a test or tests that are a marker for an organic defect no matter what the aetiology, dispute will continue as to the status of this syndrome. This is not merely an academic problem: there are numerous people who have had their lives altered by this syndrome, with profound personal and financial consequences.

Despite initial enthusiasm it now appears that the Epstein-Barr virus (EBV) does not have a role in the chronic fatigue syndrome. A placebo con-
trolled trial of acyclovir (which has some activity against EBV) failed to reveal any benefit.⁴⁹

Interestingly this trial also highlighted the fact that a significant proportion of the population are placebo responders (in their case 35%) and thus any of the numerous anecdotal claims for effective treatment for the chronic fatigue syndrome have to be viewed with scepticism, if not cynicism.

The common cold

No apology is given for including this trivial disorder amongst more serious infections. Ask a professor of clinical pharmacology what is the best treatment for hypertension and be prepared for several hours discourse. Ask about the best treatment for a common cold and you are likely to receive only anecdotal recipes and the offer of tissues. Local hyperthermia is the answer: inhalation of fully humidified air at 43°C for 20 minutes will halve the symptoms experienced by controls.⁴⁸ Unfortunately such treatment is not cure, but prevention is possible. Sauna therapy (two visits per week) has, in a controlled trial, reduced the incidence of common colds to half that of controls (after a 3 month period in which there was no benefit).⁴¹

Cryptosporidiosis

In addition to food-borne infections, some of which might be prevented by irradiation of food, there have been several large scale outbreaks of gastroenteritis caused by water borne Cryptosporidiosis infection. This organism has only recently been recognized as a cause of infective diarrhoea in humans. The most problematical infections are the AIDS patients in whom it causes a catastrophic, partially treatable, but usually incurable diarrhoeal illness. The disease has an incubation period of 3 to 7 days and is primarily a disease of children although people of all ages can be affected. Illness is usually limited to abdominal cramps and watery diarrhoea with about six motions per 24 hours at worst and lasting for about 7 days.⁴²

Infection is transmitted in faecal-oral fashion by oocysts which resist all conventional means of water purification: indeed in one outbreak there was a suspicion that a river which supplied a water purification plant was polluted with sewage from a blocked sewer. There is strong evidence of spread from animals to man but person to person contact is probably more common.⁴³

The moral is clear. Water should not be contaminated with sewage: pathogens are not defeated but are in a state of war with us and effective purification today may prove to be inadequate tomorrow. We should not rely on technological solutions to fundamental errors of food and water management. I have no doubt that someone somewhere will suggest irradiation of sewage!

Helicobacter pylori infections

Helicobacter pylori is a spiral flagellate bacterium which produces ammonia which might neutralize gastric acid in the gastric mucus-secreting epithelial cells. It is found in 60–90% of patients with peptic ulcers but not in symptomless people with no histological evidence of gastritis.

Are some instances of peptic ulcer or gastritis caused by this organism, or is it merely an incidental invader of tissue damaged by other mechanisms? Despite much research and learned opinion the answers are still not clear.⁴⁴ What is clear is that the name of the organism has been changed from Campylobacter pylori to Helicobacter pylori.

It appears that Helicobacter pylori can probably cause superficial erosive gastritis (usually affecting the gastric antrum), and chronic active gastritis in which Koch's postulates have been fulfilled.⁴⁵ Increased titres of IgG and IgA may also provide evidence of active infection with Helicobacter pylori and may be useful in assessing response to treatment and (possibly) to detect reinfection after treatment.⁴⁶

A useful review of the aetiology of duodenal ulceration⁴⁷ concluded that duodenal ulceration may have a combined causation with disturbance of gastric secretory function and/or mucosal defects with Helicobacter pylori a secondary invader or metaplasia of the duodenal bulb permits colonization from the gastric antrum or opportunistic infection contributes to the magnitude of duodenitis and increases the chances of erosion occurring to ulcer depth.

If Helicobacter pylori has a causative role in any form of peptic ulceration then antibacterial therapy may have a role and no doubt the relevant trials will provide definitive answers as to the best antibacterial therapy. It is known that ulcers can be healed with combinations of bismuth and tinidazole.⁴⁸

A ‘new’ human herpesvirus

Although initially named human B-lymphotropic virus, the cellular tropism was discovered to be wider than B lymphocytes necessitating a renaming as human herpesvirus-6 (HHV-6). Infection with this agent is not uncommon⁴⁹,⁵⁰ and there is evidence that HHV-6 is the agent responsible for exanthem subitum (roseola infantum, sixth disease).⁵¹,⁵² There is also a suspicion that HHV-6...
may cause hepatitis and a mononucleosis-like illness.\textsuperscript{53}

As herpesviruses persist for life in an infected host we may anticipate that epidemiological studies will lead to further pathological associations.

**Listeria monocytogenes**

No sooner was a scare concerning Salmonella in eggs on the wane than listeriosis became a matter of great public concern with reports that certain ready-to-eat foods, especially chicken, might be contaminated. Worse still, exotic cheeses, seemingly a staple foodstuff of the medically informed middle class, could be infected. Plainly action was required! The groups most at risk -- pregnant women, the immunocompromised, and the aged -- were advised not to eat certain types of soft cheeses and to reheat cook-chill meals and ready to eat poultry until they were `piping hot.' One problem was that *L. monocytogenes* can survive quite happily in cool domestic refrigerators (about 6°C or above). Listeria are also relatively resistant to heat: they cannot survive at 80°C; providing that food is completely cooked at 70°C for 2 minutes Listeria will be eradicated. Normal pasteurization will inactivate Listeria in milk but the margin of safety is less if high temperature short duration treatment is used.\textsuperscript{54} The risks of foodborne listeriosis have been qualified and quantified in a WHO Report.\textsuperscript{55}

One major cause of concern was that, although the annual number of cases is small the morbidity and mortality is high (the mortality rate in neonates ranging from 30 to 50%), with infection presenting as a septicemia and/or meningoencephalitis with possible endocarditis, disseminated granulomatous lesions in internal organs, and possibly skin lesions.

The diagnosis is confirmed by isolation of the organism but care has to be taken to distinguish Listeria isolates from non-pathogenic `diphtheroid' organisms. Culture may have to be prolonged at 4°C before identification can be achieved. Obviously treatment cannot wait for a confirmed isolation and a wrong suspicion that only `diphtheroid' organisms were present could be a serious mistake. The treatment of choice is ampicillin or amoxycllin with additional gentamycin in the severely ill (synergy has been demonstrated in vitro). Obviously it is important to ensure antibiotic dosages and routes of administration that give adequate penetration into the cerebrospinal fluid of those patients with meningitis.

Like many potential pathogens it is perfectly possible for humans to be healthy carriers; about 1% of humans are asymptomatic faecal carriers.\textsuperscript{56}

The medical message is simple. Our food may contain potential pathogens and adequate cooking will destroy most. The political problems are more complex as it could be argued that all commercially supplied food should be free of potential pathogens. Listerosis has been well reviewed.\textsuperscript{57--59}

**Lyme disease**

Lyme disease was first described in the USA in 1975 and is a relatively new arrival in the UK.\textsuperscript{60,61} The causative organism is a Spirochaete, *Borrelia burgdorferi*\textsuperscript{62} and the vector is the *Ixodes* tick.

The disease has three stages similar to those of syphilis and some other spirochaetal diseases. The first stage occurs a few days to a few weeks after the tick bite: there is an expanding area of redness around the bite site which may grow to 15 cm in diameter with flattened red borders and central pallor. Other similar annular lesions may develop, constituting erythema chronicum migrans (ECM). There is systemic disturbance including fatigue, headache, fever, meningism, or musculoskeletal aches and pains. The second stage occurs several weeks to several months later with cardiac manifestations (myocarditis, conduction defects or both) or neurological manifestations including meningitis and cranial nerve involvement (especially of the seventh nerve). The third stage occurs weeks to several years later (in about 80% of those with ECM) with an arthritis, usually of an intermittent nature.

Diagnosis rests on awareness of the clinical manifestations and knowledge of the prevalence of infected ticks in the areas where the patient has visited. In the absence of previous ECM a high degree of awareness of this potentially treatable infection is vital. Serology is the main means of confirming the diagnosis but unfortunately during ECM, the most obvious clinically suggestive feature, serology may be unhelpful and treatment with tetracycline 250 mg 6 hourly for 10 days on clinical grounds is reasonable. The neurological and cardiological stages have been treated with intravenous penicillin 20–24 mega units daily which reduces the duration of meningeal problems from 30 weeks to 10 days\textsuperscript{63} and causes a 55% cure rate of arthritis.\textsuperscript{64}

There is a major problem in interpreting the results of positive serological tests as these only indicate that the patient has been exposed to infection, and not that he has an active infection which must be treated. Antibodies were detected in 10 out of 40 forestry workers in England and definite symptoms of Lyme disease (specifically erythema chronicum migrans), were reported by only two workers: none had neurological illness.\textsuperscript{65}

Should such patients be treated routinely and, if so, how often if they were obviously occupationally exposed to repeated tick bites? Are such asympto-
matic patients immune or will a proportion develop later problems? All these questions will be answered subsequently in terms of percentages of populations involved but clinicians will no doubt be left wondering how to best treat individuals: in the event I suspect all seropositives will be given antibiotics.

Multiple sclerosis: a role for infection?

Meanwhile the search for possible causative pathogens continues for diseases including Kawasaki’s syndrome, rheumatoid arthritis, systemic lupus erythematosus, and numerous neoplasms. The evidence for autoimmune or microbial aetiology for multiple sclerosis has been reviewed.66 Microbial possibilities traditionally focussed on the Epstein-Barr virus, largely based on similarities in age patterns, but the authors focus on the possibility that spirochaetal infection (which may have long latency periods, exacerbations and remissions and similar clinical and histological similarities) may be relevant: there are possible links with sinusitis and Treponema denticola, and similar organisms which may cause nervous damage by subsequent spread to vascular tissue with demyelination as a secondary effect.

Plesiomonas shigelloides

Many doctors submit ‘stool culture for pathogens’ from patients with diarrhoea. Few probably appreciate that this simple request, if it were unquestioningly obeyed, would take microbiologists several weeks to complete and would result in at least several hundred organisms being identified. In practice microbiologists screen for likely pathogens. In difficult cases, where routine stool screening is unhelpful (no stool is ever negative for potential pathogens), the microbiologists cast their net a little wider and will identify many organisms some of which might have an aetiological role in the diarrhoea. One organism which might well be an enteric pathogen is Plesiomonas shigelloides. A Canadian based paper67 described 34 patients who, compared to patients with other enteric pathogens, had a more severe prolonged colitic illness. Patients showed a significant association with foreign travel, eating of seafood, and drinking of untreated water.

Prevention of infection

It might be thought that the science of vaccination is simple. If a vaccine is given to individuals, which stops them from being infected, it is always beneficial to that individual and society. True or false? Contrary to superficial reasoning the answer is – false. Appropriate vaccination in childhood may cause a significant proportion of the unvaccinated to develop infection later than they would have done otherwise and, if the complications of infection increase with age, then more harm results. With rubella a 50% vaccination rate of two year olds would cause an increase in the age group acquiring natural infection (currently about 7–9 years) and consequently an increase in congenital rubella syndrome. The chance of paralysis consequent to poliovirus infection also increases with age and incomplete vaccination of a population may cause an increase in the rate of paralysis.

Drug treatment for individuals with a chronic infection is always beneficial to the individual and society. True or false? Again the answer is – false. If the drug does not decrease infectivity then more cases might result because individuals live longer and have more chance of spreading infection.

These and many other apparent paradoxes are eloquently explained by Anderson and May.68 Interestingly, the authors offer a solution to the conflicting paradoxical requirements for an individual and society. They suggest compulsory vaccination. This of course raises highly political problems related to ‘institutionalized altruism.’

From October 1988 Measles/Mumps/Rubella vaccine was introduced, the aim being to eliminate rubella, congenital rubella syndrome and mumps. To do this it is necessary to achieve an immunization rate, not of 100%, but a rate such that a single patient with a particular infection will, on average, transmit the infection to fewer than one other person: it is thought that the target to achieve this must be 90% vaccination by 1991. In practice every child without a contraindication will need to be vaccinated.

In the past there had been worry concerning the possible teratogenicity of the rubella vaccine virus. It now appears that this does not occur.69 It is also apparent that the virus is not usually transmitted from person to person so that the pregnant contacts of a recently vaccinated woman can be doubly reassured.

In the United States indigenous measles has been almost eliminated: in 1986 there were only 6268 cases. To achieve complete eradication of indigenous measles in the United States a new policy has been adopted.70 Wherever measles persists in the community a two dose schedule is recommended with monovalent measles at 9 months of age and combined measles, mumps and rubella at 15 months. Furthermore, all attending students who were vaccinated before 1980 will be vaccinated if outbreaks occur in schools, colleges, and universities.
Non-A, non-B hepatitis. No longer a non-diagnosis?

Non-A, non-B hepatitis accounts for a substantial proportion of acute and chronic liver disease in the United States. The cloning and sequencing of hepatitis C virus (HCV), an enveloped single stranded RNA virus, and the development of serological tests have allowed a proportion of non-A, non-B hepatitis to be linked with this virus.

Non-A, non-B hepatitis is a major cause of post-transfusion hepatitis and most post-transfusion hepatitis is caused by hepatitis C, so screening blood donations for hepatitis C should become routine. Because only 5 to 10% of patients with non-A, non-B hepatitis have a history of blood transfusion (about 40% are intravenous drug abusers, in 10% sexual transmission is likely, and in 40% there is no known cause) the screening of blood donations will make only a small contribution to the overall incidence of HCV virus infection. Even more disappointingly anti-HCV may not be detected until about 6 months after the causative transfusion and indeed may only become detectable 4 months after the onset of hepatitis. Thus there is a need for at least a 6-month serological follow-up of undiagnosed hepatitis.

Non-A, non-B hepatitis is a serious condition: up to 50% of patients develop biochemical evidence of chronic liver disease and treatment with alpha interferon results in improvements in liver enzymes and histology: unfortunately such improvements were not sustained in non-A, non-B hepatitis caused by HCV.

More recently, successful cloning of enterically transmitted non-A, non-B hepatitis has been achieved and, not surprisingly, has been provisionally named hepatitis E virus. Large epidemics with this agent have occurred, affecting mostly the young and middle aged, with a high mortality in pregnant women.

Resistant streptococci

Changes in antimicrobial sensitivity of ‘old’ organisms almost justifies a label of ‘new’ pathogens. Certain centres are sadly familiar with epidemic resistant Staphylococcus aureus – MRSA and the distinction as to whether the M means methicillin or multiple is often academic – but antibiotic resistant Strep. pneumoniae has caused at least two hospital based outbreaks in Britain and in which the ‘old’ therapy – penicillin – was inappropriate.

Retroviruses

Retroviruses are RNA viruses which, after penetrating cells, are converted to DNA which then becomes integrated into the infected cell’s genetic material. Antiviral chemotherapy to eliminate such viruses will not be available in the near future and prevention of infection is the only ‘cure’ available at present.

With the development of sophisticated gene probes it is becoming increasingly apparent that persisting infection with retroviruses is associated with many immune-related or ‘idiopathic’ diseases. Already there is a suspicion that Graves’ disease may be linked with retrovirus infection. Tropical spastic paraparesis has been linked with human T-cell lymphotropic virus 1 (HTLV-1).

Six patients with multiple sclerosis have had HTLV-1 DNA detected by high amplification polymerase chain reaction: three did not have ‘standard’ antibody evidence of infection. Very interestingly, there are preliminary and, at the time of writing, unconfirmed reports that retroviral sequences have been found in patients with systemic lupus erythematosus, and antibodies to such DNA fragments have been found in patients and their healthy sexual partners. I predict that, within 10 years, this retroviral section will be the longest in this account.

Salmonella infections

Salmonella infections are not uncommon, usually presenting with gastroenteritis. Antibiotics are not usually recommended for Salmonella gastroenteritis unless there is associated septicaemia, which is difficult to determine clinically in early illness – when antibiotic treatment is likely to be most useful. A 15 year retrospective study of bacteraemia in Salmonellosis confirmed that certain serotypes were more likely to be associated with bacteraemia and that the prevalence of bacteraemia increased in older patients, a finding that suggests that there should be a lower threshold for antibiotic treatment in the elderly.

Salmonellosis is a serious infection, the more so when it occurs in hospital settings. In 1978–1987 there were 248 outbreaks of Salmonella infection in hospitals affecting over 3,000 patients and causing 110 associated (but not necessarily causally) deaths. Although each outbreak is a subject of concern there were 522 outbreaks in the previous decade. Twenty four percent of outbreaks were considered to be food borne and 30% were reported as person to person spread: the risk of being affected in an outbreak not caused by food seemed to be highest in maternity, paediatric, and geriatric units – all areas where faecal soiling is more common and difficult to control.

On a national level Salmonellosis is an important foodborne disease. The cost of one epidemic in 1982 caused by Salmonella napoli-contaminated chocolate was in the region of £0.5 million, and it
was estimated that interventions made by the Public Health authorities prevented 29,000 cases of enteritis, five deaths, and 185 admissions to hospital – an unequivocal demonstration of the cost effectiveness of public health monitoring and intervention.81

Seborrhoeic dermatitis and dandruff

Despite the fact that seborrhoeic dermatitis and dandruff have been recognized as being caused by a fungus, *Pityrosporum*, for several years it took the realization that end-stage AIDS patients developed seborrhoeic dermatitis which responds to antifungal treatment to convince the wider medical population of this. Professor Shuster provides an entertaining introduction outlining the medical resistance to obvious conclusions.82

Tuberculosis

The incidence of *Mycobacterium tuberculosis* infection has declined in the UK but its low incidence is probably related to the low incidence of primary infections with less opportunity for reactivation to cause the more easily diagnosable secondary complex tuberculosis. Indeed the incidence of primary complex tuberculosis was so low that it was thought that we could soon abandon routine BCG, which conferred reactivation-free primary infections (in the skin) and Mantoux positivity, so that we could then screen for tuberculosis by Mantoux testing: this would be in line with the American policy of omitting routine BCG vaccination and using conversions to Mantoux positivity to detect infection. The appearance of HIV may well postpone or cancel this change in policy because HIV-positive individuals without BCG-induced immunity will be very prone to reactivate infection if they are allowed to have previous primary complex tuberculosis with ‘wild’ *Mycobacterium tuberculosis*.

In HIV-positive patients and in others there is an increasing awareness that atypical mycobacteria (AM) may in certain circumstances cause significant disease. However, the identification of an AM does not necessarily imply a pathogenic role: it may be an irrelevant isolate. Criteria for regarding AM as pathogenic include (1) no other explanation for the clinical presentation, (2) repeated culture of the organism with multiple colonies, (3) less than 5 mm induration to purified protein derivative and (4) isolation of the organism from closed lesions or normally sterile sites (cerebrospinal fluid for example). In the USA, disseminated *Mycobacterium avium intracellulare* caused 4.2% of opportunistic infections in AIDS patients,83 a greater incidence than *Mycobacterium tuberculosis*. Treatment of *Mycobacterium avium intracellulare* is problematic; *in vitro* resistance to rifampicin and isoniazid is usual, but ethambutol, ethionamide, ansamycin, clofazamine, and cycloserine are usually effective. Antibacterial therapy of these AMs is not easy because there are relatively few patients (at present), the natural history of these infections is not well defined, and there is a lack of correlation between *in vitro* and *in vivo* sensitivities. Drugs not usually thought of in the context of tuberculosis (sulphamethoxazole, certain quinolones, clofazamine, ansamycin, amikacin, and rifamycin derivatives) are all therapeutic possibilities.

Tuberculosis will re-emerge as a major problem in those infected with the human immunodeficiency virus. One study of intravenous drug users reported that the prevalence and incidence of tuberculosis infection were similar for HIV-negative and HIV-positive abusers but the risk of active infection was elevated in the seropositive.84 The authors advocated aggressive use of chemoprophylaxis for seropositives with a positive reaction to purified protein derivative. One problem is that such skin tests may well be negative in the later stages of HIV infection when anergy is usual.

Between one and two thirds of certain populations in the developing world have been infected with *Mycobacterium tuberculosis*. If such people then develop HIV-induced defective cell-mediated immunity the organism may reactivate and progress rapidly and, because the host response causes the usual pathological changes, such infections may not be classical in presentation. There is much worry that there will be an upsurge of tuberculosis in certain countries.

In conclusion I note that Dr D.G. James and Dr O.M. Sharma, in their erudite review of Respiratory Diseases,85 claimed that their respiratory garden was ‘full of the most enchanting flowers.’ I am afraid they are deceived: their and other medical gardens are full of the potentially disenchanted weeds of infection!

References

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doi: 10.1136/pgmj.66.780.807

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