Journal of Infection (2000) **40**, 3–15
doi:10.1053/jinf.1999.0624, available online at http://www.idealibrary.com on IDEAL®

REVIEW ARTICLE

Emerging and Re-emerging Infectious Diseases

U. Desselberger

Clinical Microbiology and Public Health Laboratory, Addenbrooke's Hospital, Cambridge CB2 2QW, U.K.

Microbial pathogens discovered as aetiological agents of human disease over the last 25 years are reviewed. Strengthening of laboratory and public health surveillance is of paramount importance for early detection and management of emerging infectious diseases.

Introduction

Emerging infectious diseases have been made a topic of wider discussion since the Institute of Medicine of the United States convened a committee under the co-chairmanship of Joshua Lederberg and Robert Shope that conducted an 18-month study on emerging microbial threats to health.[1] A large number of microbes (bacteria, rickettsiae, chlamydiae, viruses, fungi, parasites) were identified which were either known to be pathogenic but appeared to be associated with changed disease patterns or were recognized as new human pathogens. Factors involved in their emergence/re-emergence were identified, such as changes in human behaviour, industrial and economic development, travel and mass movements, civil unrest and wars, but also microbial genomic change and adaptation.[2–10] It was further recognized that continuous surveillance using clinical, pathological (laboratory), epidemiological and public health approaches is required to allow rapid identification of newly emerging or re-emerging agents and to react swiftly with appropriate management of the diseases they cause.[11]

Since then a plethora of publications, both as books,[6,12,13] papers in journal and even a new journal devoted to "Emerging Infectious Diseases" have sprung up, matched by the emergence of a number of new pathogens in the 1990s. The major pathogens identified as causes of human disease since 1973 are listed in Table I. Many of them are viruses, some bacteria and protozoa, and, most recently, some unconventional agents.

Another aspect of the emergence of changed pathogens is based on the widespread use of antimicrobial agents (antibiotics, chemotherapeutics, antivirals, antifungals). From this practice, increasing numbers of drug-resistant microbes have arisen which pose considerable problems in hospitals, and also in the community.[14]

In the following text, particular aspects of infections with some of these new agents are briefly described. Selected agents will be dealt with in more detail in a series of articles to appear in this journal over the next 12 months. I will start by reviewing novel viruses, followed by review of the other emerging/re-emerging micro-organisms. Micro-organisms are discussed in the order of first isolation (Table I).

Small Round Structured Viruses (SRSVs)

Norwalk virus (NV) was identified as the first SRSV causing outbreaks of acute gastroenteritis in 1972.[15] In 1990 the NV genome was cloned,[16] and subsequently its genome and that of other related viruses were sequenced,[17,18] allowing their classification as members of the *Caliciviridae* family. Several genogroups of SRSV have been found which in part cocirculate and even coinfect.[19,20] The virus structure has been established by cryo-electron microscopy.[21] Expression of the NV capsid protein from baculovirus recombinants in insect cells[22] allowed assessment of the age-related seroprevalence of the virus[23] which is much more widespread as a human infection than previously thought.

Rotaviruses

Rotaviruses were discovered as the cause of infantile human gastroenteritis in 1973,[24,25] although they were then already well known as the cause of acute gastroenteritis in young animals. Since their discovery, human rotaviruses have been found to be the main aetiological agent of gastroenteritis in infants and young children worldwide.[26] There are at least seven groups (A-G), and within group A various types exist (classified as G and P

Accepted for publication 24 November 1999.

0163-4453/00/010003 + 13 $35.00/0

Table I. Major aetiological agents of infectious diseases identified since 1972.*

Year	Agent	Disease
1972	Small round structures viruses (SRSVs; caliciviruses)	Diarrhoea (outbreaks)
1973	Rotaviruses	Major cause of infantile diarrhoea worldwide
1975	Astroviruses	Diarrhoea (outbreaks)
1975	Parvovirus B19	Aplastic crisis in chronic haemolytic anaemia; fifth disease
1976	*Cryptosporidium parvum*	Acute enterocolitis
1977	Ebola virus	Ebola haemorrhagic fever
1977	*Legionella pneumophila*	Legionnaire's disease
1977	Hantaan virus	Haemorrhagic fever with renal syndrome (HFRS)
1977	*Campylobacter* spp.	Diarrhoea
1980	Human T-cell lymphotropic virus-1 (HTLV-1)	Adult T-cell leukaemia/lymphoma; tropical spastic paraparesis (TSP)/HTLV-1 associated myelopathy (HAM)
1982	HTLV-2	Hairy T-cell leukaemia
1982	*Borrelia burgdorferi*	Lyme disease
1983	Human immunodeficiency viruses (HIV-1, HIV-2)	Acquired immunodeficiency syndrome (AIDS)
1983	*Escherichia coli* 0157:H7	Haemorrhagic colitis; haemolytic uremic syndrome
1983	*Helicobacter pylori*	Gastritis, gastric ulcers, increased risk of gastric cancer
1988	Human herpesvirus-6 (HHV-6)	Exanthema subitum (Roseola infantum)
1989	*Ehrlichia* spp.	Human ehrlichiosis
1989	Hepatitis C virus (HCV)	Parenterally transmitted non-A, non-B hepatitis
1990	Human herpesvirus-7 (HHV-7)	Exanthema subitum, pityriasis rosea
1990	Hepatitis E virus (HEV)	Enterically transmitted non-A, non-B hepatitis
1991	Hepatitis F virus (HFV)	Severe non-A, non-B hepatitis
1992	*Vibrio cholerae* 0139: H7	New strain associated with epidemic cholera
1992	*Bartonella (=Rochalimaea) henselae*	CAT-scratch disease, bacillary angiomatosis
1993	Sin nombre virus	Hantavirus pulmonary syndrome ('Four corners disease')
1993	Hepatitis G virus (HGV)	Non A-C hepatitis?
1994	Sabia virus	Brazilian haemorrhagic fever
1994	Human herpesvirus-8 (HHV-8) or Kaposi sarcoma-associated herpesvirus (KSHV)	Kaposi's sarcoma; body cavity-based lymphoma; Castleman's disease
1995	Hendravirus	Meningitis, encephalitis
1996	prion (BSE?)	New variant Creutzfeldt-Jakob disease (nv-CJD)
1997	Influenza A virus (H5N1)	Influenza (Hong Kong)
1997	Transfusion-transmitted virus (TTV)	?
1997	Enterovirus 71 (EV71)	Epidemic encephalitis
1998	Nipahvirus	Meningitis, encephalitis
1999	Influenza A virus (H9N2)	Influenza (Hong Kong)
1999	West Nile-like virus (lineage 1)	Encephalitis (New York)

* Date of discovery assigned on the basis of the year of isolation or identification of aetiological agent. (Part of data from Satcher[8]).

types) and co-circulate at any one time.[26,27] After intense research, a live-attenuated, tetravalent (TV), rhesus rotavirus (RRV)-based, human reassortant vaccine was developed[28–30] which has been licensed in the U.S.A. since August 1998, and for the application of which guidelines have appeared in March 1999.[31] In the period between 1 September 1998 and 7 July 1999, during which time over 1.5 million doses of the vaccine were administered in the U.S.A., gut intussusceptions were observed in 15 infants, of whom 13 developed the condition after the first dose of the three-dose RRV-TV vaccine course, and 12 developed the symptoms within 1 week of any dose.[32] Although the number of reported cases was within the expected range by chance during the week following the receipt of any dose, the well known incompleteness of reporting through the Vaccine Adverse Event Reporting System (VAERS) led the US Centers for Disease Control (CDC) to recommend postponing administering RRV-TV to infants between July and November 1999. A complete analysis of the data has yet to be published (R. Glass, personal communication), but the ACIP recommendation has been revoked and the vaccine been taken off the market in October 1999. Alternative concepts of developing candidate rotavirus vaccines are under active investigation.

Astroviruses

Human astroviruses were first detected in 1975 by electron microscopy in stool specimens of infants and children with diarrhoea[33] and were given their name in

allusion to the star-shaped appearance of some of the particles by EM.[34] These viruses are now classified within a separate family, *Astroviridae*.[35] They carry a genome of single stranded RNA of positive polarity and 6.8 kb size, possessing three open reading frames (ORFs), of which the second encodes the single capsid protein.[36] So far, eight different human astroviruses have been recognized[37], and Noël *et al.*[38] have shown a very good correlation of serotypes and genotypes for seven astrovirus types, using ELISAs and RT-PCR, respectively. More recently, astroviruses have also been recognized as the cause of major outbreaks of gastroenteritis.[39–41]

Parvovirus B19

Parvovirus B19 was discovered as an agent infecting humans in 1975[42] and later as the cause of aplastic crisis in chronic haemolytic anaemia (sickle cell anaemia) patients.[43] It was subsequently also found to be the aetiological agent of the childhood disease erythema infectiosum (Fifth disease[44]) and to cause intrauterine infections followed sometimes by hydrops and early abortion as a clinical outcome, but mostly remaining an inapparent infection.[45,46]

Ebola Virus

This virus was found to be the cause of haemorrhagic fever with high mortality in Central Africa in the mid-1970s[47,48] and re-emerged there in the mid-1990s.[49,50] Early recognition of Ebola virus as the causative agent of the outbreaks in Kikwit hospital in Zaire in 1995 was due to a broad international collaboration of physicians, virologists, molecular biologists, epidemiologists, and public health doctors. Ebola virus (like Marburg virus) is a member of the *Filoviridae* family and has now been thoroughly characterized at the molecular level (for review see Klenk[51]). Intensive search for the true animal reservoir of these viruses is still ongoing.[52,53] Other emerging haemorrhagic fever viruses are observed in different parts of the world.[54]

Bunyaviruses

Viruses of the *Bunyaviridae* family were discovered twice as aetiological agents of the new human diseases: in 1977 Hantaan virus was found to cause haemorrhagic fever with renal syndrome (HFRS),[55] and in 1993 another member of this family, Sin nombre virus, was identified as the cause of the Hantavirus pulmonary syndrome (HPS or Four Corners disease).[56] In both cases rodents were identified as the animal reservoir, and for Sin nombre virus coevolution of virus and host species was extensively documented. Bunyaviruses are widespread in animal reservoirs.[57–59] Transmission in animals seems to occur mainly horizontally by infectious excretions, and transmission to man by inhalation of contaminated dust. Although bunyaviruses contain three segments of negative stranded RNA as their genome, reassortment has so far not been found to be a major factor of emergence of new strains (in contrast to influenzaviruses where reassortment events have repeatedly led to the emergence of pandemics strains, see below).

Human T-cell Leukaemia Viruses (HTLV)

Two types of this virus have been recognized as the cause of human disease: type 1 (HTLV-1) in 1980 being closely associated with T-cell lymphoma-leukaemia (the first human tumour firmly associated with a viral infection[60]), and type 2 (HTLV-2) in 1982 being associated with atypical T-cell leukaemia.[61] In addition, HTLV-1 was shown to cause tropical spastic paraparesis (TSP[62]), also termed HTLV-1 associated myelopathy (HAM[63]). These HTLV's are members of a large sub-family (*Oncovirinae*) of the *Retroviridae* family, which for some time have been known to be associated with a large number of tumours in animals (Rous sarcoma virus, mouse mammary tumour viruses, etc).

Human Immunodeficiency Virus (HIV)

This virus was first isolated in 1983 from a homosexual patient and termed lymphadenopathy associated virus (LAV[64]). Soon afterwards the unequivocal association of infection with this virus with the acquired immunodeficiency syndrome (AIDS) was demonstrated and the virus renamed human immunodeficiency virus (HIV). At least two types (HIV-1, HIV-2), and within them a large variety of different subtypes (clades), exist and co-circulate. This is clearly not the site to expand on HIV, for which a number of excellent reviews exist.[65–68]

New Herpesviruses (HHV-6, HHV-7, HHV-8)

Since 1988, three new human herpesviruses (HHV-6, HHV-7, and HHV-8) have been discovered. HHV-6, initially called human B-lymphotropic virus (HBLV), was discovered in patients with lymphoproliferative disorders,[69] but was later found to be the cause of the infancy and childhood disease exanthema subitum/roseola infantum.[70] Most cases of exanthema subitum are caused by the variant HHV-6B.[71] The primary infection mainly occurs within the first 3 years of life,[72] not infrequently associated with encephalitis.[73,74]

In 1990, a new human herpesvirus was isolated from a healthy carrier and termed HHV-7.[75] Like with HHV-6, infection with HHV-7 seems to occur mainly in childhood.[76–78] At present, the extent of the involvement of HHV-7 in human disease is not clear, although the virus has been isolated from cases of exanthema subitum[79] and pityriasis rosea.[80]

In 1994, cDNA sequences with homologies to herpesvirus sequences were classified as those of a new human herpesvirus type, called HHV-8. Subsequently, HHV-8 was found to be firmly associated with the occurrence of Kaposi's sarcoma (angioplastic sarcoma), and therefore also termed Kaposi's sarcoma associated herpesvirus (KSHV[81]). In 1996, a cell line (BCBL-1) propagating KSHV/HHV-8 was described.[82] Phylogenetically, KSHV is a γ2-herpesvirus[83] related to the γ1 Epstein–Barr virus (EBV). Knowledge of the epidemiology and transmission of the virus is still rudimentary.

KSHV occurs in several variants, based on sequence variations at the left and right end of the viral genome.[84–86] Several subtypes have been distinguished, subtype B mainly being found in Africa and subtypes A and C also found in Africa but mostly in Europe.[87,88] Seroprevalence data show differences in different geographical regions, also depending on the antigen used in serological assays. In general, there is an age-related increase of antibody prevalence. Transmission is mainly sexual, due to the occurrence of the virus in seminal fluid.[89] However, horizontal transmission among children has also been observed.[90,91] Parenteral transmission seems possible but needs to be supported by further studies.[91] A causative role of KSHV in a rare non-Hodgkin's lymphoma, body cavity based lymphoma, and another atypical lymphoproliferative disorder, Castleman's Disease (a plasma cell lymphoma), is also likely.[88]

New Hepatitis Viruses

Hepatitis C virus (HCV)

This field has moved tremendously fast since 1989 when, entirely by the use of molecular techniques, hepatitis C virus (HCV) was discovered as the main cause of transfusion-transmitted, non-hepatitis A, non-hepatitis B (non-A, non-B) virus infections.[92] The virus belongs to the *Flaviviridae* family, but has now been classified as a separate genus.[93] A first diagnostic test was developed in 1989,[94] but reliable second and third generation tests only became generally available in 1991, and then became obligatory for screening of every blood donation. Therefore, since then, a previously predominant transmission pathway (blood, blood products) was virtually closed, and needle sharing among intravenous drug users was left as the main transmission route. Transmission by sexual contacts and also vertical transmission are relatively rare events, compared to the frequency of use of these transmission pathways by other blood-borne viruses (HBV, HIV). The infection resolves in only 20% of the cases; in 80% a chronic hepatitis results, along with an increased risk for the development of hepatocellular carcinoma (HCC). Chronic infection is very difficult to manage. HCV-infected individuals with chronic liver disease are the most frequent sub-population of patients becoming candidates for liver transplantation.

The seroprevalence of HCV infection in blood donors worldwide is between 0.02 and 1.2%, with higher rates in Japan, Spain, Hungary, Italy and Saudi Arabia.[95] Exceptionally high donor infection rates of almost 20% have been recorded in Egypt.[96] Hepatitis C viruses are highly heterogeneous, and at least six different HCV types with 11 subtypes are recognized at present.[97]

Treatment is by alpha-interferon,[98,99] and, more recently, in combination with other antivirals (ribavirin, lamivudine), but is of limited success due to a high relapse rate after cessation of treatment. Different HCV types vary in their responsiveness to interferon treatment, with type 1 strains being more resistant than type 2 and 3 type strains.[100]

Hepatitis E virus (HEV)

Hepatitis E virus infection became known as a separate entity in the late 1980s and was termed epidemic non-A, non-B or enterically transmitted non-A non-B (ENANB) hepatitis. It followed a transmission pathway and caused disease similar to hepatitis A, but was not reactive in HAV-specific serological assays. In 1990 Reyes *et al.* succeeded in cloning and sequencing part of the genome of this virus.[101] The complete sequence of a number of isolates has now been determined[102–109] and the ENANB virus been renamed Hepatitis E virus (HEV). Its genome is similar to that of caliciviruses: however, the order of genes in HEV is not identical, and therefore HEV may be placed into a separate family or genus.

The genomes of several HEV strains from Asia and Mexico have been entirely sequenced, and partial sequences are available of some other strains.[110] In all parts of the genome the Mexican strain was most different from the sequences studied.[103] Although moderate genetic heterogeneity has been identified amongst HEV strains, evidence for serological heterogeneity is limited.[111] The course of infection in experimentally infected primates is similar to that in man.[112–115] The incubation period is 3–8 weeks, followed by an increase of liver enzymes in blood. Peak viraemia and shedding of HEV in faeces occurs during the incubation period and the very early acute phase of disease. In most cases the infection resolves completely. On the whole, however, the severity of HEV infections is

on average somewhat greater than that of HAV infections. Mortality of hepatitis E has varied in different reports and has been as high as 1%, compared to 0.2% of hepatitis A.[116] More important is the severity of hepatitis E in pregnant women, the mortality in pregnancy increasing with each preceding trimester and possibly reaching 20%.[117–120] The reason for the excessive mortality of hepatitis E in pregnancy is at present unknown.

The diagnosis is based on HEV-specific IgM and IgG ELISAs, using recombinant expressed capsid antigen.[111,119,121,122] The age-specific clinical attack rate with its peak among young adults is striking. In endemic areas the age-related prevalence of HEV antibodies reaches only 40%.[123–125] There is at present no vaccine, but protection of monkeys against experimentally induced hepatitis E by vaccination with recombinant-expressed HEV proteins has yielded encouraging results.

Hepatitis F virus (HFV)

In 1991, Phillips *et al.* described 10 cases of a syncytial giant cell hepatitis observed sporadically in the U.S.A. between 1979 and 1988 and associated with a severe clinical course. The virological studies suggested a paramyxovirus as putative cause because paramyxovirus-like nucleocapsids were found by electron microscopy in patients' livers (8/10). Chimpanzees inoculated with infected liver homogenate raised an antibody response which was cross-reactive with measlesvirus and parainfluenzavirus type 4; however, the animals did not develop a hepatitis. Although this putative viral infection figured as hepatitis F at the time, the work by Phillips *et al.*[126] has not been pursued further.

Hepatitis G virus (HGV)

This virus, also a member of the *Flaviviridae* family, was discovered in 1993 from cloned cDNA fragments in blood donations. Subsequently, sequences of this virus were found in 1–3% of all blood donations in different parts of the world, and it seemed to replicate in liver cells and was thought to be associated with hepatitis. However, a close association of infection by this virus with liver disease has so far not been secured,[127,128] and replication in the liver has not been confirmed (P. Simmonds, personal communication). Therefore, testing of blood donations for the presence of HGV sequences is at present not mandatory.

Transfusion-transmitted virus (TTV)

In 1997 TTV was discovered as the cause of some cases of hepatitis, transmitted by infected blood donations.[129] The prevalence of TTV antibodies in various populations is under test and was found to be very variable.[130] TTV is the first human member of the *Circoviridae* family (Murphy *et al.*[93]; P. Simmonds, personal communication).

The virus was found as a coinfection in HCV-infected patients but reacted variably to HCV upon interferon treatment.[131,132] In a US study a third of healthy blood donors were found to be infected with TTV. A connection with disease is still debated. Significant numbers of chickens, pigs, cows and sheep were found to be infected with this, or a closely related virus.[133] Erker *et al.*[134] found a sequence diversity of up to 30% among more than 10 full length genomic sequences of TTV isolates. This very substantial amount of variation suggests that there are at least three types of the virus. Ball *et al.*[135] followed up several chronically HCV-infected patients longitudinally and found in some a stable form of TTV over several years; however, in others there were fluctuating levels of at least seven distinct variants of the virus over a 5-year period. The natural history of TTV is rapidly explored and turns out to be very complicated.

Influenzaviruses

Type A and B influenzaviruses regularly cause outbreaks of respiratory disease and general malaise during winter and spring in large parts of the world's population. Several influenza A virus pandemics have been described (1918, 1957, 1968, 1977). Influenzaviruses have a wide animal reservoir, and, by the mechanism of reassortment, animal type A influenzaviruses have contributed genes, for instance coding for the haemagglutinin (HA) H3, to viruses which became human pandemic viruses. It has been shown that human H1N1 and also H3N2 influenza A viruses can infect pigs, and, vice versa, that related pig viruses can infect humans. By contrast, avian influenzaviruses, representing by far the biggest diversity and reservoir of influenza A viruses, were thought to circulate only within their original host or closely related species. Contribution of avian genes into viruses able to replicate in humans was thought to be possible only by reassortment, with pigs being the likely host, as these animals were shown to replicate avian influenzaviruses to a certain extent ("mixing vessel" theory of Scholtissek *et al.*[136]; Scholttissek and Naylor[137]).

Recently, however, different events were recorded. During 1997 at least 18 people in Hong Kong came down with influenza-like symptoms, some of them with severe generalized disease which was found to be caused by influenza A viruses of the H5N1 subtype. The virus isolates were very closely related in all their eight RNA segments to viruses isolated from chicken on several farms in and around Hong Kong in the spring of 1997. From the molecular data it could be excluded that reassortants between animal and human strains had been formed.

This was the probable reason for the inability of these viruses to spread from human-to-human, and thus widely within the human population. Human-to-human transmission was never convincingly recorded.

The recent isolation of H5N1 influenza A viruses from humans was seen as the possible advent of a new pandemic strain. The first virus was isolated from a 3-year old boy in May 1997 in Hong Kong who subsequently died of Reye's syndrome after treatment with aspirin. A very close surveillance ensued from this case, and in the following 8 months a total of 16 more confirmed and two suspected human cases of infection with influenza A virus of subtype H5N1 have been observed.[138] Twelve of the sixteen patients became ill in December, and the quick diagnosis was the result of intensified surveillance in hospital and healthcare centres. Seven cases were under the age of 5 years, three between 5 and 14 and six over 14 years. Whereas in patients under 5 the infection was generally mild, in the older patients there was a high rate of complications like gastroenteritis, and renal and liver dysfunction. A total of four patients have died from the infection.[139]

There was an H5N1 epidemic in chickens between March and May 1997 in Hong Kong and southern China. Extensive epidemiological surveillance has so far not revealed significant spread in man. Most importantly, a human-to-human infection has not been definitely proven. A close virological investigation, including partial sequencing of the whole genome, has shown that in at least the first cases the H5N1 isolate was a true avian isolate, i.e. all eight segments were of avian origin.[140,141] This finding greatly decreases, but does not exclude, the likelihood that these viruses may spread widely in man.

WHO and various nations have worked out plans to cope with the sudden emergence of a new pandemic influenza-virus strain (pandemic plans). In the U.K., both the Department of Health and the Public Health Laboratory Service have such plans in place. With the emergence of the first isolate in May 1997 in Hong Kong, stage 1 of the plan was activated, entailing constant review of the situation and signifying increased surveillance of both humans and animals. By the end of 1997, the Hong Kong Government took the bold step of killing the chicken population of Hong Kong (approximately 1.5 million).[142,143] The WHO have sent a fact-finding mission to southern China: they have found relatively intensive surveillance practices in place. No human cases nor seroepidemiological evidence of wider spread of this virus in animals or humans has been found so far (N. Begg, personal communication).

The finding of sixteen cases of human infection with H5N1 strains which (according to information available until now) are "pure" avian viruses is in itself a highly unusual event, and these isolates will be scrutinized very intensely for factors which might have changed their host tropism and allowed emerging pathogenicity for man. The human isolates were found to remain pathogenic for chickens.[140,141] It is possible that an unusual sequence around the trypsin cleavage site of the HA of H5N1 viruses is in part responsible for the wider host spectrum.[140,141]

In March 1999 two isolates of influenza A virus of subtype H9N2 were obtained from two children with influenza in Hong Kong. Three lineages of H9N2 viruses which have also been found in chickens, turkeys, and recently pigs, have been recognized,[141a] two of which ('G1' and 'G9') have been found to infect humans.[141b] The analysis of these viruses is ongoing, but it is likely that genomically these are purely avian viruses as well (D. Alexander, personal communication). Thus, the animal influenza virus reservoir is a permanent threat for transmission of infectious agents into man.

An influenza A virus of subtype H7N2 was isolated from the inflamed eye of a woman in Oxfordshire in 1998 who was keeping ducks on a pond. No such virus was isolated from the ducks, but molecular analysis showed the isolate to be of animal origin.[144]

There is a Damocles' sword hanging over the population of Hong Kong, southern China and the whole world in that avian influenzaviruses might reassort somewhere with viruses apt to replicate well in humans, leading to a new pandemic strain which could spread rapidly throughout the world (similarly to the Asian and Hong Kong influenzaviruses in 1957 and 1968, respectively). Such an event could indeed occur relatively easily in south-east Asia, where men and domestic animals live in very close proximity, often under the same roof. Thus, although at present there is no acute cause for alarm, a high degree of vigilance and careful surveillance of influenzaviruses of both human and animal origins are clearly indicated.

New Paramyxoviruses

In September 1994 an outbreak of severe respiratory disease affected 18 horses, their trainer and a stablehand in Queensland, Australia. Fourteen horses and one human individual died. A novel virus was isolated from those affected and named equine morbillivirus (EMV)[145] or Hendravirus. In the following months several other humans became infected with this new virus, mostly developing meningitis and encephalitis.[146] Serological evidence showed that a paramyxovirus related to EMV was present in *Pteropus*, a species of fruit bat.[145,147]

In Autumn 1998/spring 1999 an outbreak of encephalitis in pig farmers and abattoir workers in Malaysia and Singapore occurred, with more than 250 cases and over 100 deaths. There were also sick animals

(pigs/dogs/cats). A virus was grown from patient material which formed syncytia in Vero cells and yielded positive immunofluorescence with a Hendravirus-specific antiserum. The virus was termed Nipah virus and found to be homologous to 89% at the nucleic acid level with Hendravirus. However, it is clearly different from other paramyxovirus genera, so a new genus is proposed.[148]

Recently a cytopathic infectious agent has been isolated from the kidneys of an apparently healthy tree shrew (*Tupaia belangeri*) which had been captured in the area of Bangkok. The virus turned out to be a paramyxovirus termed tupaia paramyxovirus (TPMV), and partial sequences of its genome (above 4000 nucleotides) showed that this virus had highest homologies with Hendravirus.[149] This supports the hypothesis that new human morbilliviruses are likely to be derived from animal reservoirs.

Enterovirus 71

Enterovirus 71 (EV71), one of the major causative agents of hand, foot and mouth disease (HFMD), is also sometimes associated with severe central nervous system diseases. HFMD epidemics were recorded in Malaysia and Japan in 1997 and in Taiwan in 1998. They resulted in sudden death among young children, often from encephalitis and pulmonary oedema, and were mainly due to the A-2 B genotypes of this virus.[150] CNS complications have been observed in previous HFMD outbreaks.[151–154] By contrast, in large HFMD epidemics in Japan in 1973 and 1978 there was hardly any CNS involvement.[155]

Flaviviruses

Flaviviruses are widespread human pathogens causing yellow fever, dengue, Japanese encephalitis, St. Louis encephalitis, Kunjin and West Nile encephalitis. In August 1999, an outbreak of encephalitis occurred in New York City which was caused by a West Nile virus (WNV) closely related to recent isolates from Egypt and Israel.[155a,b] Birds are a major animal reservoir, and *Culex* spp. the main insect vector. The virus is likely to have been introduced recently to NYC, as there has been a high mortality of native corvides associated with this infection. Thus, this and other recent WNV-related outbreaks (in Europe and Asia[155c]) confirm the significance of these viruses as emerging infectious agents and emphasize the need for vigilant global surveillance.

Transmissible Bovine Spongiform Encephalopathy (BSE) and New Variant Creutzfeldt-Jakob disease (nv-CJD)

During the mid 1980s rapid spread of bovine spongiform encephalopathy (BSE) was observed in British cattle herds. The likely origin of this infection was probably the scrapie agent, one of the prion agents,[156] originating from meat and bonemeal used for cattle feed in 1981–1982 when a previously established processing step of extraction with solvents and hot steam was omitted. It was then calculated that an incubation period of 4–5 years had to be taken into account, and it was hypothesized that 5 years would have to pass after a ruminant protein ban was set in force in July 1988, before the epidemic would peak. The peak of the epidemic occurred in 1994. During the epidemic, BSE cases within a herd remained constant at approximately 4%, but over the years more herds became infected. The reason for this finding was likely to be the continuation of cattle-to-cattle recycling for food purposes, which may have gone on for some time after the initiation of the ruminant protein ban.

In early 1996 several cases of a rapidly progressive form of Creutzfeld-Jacob disease (CJD) were described which also seemed to differ pathologically from other forms.[157] Some molecular data point to the possibility that the causative agent of this so-called new variant CJD (nvCJD) may be the BSE agent.[158] So far approximately 45 human cases have been recorded, mainly in the U.K.[159] The predictions of how many cases may become apparent over the next 3–5 years vary grossly. One major unknown in this calculation is the uncertainty about the variability of the incubation period. There is enormous progress, but there are still questions about the nature of the transmissible agent and the molecular genetics of the prion-host relationship.[160]

Legionella

This Gram-negative, pleomorphic bacterium was first isolated after an epidemic of pneumonia in legionnaires attending an annual meeting in Philadelphia in 1976, when 192 cases were identified, of which 29 were fatal.[161] The micro-organism grows in water reservoirs of hospitals, hotels, convention centres, etc., from where it can spread epidemically; however, the infection is also associated with cases of sporadic community-acquired pulmonary disease. Over 30 species of *Legionella* have since been identified, of which several are pathogenic for man.[162]

Campylobacter

Campylobacter jejuni, a cause of acute enteritis, was rediscovered by Skirrow in 1977 after it probably had been seen by Escherich in 1886.[163] Not all infections are symptomatic. In symptomatic cases, abdominal pain and bloody diarrhoea are prominent. Guillain–Barré syndrome can be a severe complication. The incidence is almost 50 000 recognized infections in the U.K. in 1994. Campylobacter enteritis is a zoonosis, mostly transmitted

to man either directly from infected (colonized) chicken or via contaminated food, milk or water as vehicles. The control of Campylobacter infections in poultry is of paramount importance for limiting the incidence of infection in man.[164]

Lyme Borreliosis

Although the illness, a chronic skin infection termed erythema migrans, and oligoarthritis, has been known for over 100 years, the causative agent was only identified in 1982[165] as a spirochaete transmitted by bites of ticks (*Ixodes* species) and named *Borrelia burgdorferi*.[166] After entering the bloodstream, *B. burgdorferi* adheres to and infects endothelial cells, and the pathological features are likely to be due to inflammatory host responses.[167] *Borrelia* species have a large animal reservoir (rodents, deer) on which ticks feed, becoming infected and propagating the micro-organism in their midgut. As ticks are widespread, their effective control is difficult, and personal protection when camping or walking in the countryside is of the greatest importance for prevention.[168]

Escherichia coli 0157

This Gram-negative bacterial rod occurs as a Vero cytotoxin-producing species (VTEC), mostly of serogroup 0157, and has been observed as the cause of outbreaks of haemorrhagic colitis since the early 1980s,[169,170] often with significant mortality. A not infrequent complication is the haemolytic uraemic syndrome (HUS). VTEC strains are often carried by cattle, with and without disease, and outbreaks in humans have mostly been epidemiologically linked to food products of bovine and other origins, although the micro-organism has not always been isolated at source. Contaminated food and water are probably the main vehicles of VTEC transmission, and therefore safe water and hygiene handling of foodstuffs are of great importance for prevention.[170]

Helicobacter

Helicobacter pylori (originally called *Campylobacter pylori*) was identified as the cause of chronic active gastritis in 1983/84[171,172] and has since been recognized as one of the most common infections in man. Most infections are silent. The infection rate is 50–60% in the 10-year-old in developing countries, and 20–30% in the 20-year-old and 50% in the 50- to 60-year old in developed countries. The natural host is man, and therefore person-to-person transmission is the dominant mode of spread. The micro-organism is distinguished from *Campylobacter* by a number of structural and biochemical differences, and there are at least 14 different species in different hosts.[173] *Helicobacter* grows in the gastric mucus and colonizes the mucosa, where bacterial toxins cause chronic damage. Inflammatory host responses contribute to the disease symptoms, leading to gastric ulcers.[174] *Helicobacter*-infected persons, particularly above 50 years of age, have a three to six times increased chance of developing gastric cancer.[175,176] Treatment with triple therapies (bismuth or omeprazole, metronidazole, amoxycillin/tetracycline) is effective in eradicating the microorganism in 90% of cases,[177] but susceptibility testing for metronidazole has been recommended.[178]

Ehrlichia

Human ehrlichiosis was first described in 1987[179] as the cause of a febrile illness with lymphadenopathy (*E. senetsu*) or myalgia (*E. chaffeensis*), but mostly no rash. There is also a related disease, human granulocytic ehrlichiosis (HGE). The causative organisms, *Ehrlichia* spp., are intracellular parasites and members of the genus *Ehrlichia* of the *Rickettsiaceae* family. As the organisms are transmitted like borreliosis through bites of infected ticks feeding on infected animal reservoirs, personal protection in the countryside during the summer is the best means of prevention.[180] The condition has been reported more frequently in the U.S.A. in recent years, probably as it was made a notifiable disease in a number of states.[181]

Vibrio cholerae 0139

Vibric cholerae 01 is one of the earliest bacteria found to be associated with human disease.[182] However, in 1992 a variant, *V. cholerae 0139*, was first detected during cholera-like epidemics in India[183] which then spread swiftly through SE Asia.[184]

Bartonella

Cat scratch disease (CSD) has been recognized as a distinct clinical entity for many years. Although an infectious cause had been suspected, the causative agent has only recently been identified and classified as the genus *Bartonella*,[185] based on DNA homology studies (it was previously called *Rochalimaea henselae*). Bacillary angiomiatosis (BA) was found to be another clinical manifestation of *Bartonella* infection and is characterized by inflammatory

lesions of skin, liver and spleen, and sometimes brain.[186] It is mostly found in immuno-compromised (HIV-infected) persons. *Bartonella henselae* had first been propagated *in vitro* by Slater in 1989.[185] Once the organism could be grown, a specific IFA was developed.[187] The micro-organism, a Gram-negative bacterium, is endemic in cats, and after transmission to man through scratching, local dermatitis and regional lymphadenopathy develop. The micro-organism has also been found in cat fleas. Transmission is by flea excrement on abraded skin and sometimes also by infected lice. The disease is seen in two to nine cases per 100 000 persons per year in ambulatory care in the U.S.A. Treatment is mainly by rifampicin, ciprofloxacin, trimethoprim-sulphamethoxazole and erythromycin.

Cryptosporidium

Although the genus *Cryptosporidium*, small coccidian parasites, was described 50 years ago, the first cases of human cryptosporidiosis were reported in 1976.[188,189] However, the full significance of this micro-organism as the cause of severe diarrhoeal disease was only recognized when it was found to be a frequent cause of life-threatening cholera-type illness in HIV-infected patients at an advanced stage.[190] Infections with *Cryptosporidium* are widely recognized in different host species. The micro-organism is acquired by ingestion, contaminated water being the main vehicle. Infection from human-to-human also seems to be common. Sources for human infection can be calves and other animals like rodents.[190] There is a view that most human infections are indeed the result of zoonotic transmissions. However, person-to-person spread in urban populations is also important for transmission.[191] Several large waterborne outbreaks have been reported in the U.K. (Ayrshire, Scotland, and Oxfordshire, England[192]), but also in the U.S.A.[193] The incidence rate in diarhoeic faeces is 1–3%.[190] By contrast, in AIDS patients the incidence rates are 10 times higher.

Conclusion

Increases in population sizes and global travel, changes in ecology, and civic unrest and wars all contribute to the likelihood that new infectious diseases will arise in the future. It is likely that there are more viruses causing hepatitis than are recognized at present, and the number of human retroviruses associated with disease is likely to be under-recognized (including endogenous retroviruses). Recently molecular procedures have been established to try to look for the genomes of some of these viruses.

Clinical attentiveness, good laboratory facilities and comprehensive epidemiological surveillance systems for infections in both humans and animals, which often form a reservoir for infections, have to be combined. Lack of facilities can have adverse consequences and lead to misdiagnoses.[194,195] Last but not least, economic enablement in the public health sector will be necessary to allow early recognition and comprehensive management of emerging infections. Given the record of emerging/re-emerging micro-organisms as a cause of infectious diseases over the last 25 years, there is every prospect of this continuing into the 21st century, and absolute vigilance in detecting them is of paramount importance.

Acknowledgement

The author gratefully acknowledges the support of Mrs Lynne Bastow, who typed and processed the manuscript.

References

1 Lederberg J, Shope RE, Oaks SC (eds). *Emerging Infections. Microbial Threats to Health in the United States*. Washington DC: National Academy Press, 1992.
2 Berkelman RL. Emerging infectious diseases in the United States, 1993. *J Infect Dis* 1994; **170:** 272–277.
3 Krause RM. Dynamics of emergence. *J Infect Dis* 1994; **170:** 265–271.
4 Murphy FA. New emerging and re-emerging infectious diseases. *Adv Virus Res* 1994; **43:** 1–52.
5 Murphy FA, Nathanson N (eds). New and emerging virus diseases. *Semin Virol* 1994: **5:** 85–187.
6 Wilson ME, Levins R, Spielman A (eds). *Disease in Evolution. Global Changes and Emergence of Infectious Diseases. Ann NY Acad Sci* 1994; **740**.
7 Domingo E, Holland JJ. Mutation rates and rapid evolution of RNA viruses. In: Morse SS (ed). *The Evolution Biology of Viruses*. New York, NY: Raven Press, 1994; pp.165–184.
8 Satcher D. Emerging infections getting ahead of the curve. *Emerging Infect Dis* 1995; **1:** 1–6.
9 Morse SS. Factors in the emergence of infectious diseases. *Emerging Infect Dis* 1995; **1:** 7–15.
10 Desselberger U. Emerging infectious diseases. *PHLS Microbiol Dig* 1996; **12:** 141–144.
11 Dowdle WR. The future of the public health laboratory. *Ann Rev Public Health* 1993; **14:** 649–664.
12 Scheld WM, Armstrong D, Hughes JB (eds). *Emerging Infections 1*. Herndon, VA: ASM Press 1997.
13 Greenwood B, De Cock K. (eds). *New and Resurgent Infections. Prediction, Detection and Management of Tomorrow's Epidemics*. Chichester: Wiley & Sons 1998.
14 House of Lords Select Committee on Science and Technology. *Resistance to Antibiotics and other Antimicrobial Agents*. London: The Stationery Office, 1998; p. 566.
15 Kapikian AT, Wyatt RG, Dolin R, Thornhill TS, Kalica AR, Chanock RM. Visualization by immune electron microscopy of a 27 nm particle associated with acute infectious nonbacterial gastroenteritis. *J Virol* 1972; **10:** 1075–1081.
16 Jiang X, Graham DY, Wang K, Estes MK. Norwalk virus genome cloning and chacterization. *Science* 1990; **250:** 1580–1583.
17 Jiang X, Wang M, Wang K, Estes MK. Sequence and genome organization of Norwalk virus. *Virology* 1993; **195:** 51–61.

18 Lambden PR, Caul EO, Ashley CR, Clarke IN. Sequence and genome organization of a human small round structured (Norwalk-like) virus. *Science* 1993; **259:** 516–518.

19 Wang JX, Jiang X, Madore P *et al*. Sequence diversity of small round-structured viruses in the Norwalk virus group. *J Virol* 1994; **68:** 5982–5990.

20 Gray JJ, Green J, Cunliffe C, Gallimore CI, Lee JV, Neal K, Brown DWG. Mixed genogroup SRSV infections among a party of canoeists exposed to contaminated recreational water. *J Med Virol* 1997; **52:** 425–429.

21 Prasad BV, Rothnagel R, Jiang XI, Estes MK. Three-dimensional structure of baculovirus-expressed Norwalk virus capsids. *J Virol* 1994; **68:** 5117–5125.

22 Jiang X, Wang M, Graham DY, Estes MK. Expression, self-assembly and antigenicity of the Norwalk capsid protein. *J Virol* 1992; **36:** 1105–1112.

23 Gray JJ, Jiang X, Morgan-Capner P, Desselberger U, Estes MK. The prevalence of antibody to Norwalk virus in England. Detection by ELISA using baculovirus-expressed Norwalk virus capsid antigen. *J Clin Microbiol* 1993; **31:** 1022–1025.

24 Bishop RF, Davidson GP, Holmes IH, Ruck BJ. Virus particles in epithelial cells of duodenal mucosa from children with viral gastroenteritis. *Lancet* 1973; **ii:** 1281–1283.

25 Flewett TH, Bryden AS, Davies H. Virus particles in gastroenteritis. *Lancet* 1973; **ii:** 1497.

26 Kapikian AZ, Chanock RM. Rotaviruses. In: Fields BN, Knipe DM, Howley PM *et al.* (eds). *Fields Virology*, third edition. Philadelphia: Lippincott-Raven 1996; pp. 1657–1708.

27 Estes MK. Rotaviruses and their replication. In: Fields BN, Knipe DM, Howley PM *et al.* (eds). *Fields Virology*, third edition. Philadelphia: Lippincott-Raven 1996; pp. 1625–1655.

28 Rennels MB, Glass RI, Dennehy PH *et al*. Safety and efficacy of high-dose rhesus-human reassortant rotavirus vaccine – report of the National Multicenter Trial United States Rotavirus Vaccine Group. *Pediatrics* 1996; **97:** 7–13.

29 Pérez-Schael I, Guntiñas MJ, Pérez M *et al*. Efficacy of the rhesus-rotavirus-based quadrivalent vaccine in infants and young children in Venezuela. *N Engl J Med* 1997; **337:** 1181–1187.

30 Joensuu J, Koskenniemi E, Pang XL, Vesikari T. Randomized placebo-controlled trial of rhesus human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. *Lancet* 1997; **351:** 1205–1209.

31 Advisory Committee on Immunization Practices (ACIP). Rotavirus vaccine for the prevention of rotavirus gastroenteritis among children. Recommendations of the ACIP. *Morb Mort Wkly Rec* 1999; **48 (RR-2):** 1–22.

32 Editorial. Intussusception among recipients of rotavirus vaccine – United States, 1998–1999. *Morb Mort Wkly Rec* 1999; **48:** 577–581.

33 Appleton H, Higgins PG. Viruses and gastroenteritis in infants. *Lancet* 1975; **i:** 1297.

34 Madeley CR, Cosgrove BP. 28 nm particles in infantile gastroenteritis. *Lancet* 1975; **ii:** 451–452.

35 Monroe SS, Jiang B, Stine SE, Koopmans M, Glass RI. Subgenomic RNA sequence of human astrovirus supports classification of Astroviridae as a new family of RNA viruses. *J Virol* 1993; **67:** 3611–3614.

36 Carter MJ, Willcocks MM. The molecular biology of astroviruses. *Arch Virol* 1996; **12:** 277–285.

37 Lee TW, Kurtz JB. Prevalence of human astrovirus serotypes in the Oxford region 1976–1992, with evidence for 2 new serotypes. *Epidemiol Infect* 1994; **112:** 187–193.

38 Noël JS, Lee TW, Kurtz JB, Glass RI, Monroe SS. Typing of human astroviruses from clinical isolates by enzyme immunoassay and nucleotide sequencing. *J Clin Microbiol* 1995; **33:** 797–801.

39 Konno T, Suzuki H, Ishida N, Chibo R, Mochizuki K, Tsunoda A. Astrovirus-associated epidemic gastroenteritis in Japan. *J Med Virol* 1982; **9:** 11–17.

40 Oishi I, Yamazaki K, Kimoto T *et al*. A large outbreak of acute gastroenteritis with astrovirus among students and teachers in Osaka, Japan. *J Infect Dis* 1994; **170:** 439–443.

41 Belliot G, Laveran H, Monroe, SS. Outbreak of gastroenteritis in military recruits associated with serotype 3 astrovirus infection. *J Med Virol* 1997; **51:** 101–106.

42 Cossart YE, Field AM, Cant B *et al*. Parvovirus-like particles in human sera. *Lancet* 1975; **i:** 72–73.

43 Pattison JR, Jones SE, Hodgson J *et al*. Parvovirus infections and hypoplastic crisis in sickle cell anemia. *Lancet* 1981; **i:** 664–665.

44 Anderson MJ, Jones SE, Fisher-Hoch SP *et al*. Human parvovirus, the cause of erythema infectiosum (fifth disease)? *Lancet* 1983; **i:** 1378.

45 Hall SM, Cohen BJ, Mortimer PP, Anderson MJ, Pattison JR, Shirley JA, Peto TEA. Prospective study of human parvovirus (B19) infection in pregnancy. *BMJ* 1990; **300:** 1166–1170.

46 Rodis JF, Quinn DL, Gary JR Jr, Anderson LJ. Management and outcomes of pregnancies complicated by human B 19 parvovirus infection: a prospective study. *Amer J Obstet Gynecol* 1990; **163:** 1168–1171.

47 Bowen ETW, Lloyd G, Harris WJ, Platt GS, Baskerville A, Vella EE. Viral haemorrhagic fever in Southern Sudan and Northern Zaire. *Lancet* 1977; **i:** 571–573.

48 Johnson KM, Webb PA, Lange JV, Murphy FA. Isolation and partial characterization of a new virus causing acute haemorrhagic fever in Zaire. *Lancet* 1977; **i:** 569–571.

49 Muyembe T, Kipasa M. International Scientific and Technical Committee and WHO Collaboration Centre for Haemorrhagic Fevers. Ebola haemorrhagic fever in Kikwit, Zaire. *Lancet* 1995: **345:** 1448.

50 Simpson DIS. The filovirus enigma. *Lancet* 1995; **345:** 1252–1253.

51 Klenk HD (ed). Marburg and Ebola viruses. *Curr Top Microbiol Immunol*, **235.** Berlin; Springer Verlag, 1999.

52 LeGuenno B, Formenty P, Wyers H, Gounon P, Walker F, Boesch C. Isolation and partial characterisation of a new strain of Ebolavirus. *Lancet* 1995: **345:** 1271–1274.

53 LeGuenno B, Formenty P, Boesch C. Ebola virus outbreaks in the Ivory Coast and Liberia, 1994–1995. In: Klenk HD (ed). *Marburg and Ebola Viruses. Curr Top Microbiol Immunol* 1999; **235:** 77–84.

54 Barry M, Russi M, Armstrong L, Geller D, Tesh R, Danbury L, Gonzales JP *et al*. Brief report: treatment of a laboratory acquired Sabiá virus infection. *N Engl J Med* 1995; **333:** 294–296.

55 Lee H, Lee PW, Johnson KJ. Isolation of the etiologic agent of Korean hemorrhagic fever. *J Infect Dis* 1978; **137:** 298–308.

56 Nichol SE, Spiropoulou CF, Morzunov S *et al*. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. *Science* 1993; **262:** 914–917.

57 Lloyd G. Hantavirus. In: Morgan-Capner, P (ed). *Current Topics in Clinical Virology*. London: PHLS, 1991; pp. 181–204.

58 Pether JVS, Lloyd G. The clinical spectrum of human hantavirus infections in Somerset, U.K. *Epidemiol Infect* 1993; **111:** 171–175.

59 Pether JVS. Hantavirus infection: pathogenesis and immunity. *Curr Opin Infect Dis* 1994: **7:** 329–332.

60 Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci USA* 1980; **77:** 7415–7419.

61 Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M *et al*. A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. *Science* 1982; **218:** 571–573.

62 Gessain A, Vernant JC, Maurs L *et al*. Antibodies to human T-lymphotropic virus type 1 in patients with tropical spastic paraparesis. *Lancet* 1985; **ii:** 407–410.

63 Osame M, Usuku K, Izumo S *et al*. HTLV-1 associated myelopathy: a new clinical entity. *Lancet* 1986; **1:** 1031–1032.

64 Barré-Sinoussi F, Chermann JC, Ray F *et al*. Isolation of a T-lymphotropic retrovirus from a patient at risk of acquired immune deficiency syndrome. *Science* 1983; **220:** 868–871.

65 Levy JA. Pathogenesis of human immunodeficiency virus infection. *Microbiol Rev* 1993; **57:** 183–289.

66 Luciw PA. Human immunodeficiency viruses and their replication. In: Fields BN, Knipe DM, Howley PM *et al.* (eds). *Fields Virology*, third edition. Philadelphia: Lippincott-Raven 1996; pp. 1881–1952.

67 Hirsch MS, Curran J. Human immunodeficiency viruses. In: Fields BN, Knipe DM, Howley PM *et al.* (eds). *Fields Virology*, third edition. Philadelphia: Lippincott Raven 1996; pp. 1953–1975.

68 Folks TM, Khabbaz RF. Retroviruses and associated diseases in humans. In: Collier L, Balows A, Sussman M (eds). *Topley and Wilson's Microbiology and Microbial Infections vol. 1: Virology.* (Mahy B, Collier L, ed.). London: E. Arnold 1998; pp. 781–803.

69 Salahuddin SZ, Ablashi DV, Markham PD *et al.* Isolation of a new virus, HBLV, in patients with lympho-proliferative disorders. *Science* 1986; **234:** 596–601.

70 Yamanishi K, Okuno T, Shiraki K *et al.* Identification of human herpesvirus-6 as a causal agent for exanthema subitum. *Lancet* 1988; **i:** 1065–1067.

71 Dewhurst S, McIntyre K, Schnabel K *et al.* Human herpesvirus 6 (HHV-6) variant B accounts for the majority of symptomatic HHV-6 infections in a population of U.S. infants. *J Clin Microbiol* 1993; **31:** 416–418.

72 Tedder RS, Briggs M, Cameron CH *et al.* A novel lymphotropic herpesvirus. *Lancet* 1987; **ii:** 390–392.

73 Suga S, Yoshikawa T, Asano Y *et al.* Clinical and virological analysis of 21 infants with exanthema subitum (roseola infantum) and central nervous system complications. *Ann Neurol* 1993; **33:** 597–603.

74 Asano Y, Nakashima T, Yoshikawa T *et al.* Severity of human herpesvirus-6 viremia and clinical findings in infants with exanthema subitum. *J Pediatr* 1991; **118:** 891–895.

75 Frenkel N, Schirmer EL, Wyatt LS *et al.* Isolation of a new herpesvirus from human CD4+T cells. *Proc Natl Acad Sci USA* 1990; **87:** 748–752.

76 Clark DA, Freeland JML, Mackie PLK, Jarrett RF, Onions DE. Prevalence of antibody to human herpesvirus 7 by age. *J Infect Dis* 1993; **168:** 251–252.

77 Hikada Y, Liu Y, Yamamoto *et al.* Frequent isolation of human herpesvirus 7 from saliva samples. *J Med Virol* 1993; **40:** 343–346.

78 Yoshikawa T, Asano Y, Kobayashi I *et al.* Sero-epidemiology of human herpesvirus 7 in healthy children and adults in Japan. *J Med Virol* 1993; **41:** 319–323.

79 Tanaka K, Kondo T, Torigoe S *et al.* Human herpesvirus 7: another causal agent for roseola (exanthema subitum). *J Pediatr* 1994; **125:** 1–5.

80 Drago F, Ranieri E, Malaguti F, Losi E, Rebora A. Human herpesvirus 7 in pityriasis rosea. *Lancet* 1997; **349:** 1367–1368.

81 Chang Y, Cesarman E, Pessin MS *et al.* Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994; **265:** 1865–1869.

82 Renne R, Zhong W, Herndier B *et al.* Lytic growth of Kaposi's sarcoma. *Nature Med* 1996; **2:** 342–346.

83 Moore PS, Gao SJ, Dominguez G *et al.* Primary characterization of a herpesvirus-like agent associated with Kaposi's sarcoma. *J Virol* 1996; **70:** 549–558.

84 Russo JJ, Bohenzky RA, Chien M-C *et al.* Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV-8). *Proc Natl Acad Sci USA* 1996; **93:** 14862–14868.

85 Lagunoff D, Ganem D. The structure and coding organization of the genomic termini of Kaposi's sarcoma associated herpesvirus. *Virology* 1997; **236:** 147–154.

86 Neipel F, Albrecht J-C, Fleckenstein B. Cell-homologous genes in the Kaposi's sarcoma associated rhadinovirus human herpesvirus 8; determinants of its pathogenicity? *J Virol* 1997; **71:** 4187–4192.

87 Schulz TF Kaposi's sarcoma-associated herpesvirus (human herpesvirus-8). *J Gen Virol* 1998; **79:** 1573–1591.

88 Schulz TF. Epidemiology of Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8. *Adv Cancer Res* 1999; **76:** 121–160.

89 Howard R, Whitby D, Bahadur G *et al.* Detection of human herpesvirus 8 DNA in semen from HIV-infected individuals, but not healthy semen donors. *AIDS* 1997; **11:** F15–F19.

90 Calabrò ML, Sheldon J, Favero A *et al.* Seroprevalence of Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 in several regions of Italy. *J Human Virol* 1998; **1:** 207–213.

91 Mayama S, Cuevas L, Sheldon J *et al.* Prevalence and transmission of Kaposi's sarcoma associated herpesvirus (human herpesvirus 8) in Ugandan children and adolescents. *Int J Cancer* 1998; **77:** 817–820.

92 Choo Q-L, Kuo G, Weiner AJ, Oberby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989; **244:** 359–362.

93 Murphy FA, Fauquet CM, Bishop DHL *et al. Virus Taxonomy. Sixth Report of the International Committee on Taxonomy of Viruses.* Wien-New York: Springer Verlag, 1995.

94 Kuo G, Choo Q-L, Alter HJ *et al.* An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science* 1989; **244:** 362–369.

95 Van der Poel CL. Hepatitis C virus. Epidemiology, transmission and prevention. In: Reesink HW (ed.) *Hepatitis C Virus.* Amsterdam-Basel: Karger 1994; pp. 137–163.

96 Hibbs RG, Corwin AL, Hassan NF *et al.* The epidemiology of antibody to hepatitis C virus in Egypt. *J Infect Dis* 1993; **168:** 789–790.

97 Simmonds P, Holmes EC, Cha T-A *et al.* Classification of hepatitis C viruses into six major genotypes and a series of subtypes by phylogenetic analysis of the NS-5 region. *J Gen Virol* 1993; **74:** 2391–2399.

98 Davis GL, Balart LA, Schiff ER *et al.* Treatment of chronic hepatitis C with recombinant interferon alpha: a multicenter, randomized, controlled trial. *N Engl J Med* 1989; **321:** 1501–1506.

99 Marcellin P, Boyer N, Giostra E *et al.* Recombinant human alpha-interferon in patients with chronic non-A, non-B hepatitis: a multicenter, randomized controlled trial from France. *Hepatology* 1991; **13:** 393–397.

100 Chemello L, Alberti A, Rose K, Simmonds P. Hepatitis C serotype and response to interferon therapy. *N Engl J Med* 1994; **330:** 143.

101 Reyes GR, Prudy MA, Kim JP *et al.* Isolation of cDNA from the virus responsible for enterically transmitted non-A, non-B hepatitis. *Science* 1990; **247:** 1335–1339.

102 Tsarev SA, Emerson SU, Reyes GR *et al.* Characterization of a prototype strain of hepatitis E virus. *Proc Natl Acad Sci USA* 1992; **89:** 559–563.

103 Huang C-C, Nguyen D, Fernandez J *et al.* Molecular cloning and sequencing of the Mexico isolate of hepatitis E virus (HEV). *Virology* 1992; **191:** 550–558.

104 Bi SL, Purdy MA, McCaustland KA, Margolis HS, Bradley DW. The sequence of hepatitis E virus isolated directly from a single source during an outbreak in China. *Virus Res* 1993; **28:** 233–247.

105 Yin SR, Purcell RH, Emerson SU. A new Chinese isolate of hepatitis E virus: comparison with strains recovered from different geographical regions. *Virus Genes* 1994; **9:** 23–32.

106 Tam AW, Smith MM, Guerra ME *et al.* Hepatitis E virus (HEV): molecular cloning and sequencing of the full-length viral genome. *Virology* 1991; **185:** 120–131.

107 Aye TT, Uchida T, Ma X *et al.* Sequence comparison of the capsid region of hepatitis E virus isolated from Myanmar and China. *Microbiol Immunol* 1992; **36:** 615–621.

108 Aye TT, Uchida T, Ma X *et al.* Complete nucleotide sequence of a hepatitis E virus isolated from the Xinjiang epidemic (1986–1988) of China. *Nucleic Acids Res* 1992; **20:** 3512.

109 Aye TT, Uchida T, Ma X *et al.* Sequence and gene structure of the hepatitis E virus isolated from Myanmar. *Virus Genes* 1993; **7:** 95–110.

110 Fry KE, Tam AW, Smith MM *et al*. Hepatitis E virus (HEV): strain variation in the nonstructural gene region encoding consensus motifs for an RNA-dependent RNA polymerase and an ATP/GTP binding site. *Virus Genes* 1992; **6:** 173–185.

111 Yarbough PO, Tam AW, Fry KE *et al*. Hepatitis E virus: identification of type-common epitopes. *J Virol* 1991; **65:** 5790–5797.

112 Bradley DW, Krawczynski K, Cook EH *et al*. Enterically transmitted non-A, non-B hepatitis: serial passage of disease in cynomolgus macaques and tamarins and recovery of disease-associated 27- to 34-nm viruslike particles. *Proc Natl Acad Sc USA* 1987; **84:** 6277–6281.

113 Ticehurst J, Rhodes LL, Krawczynski K *et al*. Infection of owl monkeys (*Aotus trivirgatus*) and cynomolgus monkeys (*Macaca fascicularis*) with hepatitis E virus from Mexico. *J Infect Dis* 1992; **165:** 835–845.

114 Tsarev SA, Emerson SU, Tsareva TS *et al*. Variations in course of hepatitis E in experimentally infected cynomolgus monkeys. *J Infect Dis* 1993; **167:** 1302–1306.

115 Uchida T, Win KM, Suzuki K *et al*. Serial transmission of a putative causative virus of enterically transmitted non-A, non-B hepatitis to *Macaca fascicularis* and *Macaca mulatta*. *Japan J Exp Med* 1990; **60:** 13–21.

116 Purcell RH, Hoofnagle JH, Ticehurst J, Gerin JL. Hepatitis viruses. In: Schmidt NJ, Emmonds RW (eds). *Diagnostic Procedures for Viral, Rickettsial and Chlamydial Infections*, 6th ed., Chapter 28. Washington DC: American Public Health Association, 1989; pp. 957–1065.

117 Balayan MS, Andjaparidze AG, Savinskaya SS, Ketiladze ES, Braginsky DM, Savinov AP. Evidence for a virus in non-A, non-B hepatitis transmitted via the fecal-oral route. *Intervirology* 1983; **83:** 23–31.

118 Purcell RH, Ticehurst JR. Enterically transmitted non-A, non-B hepatitis: epidemiology and clinical characteristics. In: Zuckerman A (ed). *Viral Hepatitis and Liver Disease*. New York: Alan R. Liss, 1988; 131–137.

119 Cao X-Y, Ma X-Z, Liu Y-Z *et al*. Epidemiological and etiological studies on enterically transmitted non-A, non-B hepatitis in the south part of Xinjiang. In: Shikata T, Purcell RH, Uchida T, (eds.) *Viral hepatitis C, D and E*. New York: Elsevier Science Publishers B.V., 1991: 297–312.

120 Khuroo MS. Hepatitis E: the enterically transmitted non-A, non-B hepatitis. *Indian J Gastroenterol* 1991; **10:** 96–100.

121 Mushahwar IK, Dawson GJ, Bile KM, Magnius LO. Serological studies of an enterically transmitted non-A, non-B hepatitis in Somalia. *J Med Virol* 1993; **40:** 218–221.

122 Tsarev SA, Tsareva TS, Emerson SU *et al*. ELISA for antibody to hepatitis E virus (HEV) based on complete open-reading frame-2 protein expressed in insect cells: identification of HEV infection in primates. *J Infect Dis* 1993; **168:** 369–378.

123 Lok ASF, Kwan WK, Moeckli R *et al*. Seroepidemiological survey of hepatitis E in Hong Kong by recombinant-based enzyme immunoassays. *Lancet* 1992; **340:** 1205–1208.

124 Lee S-D, Wang YJ, Lu R-H, Chan C-Y, Lo K-J, Moeckli R. Seroprevalence of antibody to hepatitis E virus among Chinese subjects in Taiwan. *Hepatology* 1994; **19:** 866–870.

125 Arankalle VA, Tsarev SA, Chadha MS *et al*. Age-specific prevalence of antibodies to hepatitis A and E viruses in Pune, India, 1982 and 1992. *J Infect Dis* 1995; **171:** 447–450.

126 Phillips MJ, Blendis LM, Poncell S *et al*. Syncytial giant cell hepatitis. Sporadic hepatitis with distinctive pathological features, a severe clinical course, and paramyxoviral features. *N Engl J Med* 1991; **324:** 455–460.

127 Alter HJ. The cloning and clinical implications of HGV and HGBV-C. *N Engl J Med* 1996; **334:** 1536–1537.

128 Alter HJ, Nakatsuji Y, Melpolder J *et al*. The incidence of transfusion-associated hepatitis G virus infection and its relation to live disease. *N Engl J Med* 1997; **336:** 747–754.

129 Simmonds P, Davidson F, Lycett C *et al*. Detection of a novel DNA virus (TT virus) in blood donors and blood products. *Lancet* 1998; **352:** 191–195.

130 Prescott LE, Simmonds P. Global distribution of transfusion-transmitted virus. *N Engl J Med* 1998; **339:** 776.

131 Hohne M, Berg T, Muller AR *et al*. Detection of sequences of TT virus, a novel DNA virus, in German patients. *J Gen Virol* 1998; **79:** 2761–2764.

132 Chayama K, Kobayashi M, Tsubota A *et al*. Susceptibility of TT virus to interferon therapy. *J Gen Virol* 1999; **80:** 631–634.

133 Prescott LE, MacDonald DM, Davidson F *et al*. Sequence diversity of TT virus in geographically dispersed human populations. *J Gen Virol* 1999; **80:** 1751–1758.

134 Erker JC, Leary TP, Desai SM *et al*. Analyses of TT virus full-length genomic sequences. *J Gen Virol* 1999; **80:** 1743–1750.

135 Ball JK, Curran R, Berridge S *et al*. TT virus sequence heterogeneity *in vivo:* evidence for co-infection with multiple genetic types. *J Gen Virol* 1999; **80:** 1759–1768.

136 Scholtissek C, Burger H, Kistner O, Shortridge KF. The nucleoprotein as a possible major factor in determining host specificity of influenza H3N2 viruses. *Virology* 1985; **147:** 278–294.

137 Scholtissek CH, Naylor E. Fish farming and influenza pandemics. *Nature* 1988; **331:** 215.

138 Anonymous. Influenza A virus subtype H5N1 infections in Hong Kong – update. *CDR* 1998; **8:** 15.

139 Yuen KY, Chan PKS, Peiris M *et al*. members of the H5N1 study group. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* 1998; **351:** 467–471.

140 Subbarao J, Klimov A, Katz J *et al*. Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness. *Science* 1998; **279:** 393–397.

141 Claas ECJ, Osteshaus DME, van Beck R *et al*. Human influenza A H5N1 virus related to a highly pathogenic avian influenzavirus. *Lancet* 1998; **351:** 472–477.

141a Guan Y, Shortridge KF, Krauss S, Webster G, Molecular characterization of H9N2 influenza viruses: were they the donors of the "internal" genes of H5N1 viruses in Hong Kong? *Proc Natl Acad Sci USA* 1999; **96**: 9363–9369.

141b Peiris M, Yuen KY, Leung CW *et al*. Human infection with influenza H9N2. *Lancet* 1999; **354**: 916–917.

142 Vogel G (editorial). Sequence offers clues to deadly flu. *Science* 1998; **279:** 3224.

143 Belshe RB. (Editorial). Influenza as a zoonosis: how likely is a pandemic? *Lancet* 1998; **351:** 460–461.

144 Kurtz J, Manvell RJ, Banks J. Avian influenzavirus isolated from a woman with conjunctivitis. *Lancet* 1996; **348:** 901–902.

145 Murray K, Rogers R, Selvey L *et al.* A novel morbillivirus pneumonia of horses and its transmission to humans. *Emerg Infect Dis* 1995; **1:** 31–33.

146 O'Sullivan JD, Allworth AM, Patterson DL *et al*. Fatal encephalitis due to novel paramyxovirus transmitted from horses. *Lancet* 1997; **349:** 93–95.

147 Young PL, Halpin K, Selleck PW *et al.* Serologic evidence for the presence in *Pteropus* bats of a paramyxovirus related to equine morbillivirus. *Emerg Infect Dis* 1996; **2:** 239–240.

148 Harcourt B, Tamin A, Rollin P ` Molecular characterization of Nipahvirus, a newly emerging highly pathogenic paramyxovirus. Poster presentation, Annual Meeting of the American Society of Virology, Amherst, Mass, 1999.

149 Tidona CA, Kurz HW, Gelderblom HR, Darai G. Isolation and molecular characterization of a novel cytopathogenic paramyxovirus from tree shrews. *Virology* 1999; **258:** 425–434.

150 Shimizu H, Utama A, Yoshii K *et al*. Enterovirus 71 from fatal and nonfatal cases of hand, foot and mouth disease epidemics in Malaysia, Japan and Taiwan in 1997–1998. *Jpn J Infect Dis* 1999; **52:** 12–15.

151 Ishimaru Y, Nakano S, Yamaoka K, Takami S. Outbreaks of hand, foot, and mouth disease by enterovirus 71. High incidence of complication disorders of central nervous system. *Arch Dis Child* 1980; **55:** 583–588.

152 Samuda GM, Chang WK, Yeung CY, Tang PS. Monoplegia caused by Enterovirus 71: an outbreak in Hong Kong. *Pediatr Infect Dis J* 1987; **6:** 206–208.

153 Gilbert GL, Dickson KE, Waters MJ, Kennett ML, Land, SA, Sneddon M. Outbreaks of enterovirus 71 infection in Victoria, Australia, with a high incidence of neurologic involvement. *Pediatr Infect Dis J* 1988; **7:** 484–488.

154 Alexander Jr, JP, Baden L, Pallansch MA, Anderson LJ. Enterovirus 71 infections and neurologic disease – United States, 1977–1991. *J Infect Dis* 1994; **169:** 905–908.

155 Tagaya I, Takayama R, Hagiwara A. A large scale epidemic of hand, foot and mouth disease associated with enterovirus 71 infection in Japan in 1978. *Jpn J Med Sci Biol* 1981; **34:** 191–196.

155a Briese T, Jia X-Y, Huang C, Grady LJ, Lipkin W. Identification of a Kunjin/West Nile-like flavivirus in brains of patients with New York encephalitis. *Lancet* 1999; **354**: 1261–1262.

155b Jia X-Y, Briese T, Jordan I *et al.* Genetic analysis of West Nile New York 1999 encephalitis virus. *Lancet* 1999; **354**: 1971–1972.

155c Hubalék Z, Halouzka J. West Nile fever: a re-emerging mosquito-borne viral disease in Europe. *Emerg Infect Dis* 1999; **5**: 643–650.

156 Prusiner SB. Prions of humans and animals. In: Collier L, Balows A, Sussman M (eds). *Topley & Wilson's Microbiology and Microbial Infections, 9th edition, vol 1: Virology* (Mahy B, Collier L, eds). London: E. Arnold 1998; pp. 805–831.

157 Weissmann C, Aguzzi A. Bovine spongiform encephalopathy and early onset variant Creutzfeldt-Jakob disease. *Curr Opin Neurobiol* 1997; **7:** 695–700.

158 Bruce ME, Will RG, Ironside JW *et al*. Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature* 1997; **389:** 448–450.

159 Will R, Cousens S, Farrington C, Smith P, Knight R, Ironside J. Deaths from variant Creutzfeldt-Jakob disease. *Lancet* 1999; **353:** 9157–9158.

160 Aguzzi A, Brandner S. The genetics of prions – a contradiction in terms? *Lancet* 1999; **354:** st22–st25.

161 Fraser DW, Tsai TR, Orenstein W *et al*. Legionnaires' disease: description of an epidemic of pneumonia. *N Engl J Med* 1977; **297:** 1189–1197.

162 Edelstein PH, Meyer RD. *Legionella*' pneumonias. In: Pennington JG (ed.) *Respiratory Infections: Diagnosis and Management, 3rd edition*. New York: Raven Press, 1994; pp. 455–484.

163 Skirrow MB. Campylobacter enteritis: a 'new' disease. *BMJ* 1977; **2:** 9–11.

164 Skirrow MB. Infection with campylobacter and areobacter. In: Collier L, Balows A, Sussman M (eds). *Topley and Wilson's Microbiology and Microbial Infections*, Ninth edition, vol. 3. London: E. Arnold 1998; pp. 567–580.

165 Burgdorfer W, Barbour AG, Hayes SF *et al*. Lyme disease – a tick-borne spirochetosis? *Science* 1982; **216:** 1317–1319.

166 Johnson RC, Hyde FW *Borrelia burgdorferi* nov. etiologic agent of Lyme disease. *Int J Syst Bacteriol* 1984; **34:** 496–497.

167 Hurtenbach V, Museteanu C *et al*. Studies on early event of *Borrelia burgdorferi*-induced cytokine production in immunodeficient SCID mice by using a tissue/chamber model for acute inflammation. *Int J Exp Pathol* 1995; **76:** 111–123.

168 Wilson HL, Deblinger RD. *Ecology and Environmental Management of Lyme Disease*. New Brunswick: Rutgers University Press 1993; pp. 126–156.

169 Riley LW, Remis RS *et al*. Hemorrhagic colitis associated with a rare *Escherichia coli* serotype. *N Engl J Med* 1983; **308:** 681–685.

170 Smith HR, Cheasty T. Diarrhoeal diseases due to *Escherichia coli* and *Aeromonas*. In: Collier L, Balows A, Sussman M (eds). *Topley and Wilson's Microbiology and Microbial Infections*, Ninth edition, vol. 3. London: E. Arnold 1998; pp. 513–537.

171 Warren JR, Marshall J. Unidentified curved bacilli on gastric epithelium in chronic active gastritis. *Lancet* 1983; **i:** 1273–1275.

172 Warren JR, Marshall BJ. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **i:** 1311–1315.

173 Goodwin CS, Armstrong JA. Transfer of *Campylobacter pylori* and *Campylobacter mustelae* to *Helicobacter* gen. nov. as *Helicobacter pylori* comb. nov. and *Helicobacter mustelae* comb. nov., respectively. *Int J Syst Bacteriol* 1989; **39:** 397–405.

174 Mai UE, Perez Perez GIU Wahl LM *et al*. Soluble surface proteins from *Helicobacter pylori* activate monocytes/macrophages by lipopolysaccharide-independent mechanism. *J Clin Invest* 1991; **87:** 894–900.

175 Forman D, Newell DG, Fullerton F *et al*. Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *BMJ* 1991; **302:** 1302–1305.

176 Kuipers EJ, Uyterlinde AM, Pena AS *et al*. Long-term sequelae of *Helicobacter pylori* gastritis. *Lancet* 1995; **345:** 1525–1528.

177 Tytgat GN. Review article: treatments that impact favourably upon the eradication of *Helicobacter pylori* and ulcer recurrence. *Aliment Pharmacol Ther* 1994; **8:** 359–368.

178 Glupczynski Y. Results of a multicentre European survey in 1991 on metronidazole resistance in *Helicobacter pylori*. *Eur J Clin Microbiol Infect Dis* 1992; **11:** 777–781.

179 Maeda K, Markowitz N. Human infection with *Ehrlichia canis*, a leukocytic rickettsia. *N Engl J Med* 1987; **316**: 853–856.

180 McDade JE. Rickettsial diseases. In: Collier L, Balows A, Sussman M (eds). *Topley and Wilson's Microbiology and Microbial Infections, 9th* edition, vol. 3. London: E. Arnold 1998; pp. 995–1011.

181 McQuiston JH, Paddock CD, Holman RC, Child JE. The human ehrlichioses in the United States. *Emerg Inf Dis* 1999; **5:** 635–640.

182 Koch R. An address on cholera and its bacillus. *BMJ* 1884; **2**: 403–407.

183 Ramamurthy T, Garg S, Sharma S *et al*. Emergence of a novel strain of *Vibrio cholerae* with epidemic potential in southern and eastern India. *Lancet* 1993; **341**: 1347.

184 Tauxe RV. Cholera. In: Collier L, Balows A, Sussman M (eds). *Topley and Wilson's Microbiology and Microbial Infections*, 9th edition, vol 3. London Arnold 1998; pp. 495–512.

185 Slater N, Welch DF, Hensel D, Coody DW. 1989. A newly recognized fastidious gram negative pathogen as a cause of fever and bacteremia. *N Eng J Med* 1989; **323:** 1587–1593.

186 Slater LN, Welch DF, Min KW. *Rochalimaea henselae* causes bacillary angiomatosis and peliosis hepatis. *Arch Intern Med* 1992; **152:** 602–606.

187 Regnery RL, Olson JG, Perking BA. Serological response to *Rochalimaea henselae* antigen in suspected cat scratch disease. *Lancet* 1992; **339:** 1443–1445.

188 Meisel JL, Perera DR *et al*. Overwhelming watery diarrhea associated with *Cryptosporidium* in an immunosuppressed patient. *Gastroenterology* 1976; **70:** 1156–1160.

189 Nime FA, Burek JD *et al*. Acute enterocolitis in a human being infected with the protozoan *Cryptosporidium*. *Gastroenterology* 1976; **70:** 592–598.

190 Current WL, Garcia LS. Cryptosporidiosis. *Clin Microbiol Rev* 1991; **4:** 325–358.

191 O'Donoghue PJ. *Cryptosporidium*, and cryptosporidiosis in man and animals. *Int J Parasitol* 1995; **25:** 139–195.

192 Smith HV, Girdwood RWA, Patterson WJ *et al*. Waterborne outbreak of cryptosporidiosis. *Lancet* 1988; **ii:** 1484.

193 MacKenzie WR, Hoxie NJ *et al*. A massive outbreak in Milwaukee of *Cryptosporidium* infection transmitted through the public water supply. *N Engl J Med* 1994; **331:** 161–167.

194 Johns TJ. Learning from plague in India. *Lancet* 1994; **344:** 972.

195 Johns TJ. India: Is it plague? *Lancet* 1994; **344:** 1359–1360.