Global aspects of infectious disease pathology
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INTRODUCTION

The unique challenge inherent in the subspecialty of infectious diseases pathology lies in the fact that, unlike many other disease processes, infectious diseases vary significantly around the globe. For this reason, the odds of observing a particular pathogen depend to a large extent on patient demographics and geography. The few pathologists who practice full-time in this subspecialty often work in public health or referral centers. For them, the pressure to stay current on the ever-growing list of potential infectious agents, and the time-consuming process of observing them in tissue, are constant additional challenges.

The objective of this symposium and slide seminar on infectious diseases is to illustrate the diversity of diseases seen, and to show which factors are important in determining their prevalence and natural history in a given venue. Several of the speakers will address the identification of new and emerging infections.

Infectious diseases in a particular location are broadly classified as endemic, epidemic, imported, emerging or iatrogenic. The important variables influencing disease prevalence are listed below:

| Population Factors                          | Population Factors                              | Population Factors                     |
|--------------------------------------------|------------------------------------------------|----------------------------------------|
| Cultural practices                         | Disease vectors/reservoirs                      | Immunosuppression (infection, therapy, age) |
| Genetic susceptibility                      | Geoclimatic conditions/seasonal variations      | Natural and acquired immunity (vaccines and exposure) |
| Health status/standard of living           | Sanitation                                      |                                        |
| Infrastructure                              | Urban vs. rural                                |                                        |
| Population density                         | Host Factors                                    | Parasite Factors                        |
| Travel/immigration                          | Diet/lifestyle (jobs, hobbies, pets, sexual activity) | Latency                                |
| Cultural practices                         | iatrogenic/hospital-acquired infections/blood products | Mutation/drug resistance               |
| Genetic susceptibility                      |                                               | Pathogenicity                           |
| Health status/standard of living           |                                               | Route(s) of transmission                |
| Infrastructure                              |                                               | Virulence                               |
| Population density                         |                                               |                                        |
| Travel/immigration                          |                                               |                                        |
| Environmental Factors                       |                                               |                                        |
| Changes in ecology (dams, construction, intrusion on wildlife areas, etc) |                                               |                                        |

Disadvantaged populations in industrial and resource-poor countries carry a large proportion of disease burden. They have increased risk of exposure and limited access to effective care. Travel, military and development operations, and immigration can change disease patterns. Pathogens that are spread exclusively by human-to-human contact, including those spread via respiratory droplets or sexual activity, can be transported to any part of the world. The success of the disease in a new environment depends on microbial and environmental factors, as well as the number of susceptible hosts. A respiratory infection such as influenza spreads rapidly in closed environments such as airplanes, but the spread of HIV or cholera is limited by host behavior and environmental conditions. Numerous refugee camps around the globe have become incubators of infectious diseases. Failure to immunize susceptible populations has led to the resurgence of polio and measles.

Although more than 60% of infections are spread directly by human-to-human contact, many new and emerging diseases are zoonotic. The extended geographic distribution of insect vectors, the importation of exotic pets, and the globalization of the food market have led to the emergence of many zoonoses in unexpected places.

Infections as complications of therapy have increased rapidly in geriatric and transplant populations and often involve resistant microbial strains. Trauma and surgery, transfusions, indwelling lines, hypoxia, nutritional status, use
of antibiotics, all increase susceptibility to health care-associated infections. The trend toward group living for geriatric and medically disabled persons also promotes the transmission of infection and the development of microbial resistance.

Intravenous drug use predisposes to bloodborne, sexually transmitted, and community acquired infections. The obvious risk factors such as use of dirty needles, contaminated drugs, and the sex-for-drugs economy are complicated by societal marginalization of these individuals, with resultant poor access to health care, poor treatment compliance, coexisting HIV infection, malnutrition, and alcoholism.

In countries with adequate access to health care and highly active antiretroviral therapy, HIV infection has become a chronic disease; viral-related malignancies and treatment complications may be more common than opportunistic infections. But most countries with a heavy HIV burden are resource-poor, and comorbid conditions of tuberculosis and bacterial, fungal, and protozoal diseases are the major causes of death among HIV patients.

Some chronic diseases and neoplasias are linked to specific infections: ulcer and MALTomas with *H. pylori*; Kaposi sarcoma and systemic Castleman disease with human herpesvirus 8 (HHV8); cirrhosis and hepatocellular carcinoma with hepatitis B and C; anogenital carcinoma with human papillomavirus (HPV); and lymphomas with Epstein-Barr virus (EBV).

**ROLE OF THE PATHOLOGIST**

Historically, the pathologist has played an important role in public health by identifying pathogens and describing pathogenesis and morbid anatomy. Biopsy and autopsy series are essential in establishing data on prevalence and natural history.

In recent years, there have been numerous unexplained respiratory deaths throughout the world, for which epidemiology, serology, and culture studies were insufficient to determine the etiologic cause of death. Careful histopathology studies carried out at the US Centers for Disease Control and Prevention identified a respiratory hantavirus in Southwestern United States, leptospirosis in Central America, and a coronavirus in Asia.

Pathology has also played an important role in the diagnosis of the causative agent of several human and animal outbreaks of viral infections in Malaysia. Having the appropriate facilities and trained personnel to perform autopsies is essential, as is a global network of referral laboratories. Surveillance for diseases in resource-poor countries (e.g. *Mycobacterium ulcerans* (Buruli ulcer), Ebola and other hemorrhagic fevers) is aided by histopathology studies. Many nonculturable pathogens can only be identified by histology aided by immunohistochemistry and polymerase chain reaction. Much of what is known about the natural history and pathogenesis of infections is based on comparative studies of material obtained in outbreaks and archived material.

Pathologists must realize the importance of correct and prompt histopathological diagnosis of a wide variety of infectious diseases in both immunocompetent and immunocompromised patients. Understanding the defense mechanisms against pathogens (neutrophils vs. T lymphocytes vs. antibodies) and how they are altered by a variety of immunosuppressive conditions is essential for adequate diagnosis and subsequent therapy. In post-transplant patients, the pathologist may be called upon to determine if a reaction is due to graft-vs.-host response or infection. It is equally important to rule out a viral or fungal pathogen. Early diagnosis of an infection may save not only the organ, but also the patient, and may help to prevent nosocomial (hospital-acquired) infections with MRSA and tuberculous bacilli.

HIV infection has affected the prevalence and natural history of infectious diseases and viral-induced tumors. The profile of the disease varies by risk group, endemic diseases, and access to health care. Symposium presentations will cover aspects of the disease in London, Johannesburg, and Mumbai.

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**Unidentified pulmonary pathogens: An approach to diagnosis**

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Infectious diseases continue to produce extensive mortality and morbidity, and on a global scale, are the leading cause of death. During the past three decades, the world has witnessed the emergence of many new infectious diseases as well as the reemergence of previously known diseases. Notable recent infectious disease challenges faced by public health professionals include Legionnaires’ disease, acquired immunodeficiency syndrome, cat scratch disease, *Helicobacter pylori*-associated disease, ehrlichiosis, hepatitis C, hantavirus pulmonary syndrome, Ebola hemorrhagic fever, leptospirosis, severe acute respiratory syndrome (SARS), and new-variant Creutzfeldt-Jakob disease. Effective surveillance systems are essential to the timely recognition of
emerging infections before they become major public health problems. These systems require a thorough understanding of the epidemiology of infectious diseases, good communication and collaboration among health care professionals and the public health community, and very importantly, effective diagnostic capabilities.

Infectious disease pathologists have a longstanding history of contributing to the diagnosis and identification of infectious disease agents. Pathologists are characterized among the first health care workers involved in recognizing infectious disease outbreaks and hence are in an excellent position to discover new pathogens and infectious disease syndromes. These discoveries have been accomplished by collaborative research with colleagues from other scientific disciplines, such as epidemiology, clinical care, veterinary medicine, and microbiology.

Traditionally, anatomic pathologists have relied on routine histopathology or special stains to arrive at a diagnosis. Some pathogens, such as certain species of fungi and bacteria, are morphologically distinctive and can be readily identified by microscopy or special tissue stains. Viral pathogens, such as measles virus, herpes viruses, parvovirus, and rabies virus, produce characteristic intracellular inclusions which may support a specific diagnosis.

Observations of patterns of tissue injury and host responses are also important because tissues often react to infections in specific and predictable ways, making it possible to suspect certain infections. Nonetheless, in many cases it is impossible to identify a specific infectious agent by morphologic observations alone. Recent experience at the Centers for Disease Control and Prevention (CDC) and other institutions has shown that combining traditional morphology with immunologic and molecular pathology techniques is an extremely useful approach in confirming diagnoses for patients with otherwise unexplained pulmonary infections.

The diagnosis of viral pneumonia, suspected by history and clinical manifestations, also can be supported histopathologically, and the overall pattern of histopathologic lesions may suggest a specific diagnosis. Many viruses can be identified in lung by examining the tissue response and cytopathic changes. Some of these viruses cause recognizable tissue reaction patterns including necrotizing tracheobronchitis, bronchiolitis, and interstitial pneumonia. Only certain viruses can cause cytopathic changes that are morphologically distinctive enough to enable the pathologist to recognize a specific diagnosis on routine histologic examination of lung specimens. With the availability of special diagnostic techniques, such as immunohistochemistry (IHC) and in situ hybridization (ISH), many viruses can be detected in formalin-fixed, paraffin-embedded tissue samples even if specific viral inclusions cannot be found in histologic examination of tissue sections. Among the techniques, IHC utilizing specific antibodies can be routinely performed on formalin-fixed tissue and can enhance the pathologist’s accuracy in identifying organisms in tissue specimens.

Immunologic and molecular methods, such as IHC, ISH, and polymerase chain reaction (PCR), have revolutionized the ability of pathologists to diagnose and study infectious diseases. These techniques allow detection of microbial antigen or nucleic acid sequences in formalin-fixed, paraffin-embedded tissues. In this context, unexplained pulmonary infectious diseases may be investigated prospectively, as well as retrospectively, in archival tissues. Traditionally, microbial identification has relied primarily on serologic assays and culture techniques. Serologic assays characteristically require the collection of paired serum samples to demonstrate rising antibody titers against a specific pathogen. Certain circumstances, including immunocompromised states, early therapy, or rapid death, may preclude the development of diagnostic antibody responses. Finally, serologic tests may occasionally give a nonspecific result, especially if only a single sample is available for evaluation. Visualization of microbial antigens or nucleic acids in the context of pathology allows the pathologist to assess the clinical significance of serologic test results or microbial isolation.

Culture of fastidious pathogens and obligate intracellular viruses and bacteria is often labor intensive, may require biosafety facilities not readily available, and may take weeks or months to yield results. By comparison, the use of molecular pathologic techniques offers several distinct advantages over traditional microbiologic methods, including speed, sensitivity, reduced risk of exposure to laboratory personnel, and tissue localization of pathogens. The unique role of molecular pathology in the confirmation of infection in seronegative patients and detection of fastidious or non-culturable organisms cannot be overemphasized. A prompt, specific diagnosis can prevent the use of unnecessary therapeutic regimens, reduce the need for invasive diagnostic procedures, and alert the medical community to institute appropriate therapeutic and precautionary measures that can control or halt the spread of the disease.

The presentation will highlight some of the contributions of CDC pathologists in addressing some of the challenges posed by pulmonary pathogens including SARS, Hantavirus, Nipah virus, Legionella, leptospirosis, and anthrax among others.

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Infection I. Unusual pneumonias. In: Katzenstein and Askin’s surgical pathology of non-neoplastic lung disease. Ed. Katzenstein
Features of strongyloidiasis

Strongyloidiasis, an intestinal parasitosis seen in the tropical and subtropical countries, is caused by percutaneous infection of *Strongyloides stercoralis*. In Japan, this disease is encountered only in the southern islands (Kyushu, Amami and Okinawa). This small Nematoda can survive in the moist warm soil as free-living (rhabditiform) adults of both sexes. When the temperature in the atmosphere becomes less than 30 degree C, the larvae turn to be an infective filariform. Parasitic adults are solely female, and hatch filariform larvae within the intestinal lumen as a result of ‘parthenogenesis’. Autoinfection causes chronic infestation sustaining for years. Hyperinfection may lead to severe diarrhea and emaciation, in association with abdominal pain and steatorrhea. When the parasites are seen in the gastric biopsy samples, we should regard it as hyperinfection. As far as the infection is confined within the gut lumen, eosinophilia is hardly provoked.

It is of note that all the ova are hatched in the gut lumen, and no ova can be seen in the stool: Routine coprologic examination for parasitic eggs turns to be negative. An agar plate method is sensitive enough to identify the larvae in the stool, since they actively move around on the plate, resulting in bacterial colony formation along the track. Specific diagnostic term ‘strongyloidiasis’ is requested for pathologists, particularly when the parasites are seen in gastric biopsy samples: The histopathological diagnosis of ‘parasite infection’ is never suitable. Hyperinfection may threaten the patient’s life.

Another important aspect of strongyloidiasis is that the disease is manifested as opportunistic infection, as was so in this case, in which strongyloidiasis was prodromal to ATL. In Japan, ATL, particularly the smoldering form, is often associated with this parasitosis. In fact, ATL is endemic in the southern part of Japan. In the tropical countries such as Thailand, disseminated strongyloidiasis can be a fatal complication in AIDS patients. In histologic specimens, filariform larvae can be seen in the wall of the appendix and colon, provoking granulomatous reactions and tissue eosinophilia. Cytology specimens of the sputum and effusions may contain the small-sized larvae.

In the present case, bleeding from open duodenal peptic ulcer became uncontrollable. This was probably related to hyperinfection of *S. stercoralis*. Fortunately, no disseminated infection occurred, and infection could be suppressed by chemotherapy.

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CASE 2: ISOSPORA BELLI INFECTION ASSOCIATED WITH ADULT T-CELL LEUKEMIA (ATL)

The diagnosis of a smouldering type adult T-cell leukemia (ATL) was made 15 months earlier in a 45-year-old Japanese male. He suffered from a long-standing intractable diarrhea (ATL) was made 15 months earlier in a 45-year-old Japanese male. He suffered from a long-standing intractable diarrhea. Endoscopic examination was performed. The gastric mucosa was unremarkable without Helicobacter pylori infection, while the duodenal mucosa was diffusely hyperemic and atrophic. Duodenal biopsy was performed.

Histologic findings
Active and severe chronic inflammation is seen, in association with shortening of the duodenal villi. Round-shaped protozoan bodies (schizonts) are distributed among the intestinal columnar epithelium. Eosinophils are increased in the lamina propria mucosae. Close examination revealed both schizonts and merozoites among the intestinal epithelium.

Features of isosporiasis
Isosporiasis is caused by infection of Isospora belli (belli = war), which may cause persistent intractable diarrhea. The size of protozoa is much larger than Cryptosporidium parvum. The final host of I. belli is the human (not zoonotic). Anti/protozoan agents are effective. In Japan, more than half of patients with isosporiasis suffer from ATL. In Africa, isosporiasis is listed as a lethal bowel complication of AIDS patients. It is of note that gallbladder cancer may be associated with chronic persistent isosporiasis.

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CASE 3. DIPHTHERIA IN THE AGED

A 68-year-old Japanese male suffered from acute and severe respiratory distress with wheezing. No fever was associated. His consciousness level was comatous. Laryngeal examination in the emergency suite revealed thick and white pseudomembranes on the throat of the patient. Intubation was technically difficult, and a small piece of the pharyngeal mucosa obtained during the manipulation was submitted for histologic evaluation. The patient soon died of respiratory failure. No autopsy was performed.

Histologic findings
The pharyngeal squamous mucosa is densely covered with faintly basophilic material, namely pseudomembranes. Submucosal inflammation beneath the pseudomembranes is relatively mild. By Gram staining, numbers of large-sized Gram-positive rods are embedded within the pseudomembranes. The diagnosis should be diphtheria. Scanning electron micrograph of pathogens floating in the fixative disclosed club-shaped rods without flagella or capsule, being consistent with the Corynebacterium species (‘coryne’ means club).

Features of diphtheria
Diphtheria is caused by acute infection of Corynebacterium diphtheriae, a club-shaped, aflagellated Gram-positive rods. The bacilli proliferate on the pharynx, larynx, trachea and nasal mucosa to form thick pseudomembranes. Diphtheria toxin production may lead to motor paralysis of the heart and striated muscles. Vaccination as a form of DPT combination is effective to prevent this lethal infection. Droplet transmission should be avoided. Russian endemic of diphtheria after recent evolutionary political change has been a serious public health problem.

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CASE 4. DOUBLE INFECTIONS OF ADENOVIRUS AND BK VIRUS AFTER BONE MARROW TRANSPLANTATION (BMT)

A 10-year-old Japanese boy, who had suffered from recurrent acute lymphoblastic leukemia (L1), received bone marrow transplantation (BMT) from his HLA-mismatched father. CD34-positive stem cells were selected from the aspirated marrow fluid. One week after transplantation, diarrhea started, and hematochezia followed in two weeks. Massive bowel hemorrhage, one liter per day, continued for three months to lead the patient to death. No hematuria was recorded during the clinical course. At autopsy, histological features of acute graft versus host disease were observed in the skin, liver and colonic mucosa.
Histologic findings
In the small bowel epithelium, numerous intranuclear inclusions of either full (smudge) type or Cowdry’s type A were identified. Similar nuclear inclusion bodies were further observed in the superficial part of the urinary bladder epithelium. Systemic infection of adenovirus was suspected at the light microscopic level.

Ultrastructural studies of the inclusion bodies were performed using H&E-stained paraffin sections. In the gut epithelium, enveloped viral particles were 70nm in diameter and hexagonal in shape, and were arranged in a regular geometrical pattern. Some virions appeared empty and lacked cores. These EM features were diagnostic of adenovirus. Adenovirus infection was also observed in the bronchial epithelium. In contrast, the inclusion bodies in the urothelium showed unenveloped 40nm round particles, irregularly clustered in the nuclei. The EM features were consistent with papova virus, particularly BK virus of polyoma virus group. Therefore, dual opportunistic infection of two kinds of DNA virus was ultrastructurally confirmed. The usefulness of the targeted EM study utilizing H&E-stained paraffin sections was shown here.

Features of opportunistic viral infections after BMT
BMT provides the recipient with lethal opportunistic infections of a variety of pathogens that are usually indolent for immunocompetent individuals, such as fungi, Pneumocystis carinii, and cytomegalovirus. Opportunistic infection of adenovirus seen in the BMT recipients often involves the bladder and kidney, manifesting gross hematuria and cystitis symptoms (hemorrhagic cystitis). Renal failure due to renal tubular involvement by this double-stranded DNA virus may occur. Most commonly, serological type 11 is demonstrated. Necrotizing pneumonia and hemorrhagic enteritis may also be encountered. This is the case of adenovirus-induced hemorrhagic enteritis (and bronchitis) without urinary tract involvement. Most likely serotypes include types 40 and 41.

BK virus (named after the initials of the patient) belongs to the polyoma virus, and the latent infection of BK virus has been shown in most healthy individuals. This small-sized, double-stranded DNA virus is opportunistically reactivated in the urinary tract of immunosuppressed patients or transplant recipients. Hemorrhagic cystitis is common. In some cases, no hemorrhagic or necrotizing changes are observed in the bladder mucosa, in which nuclear inclusion bodies in the urothelium should merely be the incidental histological findings, as was so in the present case. In urine cytology specimens, enlarged urothelial cells with smudgy nucleoplasm, so-called ‘decoy cell’, may be seen in the clear non-inflammatory background. Urinary tract co-infection with JC virus, another polyoma virus typically causing progressive multifocal leukoencephalopathy in immunocompromised patients, has also been reported. Recent topics are the oncogenic roles of variant BK virus in brain, renal, urothelial and prostatic tumors.

Usefulness of Electron microscopic study using paraffin-embedded sections
Because of their distinct particulate organizations and thick membrane-bound structures, the ultrastructural morphology of pathogens such as bacteria and viruses tends to be preserved even in routinely processed archival paraffin sections. Very frequently, the pathogens are localized in certain small areas of tissues and organs, and thus random sampling from a fresh material may be fruitless for the EM study. When pathologists recognize pathogens only in a few cells in H&E preparations, the cells of focus can be examined in a targeted way by additionally cutting paraffin sections. To do this, an inverted beam capsule method should be applied to the area containing the infected cells after performing H&E staining. If specific antibodies or probes are available, this approach can be performed after diaminobenzidine-mediated immunoperoxidase staining (pre-embedding immunoelectron microscopy) or in situ hybridization histochemistry. Because of excellent permeability into the tissue sections, false negativity by insufficient penetration of antibodies or probes occurs very infrequently. This also helps us confirm the specificity of the antibodies and probes.

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Infectious diseases in an immigrant population in London
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INTRODUCTION
Britain invented the concept of tropical diseases. Dr Patrick Manson, who had worked in China in the late 19th century,
instituted the Hospital for Tropical Diseases (HTD) in London. It was primarily for the care of the sons (and daughters) of the colonial empire, when they returned sick from working in hot climates. Death rates among expatriates in, for example, West Africa from malaria and yellow fever were startlingly high in the 18th and 19th centuries, as the gravestones there attest. Of course, observed mortality back in London was less since the long passage back home by ship resulted in death or cure.

The HTD now caters less for civil servants, and more for business, the armed forces, and tourist patients; and increasingly, in the last decade, for immigrants from the tropics. The most notable influx has been refugees and immigrants from sub-Saharan Africa.

Because of air travel, travellers can return from any parts of the globe to UK within 24 hours. So the incubation period for serious diseases is rendered less important, and even viral haemorrhagic fever and rabies cases are encountered every year or so in the UK.

Demography is the major determinant of what medical services encounter; where the patients come from, where they locate (or are dispersed to, under regulation by the Home Office in the case of many immigrants), and what latent, endemic and epidemic infections they bring with them. This is a moving target, and all laboratories in the UK must expect to see some ‘unusual’ imported infections.

The commonest significant imported infections include:

- Falciparum malaria
- Tuberculosis
- HIV/AIDS
- Hepatitis C
- Leishmaniasis
- Schistosomiasis

Populations within the UK in 2001 (Great Britain):

- England & Wales 52 million
- Scotland 5 million
- Northern Ireland 1.6 million
- Total 58.8 million

FALCIPARUM MALARIA

About 1000 cases of malaria are reported annually in England & Wales, the great majority being *P. falciparum* infection, and about two-thirds being diagnosed in London. The case fatality rate is declining, with between 2-10 deaths a year. Most of these deaths result from late presentation and diagnosis, a few from chemotherapy. The pathology of malaria is seen in biopsies (particularly placenta and liver) and in cadavers. In the deaths, cerebral malaria is the usual finding, with additional pathologies resulting from intensive care procedures (eg shock lung).

**Hepatitis C infection**

The Health Protection Agency (HPA, ex-PHLS) collects data from laboratories on HCV diagnoses. The number of annual reported cases has increased from 241 in 1992 to 6477 (provisional total) in 2003; by the mid-1990s it was about 3000 per annum, and the rise has not slowed.

Interestingly unlike TB and HIV, HCV is not a London-dominated disease, the largest area with reported cases being the north-west (which includes Manchester and Liverpool). Injection drug use is still the single largest associated risk factor.

Pathologically, increasing numbers of liver biopsies are received for staging of HCV liver disease, with a view to determining the use and timing of therapy. The standard best practice treatment is now pegylated interferon-alpha and ribavirin. The costs are high, and the success rate suboptimal.

A particular co-epidemic of concern in the UK is HCV with HIV. There is good evidence that HIV accelerates the progression of HCV disease to end-stage liver disease, and renders anti-HCV viral therapy less effective. Whether HCV reciprocally affects the progression of HIV disease is still undetermined, there being evidence both for and against.

**TUBERCULOSIS**

Although nothing like the numbers of tuberculosis (TB) cases that were seen in the 19th and first part of the 20th centuries, the current incidence of TB in the UK is worryingly increasing. Since 1988 to 2002, the numbers reported have increased by 50% from 4660 to 6910, and the % change is still about 5% per year upward (HPA data).

The overall incidence in England & Wales is 12.9/100,000 persons per year. This figure hides huge regional and ethnic differences; for example, in England it is 13.6, but in Northern Ireland it is only 3.9. However 43% of all TB is reported from London, with an average incidence of 40/100,000. This also hides considerable ethnic disparities as shown in the Table (data from 2002)

| Ethnic group | Tuberculosis incidence rate (per 100,00 pa) |
|--------------|--------------------------------------------|
| White        | 5                                          |
| Indian, Pakistani, Bangladeshi | 130                                      |
| Black African | 270                                      |
| Black Caribbean | 35                                      |
| Chinese      | 60                                         |

About 63% of this tuberculosis is therefore in persons born abroad, and most probably contracted abroad.

Pathologically, 60% of TB is pulmonary and 40% extra-pulmonary at diagnosis. The importance of FNA diagnosis of lymph node tuberculosis has increased corresponding with the changing epidemiology.

There is a significant association of TB with HIV infection. In Africa, 31% of all TB is associated with HIV; in UK the HIV prevalence among those aged 15-65 years with TB is about
4%, though higher in the 35-39 year age group. This is undoubtedly increasing and underestimated. Pathologically, HIV has major impact on TB clinical pathology, and there is a serious rate of under-diagnosis of TB in HIV+ patients until it is too late to render effective therapy (pers. comm., autopsy data).

Multi-drug resistant TB (MDRTB) is, at present, not a significant problem in the UK, with a prevalence among the newly diagnosed of <2%, and no significant temporal change. With improving implementation of controlled anti-TB therapy, MDRTB can be controlled. But there is concern that, with the accession to the European Union in May 2004 of many eastern European states that have significant IV drug use, HIV and TB problems, there is likely to be an increase in MDRTB as people cross borders the more easily.

LEPROSY

Leprosy has not been transmitted within the UK since the early 1900s, and about 16-20 new cases a year are diagnosed. This is predominantly among immigrants from India, Africa and south east Asia. Depressingly, the median time from first presentation to a health care worker to leprosy diagnosis is 2.2 years. Many patients are seen by rheumatologists, orthopaedic surgeons, neurologists and dermatologists, and considered to have other diagnoses (eg Wegener’s granulomatosis, chronic inflammatory neuropathy, arthritis). This is unfortunate since early diagnosis and effective curative therapy can prevent the major complication of irreversible peripheral nerve damage.

Pathologists in the UK have an overall good record in picking up leprosy in diagnostic material. Leprosy is usually over-suspected rather than under-diagnosed, and there are a few experts available who can provide a confident confirmation or refutation.

LEISHMANIASIS

The total number of leishmaniasis cases imported into the UK is not known, because it is not mandatory to report them. From HTD experience, there are about 100 cases a year of cutaneous leishmaniasis and about 20 of visceral leishmaniasis. Muco-cutaneous leishmaniasis (MCL) is encountered about once a year.

These infections reflect travel abroad, and also underlying diseases. MCL presents in occasional visitors from South America, following a skin lesion that may have healed. It is important to keep MCL in mind when evaluating chronic inflammatory nasal lesions; the parasite density is likely to be minimal or zero, and culture or PCR on even tissue can confirm the diagnosis.

Many of the VL patients in the UK have underlying HIV disease, the leishmaniasis being a reactivation from previous infection around the Mediterranean basin. It may present with intestinal, lymph node and liver disease, and the parasites are usually abundant. Differential diagnosis is from Histoplasma capsulatum fungal infection.

HIV/AIDS

The most important infection now in the UK, epidemiologically and pathologically, is HIV. From being a minimal problem in the early 1980s, it is now a major determinant of hospital and community health care budgets, particularly with the advent of effective, albeit expensive, anti-retroviral therapy (HAART).

The total of known HIV infected persons in the UK is about 61,000. It is estimated that presently there are over 50,000 persons living with HIV, of whom one third do not know they are infected. The opportunities for early diagnosis are complex, and there is pressure on all health care workers to ‘think HIV’ when patients, particularly those in so-called high-risk groups, present with both standard and unusual disease symptoms and signs. Unfortunately, too-late diagnosis, through unquantified, is still frequent.

In 2003, >6000 new cases of HIV infection were identified, the majority acquired heterosexually—and most of that acquired in Africa, in diagnosed in recent immigrants from that continent. The size of this risk group shows no signs of plateauing or slowing down. HIV acquired by men having sex with men (MSM) continues at a steady rate. IV drug users are a small proportion now, and mother-to-child transmission (MTC) is very low, with the roll-out of increasingly universal ante-natal testing for HIV.

London and the south east of UK has the majority of HIV cases, about 70%, but there is an increasing diaspora to all parts of the country, determined by non-medical factors such as employment opportunities and government policy on dispersal of immigrants.

The death rate has been low since the advent of HAART in the late 1990s. In 1995 there were 1719 deaths in HIV infected persons. In 2003 there were (only) 400 deaths, roughly half due to AIDS, and half in persons without AIDS (mainly illicit drug overdose, and complications of HCV co-infection and liver disease, and some suicides). The death rate is expected to rise with the ever increasing number of infectees.

The pathology that this epidemic brings is wide-ranging. Essentially there are five aspects in practical work:

• Diagnosis of opportunistic infections
• Diagnosis of cancers and lympho-proliferations
• Diagnosis of complications of HIV and related chemotherapy
• Diagnosis of HCV-related liver disease
• Diagnosis of pathology in those who die

In London practice, because of the large African immigrant population with HIV, tuberculosis is the most important co-
infection encountered. It often presents with atypical signs and imaging, and must always be considered. The second point is that the range of pathology appears infinite, with new diseases and new versions of known diseases appearing constantly.

The most important complications of therapy are liver damage (particularly steatosis with lactic acidosis), and IRIS (immune restoration inflammatory syndrome) to many infections. Whether the biologically predicted epidemic of coronary artery disease related to chemotherapy will translate into real pathology is unclear at present.

OTHER DISEASES

1. SARS (severe adult respiratory syndrome): although several industrialised countries outside south east Asia have had significant numbers of imported cases, there have been none in the UK (yet).
2. Viral haemorrhagic fever: about once a decade there is a death from Lassa fever in the UK, acquired in west Africa. No cases of Ebola have been imported. More frequent is Crimean-Congo HF, with a case every few years. None of these seem to come to autopsy.
3. Rabies: with a ban on importation of pets in the UK, rabies is rare. Only one authochthonous human case has occurred in the last 50 years (acquired from a bat in a laboratory), and the others are imported from India and Africa. From one per decade, the rate has increased to one every 3 years or so. The majority of prophylaxis is, necessarily, at the autopsy table. It is recommended that all mortuary workers and pathologists who work in London and near international airports have up to date rabies vaccination.

Practical health and safety issues
Within diagnostic histopathology and cytopathology, standards of practice and processing of specimens is now so well standardised that there is little significant risk of cellular pathology health care workers acquiring a serious communicable disease within the laboratory. In the autopsy suites, however, it is different. As is evident from the above, the actual likelihood of encountering a cadaver with a hazard group 3 infection (TB, HIV, HCV particularly) is increasing. Many mortuaries are not well equipped for this, and many pathologists and anatomical pathology technologists do not wish to undertake this work. It is likely that the examination of these known and suspected cadavers will increasingly be concentrated in a small number of regional centres, where the capability and the expertise in interpreting the pathology is present.

The next decade will also see profound changes in how autopsies in England & Wales are commanded. The decline in consented autopsies may continue, and it is expected that fewer ‘routine’ medico-legal autopsies will be commanded, as the Coroner’s Service and Death Certification procedures are changed and (hopefully) improved. However, it means that the proportion of cadavers with known or suspected significant infections will probably increase. Guidelines on autopsy practice in this area can be found on the Royal College of Pathologists web site.

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For epidemiological data on serious communicable diseases (HIV, TB, HCV, malaria), view the website of the Health Protection Agency: www.hpa.org.uk
Guidelines for Autopsy Practice, 2002, Royal College of Pathologists: www.rcpath.org

The enigma of Kaposi’s Sarcoma and the role of human herpes virus -8 infection

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Kaposi’s sarcoma has had an interesting history right from the time that Moriz Kaposi described the entity in 1872.1 Moriz Kaposi was born Moriz Kohn in Kaposvár, Hungary and after obtaining his medical degree worked with Ferdinand von Hebra, whose daughter he fell in love with, and married. As he was Jewish and Hebra was Catholic he changed his name to Kaposi—derived from his place of birth, Kaposvár, Hungary.

Up until the advent of the worldwide pandemic of infection caused by the Human Immunodeficiency virus and the development of the Acquired Immunodeficiency Syndrome (AIDS) it was possible to identify four distinct categories of Kaposi’s sarcoma: those occurring as second malignancies in elderly males of Mediterranean origin suffering from lymphoreticular malignancy; those being found on the extremities of middle aged African males; lymphoreticular lesions in African children and those occurring as a complication in transplant patients receiving immunosuppressive therapy. Males are typically affected more commonly in all forms of the disease.

Disease progression and prognosis also shows substantial variation amongst these groups with disease in the Mediterranean and African males being of an indolent nature2, that affecting the lymph nodes in African children being aggressive and more likely to result in death of the patient3, and the waxing and waning course of disease in transplant patients in relation to their immunosuppressive therapy4,5. This spectrum of disease manifestation has led to repeated controversy as to whether Kaposi’s sarcoma is a reactive or neoplastic process or a natural progression from the former to the latter. This debate remains unresolved.

This spectrum of disease presentation is interesting in its own right, but did little to stimulate significant research
interventions, probably because the burden of disease was hidden in the African continent. The indolent nature of the disease, whilst contributing to significant patient morbidity was not seen as a medical priority in the face of sub-optimal research resources in a continent which was and continues to grapple with diseases that have a much greater socio-economic impact.

Recognition that the world was facing the identification of a new disease, to become known as the Acquired Immunodeficiency Syndrome (AIDS), was prompted by the identification of a cohort of young homosexual males all suffering from Kaposi’s sarcoma. Over the ensuing years and up until the end of March 1989, 88 739 USA residents suffering from AIDS had been reported to the Centers for Disease Control (CDC) of whom 13 616 had been diagnosed with Kaposi’s sarcoma. Based on local incidence rates the expected number of patients with Kaposi’s sarcoma for this group should have been 0.5 and based on transplant patients with Kaposi’s sarcoma, 45.5. Thus the true risk of Kaposi’s sarcoma in the AIDS group was determined to be at least 20 000 greater than the general population and 300 times greater than patients with immunosuppression due to other causes. The vast discrepancy between these figures was unexplained at the time and a number of postulates were proposed, including a viral aetiology and environmental agents such as nitrite ‘poppers’, all of which offered an aetiological cause for Kaposi’s sarcoma, but were unable to account for differences in incidence. Clearly there appears to be a multi-factorial basis to the development of Kaposi’s sarcoma.

Human Herpesvirus 8 (HHV-8) was discovered by Chang and Moore in 1994. The virus, which is also known as the Kaposi’s sarcoma-associated herpesvirus, (KSHV) belongs to the gammaherpesvirus subfamily. It is closely related to the Epstein-Barr virus to which it has 30–50% homology and herpesvirus saimiri, both of which have the ability to transform cells into malignant phenotypes, particularly of a lymphoproliferative type. The virus, which is a rhadinovirus, is 165 kb long, is characterised by up to 80 open reading frames (ORF) and has genes with transforming potential. It has a predilection for lymphocytes, endothelial cells, keratinocytes and bone marrow stromal cells.

Sero-epidemiological studies have demonstrated worldwide variation in the infection rates of the population with HHV-8. In Johannesburg, South Africa an infection rate of 30% was found in HIV-1 negative patients and that the prevalence of infection increased with advancing age. This suggests, that transmission may be horizontal in nature.

In addition to Kaposi’s sarcoma, infection by Human Herpesvirus 8 is associated with a number of other neoplastic entities including multicentric Castleman’s disease, body cavity B cell lymphomas (also known as primary effusion lymphomas) and has recently been described in association with plasmablastic lymphoma of the oral cavity, the latter also in association with co-existent Epstein-Barr virus infection.

Human Herpesvirus 8 DNA has been identified in all clinical forms of Kaposi’s sarcoma suggesting that it plays an integral role in the development of the lesion. The transforming genes that have been identified in HHV-8 can be divided into two groups, namely those associated with the lytic phase of infection and those associated with latent infection. Gene products derived from the lytic phase appear to be important for angiogenesis and the inflammatory component of the disease. These include viral G-protein-coupled receptor (vGPCR, ORF 74), viral macrophage inhibitory protein II (vMIP-II, ORF K6), vK1 (ORF K1), viral interferon regulatory factor-1 (vIRF-1, ORF K9) and surface glycoprotein B (gB, ORFK8.1). The angiogenic phenotype initiated by the receptor vGPCR is mediated via vascular endothelial growth factor (VEGF), an angiogenesis and Kaposi’s-spindle-cell growth factor and is a paracrine effect. Interferon is prevented from repressing the c-myc oncogene by vIRF.

Gene products from latent expression are responsible for tumour growth and spindle cell proliferation and include latency-associated nuclear antigen (LANA, ORF73), vCyclin (ORF 72), vFLIP (FLICE inhibitory protein, ORF 71) and Kaposin (ORF K12). LANA is expressed in all latently infected cells and is responsible for the inhibition of p53 and retinoblastoma gene which are the two principal tumour-suppressor genes that regulate cellular senescence and apoptosis. The viral gene v-cyclin mimics cellular cyclin D and is responsible for the phosphorylation and inactivation of the retinoblastoma tumour suppressor protein.

Interaction of the gene products from the lytic and latent groups may also occur as demonstrated by the ability of vGPCR to induce angioproliferative lesions and at the same time to promote tumour formation by cells expressing KSHV latent genes.

HHV-8 encodes a gene for vIL6 which is homologous to human IL6 and is responsible for increased haematopoiesis, plasmacytosis and vascularisation. Increased levels of VEGF have also been found suggesting that this is a multifunctional cytokine and that it may play an important role in the development of Kaposi’s sarcoma.

A viral homologue of cellular bcl-2 produced by HHV-8 has been identified and demonstrated to inhibit apoptosis in vitro.

It has been shown that inflammatory cytokines, especially interferon gamma, induce a KS-like phenotype in endothelial cells and increase the HHV-8 viral load in peripheral blood mononuclear cells. It is possible that when circulating Kaposi’s sarcoma progenitor cells are exposed to inflammatory sites, latent HHV-8 is reactivated leading to the expression of early pathogenic genes such as vIL6 and vGPCR coupled with replication of the virus. The pathogenic genes then exacerbate the inflammatory-angiogenic environment,
and with recruitment of infectable cells result in the development of a Kaposi's sarcoma lesion.

HHV-8 and HIV-1 have been shown to exhibit up-regulation of gene expression of each other\(^2\). The KIE2 gene product of HHV-8 up regulates HIV-1 expression whilst the HIV Tat protein increases HHV-8 expression. This may provide an explanation for the marked increase in immunosuppression-independent development of Kaposi's sarcoma in HIV-1 positive patients and its relative absence in patients with HIV-2 infection\(^2\). HIV-1 Tat has also been shown to activate the KDR receptor of VEGF and to promote chemotactic migration of Kaposi's sarcoma cells, both of which can be blocked by the application of an anti-KDR antibody\(^2\).

The use of highly active antiretroviral therapy (HAART) significantly contributes to a decline in the incidence of AIDS-associated Kaposi's sarcoma\(^2\) and it is possible that this may be mediated by restoration of NK cell-mediated immunity\(^2\).

The issue of whether Kaposi's sarcoma is a monoclonal or polyclonal process remains unresolved and there have been studies supporting either option. Current opinion proposes that Kaposi's sarcoma begins as a polyclonal entity which becomes monoclonal when specific circumstances allow\(^2\).

The pathogenesis of Kaposi's sarcoma is complex but has the potential to be better understood following the recognition that there is a complex interaction of cytokines, viral gene products, their effect on target cells and the synergistic interaction between HHV-8 and HIV. These are early first steps in a journey, which will require that solutions to numerous questions be found before the enigma of Kaposi's sarcoma is resolved.

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HIV and AIDS in India

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India has been referred to as the new hotbed of HIV infection. The onset of HIV epidemic in India was heralded by detection of an HIV infected commercial sex worker and by a case of AIDS in Chennai and Mumbai respectively in 1986.\(^1\)\(^2\) Since then the prevalence of HIV infection has been increasing every year and by March 2004, 4.58 million cases of HIV infection had been reported by National AIDS Control Organisation (NACO), Ministry of Health and family welfare, New Delhi.\(^3\) It appears that HIV infection is spreading through all strata of Indian society and all parts of the country including urban, rural and tribal areas.\(^4\)\(^-\)\(^6\) The predominant route of HIV transmission in Indian patients is through sexual contact. Although there is high prevalence of HIV/AIDS, only few reports on pathologic aspects of AIDS are described in Indian literature.\(^7\)\(^-\)\(^21\)

The spectrum of pathologic lesions observed in one of the largest autopsy study in patients with AIDS from Mumbai demonstrated high frequency of secondary infections.\(^22\) The spectrum of diseases identified in this report were: tuberculosis 95(59%), bacterial pneumonia 25(15%), CMV infection 25(15%), toxoplasmosis 15(9%), cryptococcosis 12(7%), pneumocystis carinii pneumonia 8(5%), candidiasis 6(4%), cryptosporidiosis 5(3%), aspergillosis 4(2%), strongyloides stercoralis 3(2%). AIDS associated tumors were identified in 4 cases which comprised of lymphoma in 3(2%) cases and Kaposi’s sarcoma in 1(1%) case. This study shows both pulmonary and extrapulmonary tuberculosis in 77/95(48%) cases while 18/95(11%) cases showed isolated pulmonary tuberculosis. High prevalence of tuberculosis is also observed in HIV infected patients from South India.\(^16\) The overall high prevalence of tuberculosis in Indian patients suggests that physicians should maintain a high index of suspicion for this disease in AIDS patients. In our geographical setting, tuberculosis is most likely caused by Mycobacterium tuberculosis species. A recent study from Mumbai in 24 patients with AIDS in whom diagnosis of tuberculosis was suspected, showed growth of mycobacterium tuberculosis on blood culture in all 24 patients, demonstrating importance of blood culture in confirming diagnosis of tuberculosis.\(^23\) PCP remains the most common AIDS associated infection in developed countries, however Indian studies show 5%–14% prevalence of PCP.\(^16\)\(^,\)\(^20\)\(^,\)\(^22\) There are no reports of extrapulmonary PCP in Indian literature.

Although not reported in adult population from India in the pre-AIDS era, toxoplasmosis was the most frequently observed CNS opportunistic infection identified in 9%–20% of HIV infected patients.\(^18\)\(^,\)\(^22\) The temporal trends observed in the prevalence of toxoplasmosis emphasise the importance of autopsy studies in not only documenting such a change, but also in increasing the awareness for such hitherto unsuspected lesions. Co-existent toxoplasmosis and acanthamoeba of brain is also described in Indian patients.\(^19\) There are no reports of HIV associated encephalopathy and primary CNS lymphoma.\(^15\) Few reports of spectrum of hepatic diseases in patients with AIDS are described in Indian literature.\(^24\)\(^-\)\(^26\) The hepatic abnormalities associated with AIDS are predominantly secondary infections and tuberculosis of liver is most frequently identified infection in 41% patients.\(^26\) Liver abscesses due to tubercle bacilli are an unusual manifestation of the natural history of tuberculosis infection. There are few reports of tuberculous abscesses in patients with AIDS.\(^24\)\(^-\)\(^26\)

Pathology of kidney observed in these patients predominantly showed infectious diseases.\(^5\) Reports of HIV associated nephropathy are not described in Indian literature. The heart is frequently affected in patients with AIDS, however most of the clinical events are subtle. Cardiac lesions described in patients with AIDS show high prevalence of infectious diseases of the heart.\(^10\) Occasional report of cardiac toxoplasmosis is also documented in Indian literature.\(^10\) The spectrum of gastrointestinal lesions associated with AIDS in Indian patients show cytomegalovirus, cryptosporidium, strongyloides stercoralis, hookworm, candidiasis, cryptococcosis and tuberculosis. The prevalence of Isospora belli is identified in 13% of patients with AIDS presenting with chronic diarrhoea.\(^14\) There are no reports of microsporidiosis in Indian literature.\(^13\) Skin lesions are most common site of AIDS diagnostic diseases in our patients. Infectious diseases are described in 38%–53% of our patient population.\(^7\)\(^,\)\(^17\)\(^,\)\(^27\) Report of disseminated infection caused by penicillium marneffei is documented from the Manipur state of India.\(^28\) Squamous cell carcinoma of penis is identified in 5% of young adults with AIDS.\(^7\) Occasional reports of Kaposi’s sarcoma are described in Indian literature,\(^17\)\(^,\)\(^21\) however there is a strikingly low incidence of Kaposi’s sarcoma in our patients. Although accurate estimates of HIV/AIDS in children in India are not available, few reports on pathology of AIDS in children are described.\(^29\)\(^,\)\(^30\)

In summary, the reports on pathology of HIV/AIDS in India underline the overwhelming prevalence of tuberculosis, PCP remains less common in our patients. It appears that major laboratory efforts be directed to identifying infectious agents.

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