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Commentary

Pathology and Emerging Infections—Quo Vadimus?

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There have been dramatic changes in the occurrence of infectious diseases throughout the world in the previous two decades. The emergence of new microbial agents, and the reemergence of infections previously believed to be controlled, threatens the health of all populations. The emergence of these infectious diseases has occurred during a period of breakdown in the capabilities of the public health surveillance systems, prevention programs, and disease control efforts. Expertise in pathology is critical to provide a strong national control program for emerging and reemerging infectious diseases. Despite the many significant achievements made by pathologists in improving understanding of the pathogenesis and diagnosis of infectious diseases, the field of pathology remains largely oriented toward neoplastic diseases, and has not yet identified infectious disease diagnosis as an important component of anatomic pathology training and research, even in the face of the current threats posed by microbial agents. In addition, there is currently a dearth of infectious disease pathologists in the United States and elsewhere in the world, and the use of the autopsy, a prime pathological tool for diagnosis of emerging infections, is on the wane. The most serious problem is that no formal training program for infectious disease pathology currently exists in the United States or elsewhere in the world. As a consequence of this lack of training opportunities, there is a severe deficiency of young, well-educated pathologists with infectious disease expertise. This article explores the historical linkages between the disciplines of infectious diseases and pathology, and suggests that infectious disease pathology as a subspeciality be strengthened and training programs be initiated. (Am J Pathol 1995, 147:1525–1533)

The last 20 years have been witness to a rapid change in the spectrum of infectious diseases in both developing and developed countries (Table 1).[1–9] The emergence of novel microbial pathogens, and reemergence of old ones, currently threatens the health of populations throughout the world. Conditions conducive to the emergence and reemergence of infectious diseases involve complex interplay between environmental, microbial, and human behavioral, socioeconomic, and cultural factors. These latter include population growth; poverty; human migration caused by war, famine, and geopolitical conditions; modern technology; rapid and increasing international travel; and misuse of antimicrobial agents. Newly emergent infectious agents may arise from evolutionary changes in existing organisms; previously known organisms may spread to new geographic areas or nonimmune populations; or unrecognized infections may occur in persons visiting or residing in areas undergoing ecological changes that result in exposure to insects, animals, or other environmental sources of novel or zoonotic infections. Reemergent infections can oc-

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Table 1. *Examples of Emerging and Reemerging Infections*

Retroviridae (HTLV-I,II; HIV-1,2)
Bunyaviridae [Hantaviruses](Sin Nombre, Hantaan, Seoul, Rift Valley, Oropouche)
Togaviridae (Chikungunya, Ross River)
Flaviviridae (dengue, yellow fever, Japanese encephalitis, Kyasanur Forest)
Arenaviridae (Sabía, Machupo, Junin, Lassa, Guanarito)
Filoviridae (Marburg, Ebola)
Poxviridae (Monkeypox)
Influenza viruses
Hepatitis E virus
Human herpesviruses types 6,7,8
Bartonella henselae [bacillary angiomatosis, cat scratch disease]
Escherichia coli O157:H7
Helicobacter pylori
Staphylococcus aureus [toxic shock syndrome]
Drug-resistant *Enterococcus* species and *Streptococcus pneumoniae*
Borrelia burgdorferi [Lyme disease]
Multi-drug resistant *Mycobacterium tuberculosis*
Vibrio cholerae
Hemophilus influenzae, biotype aegyptius [Brazilian purpuric fever]
Bacillus anthracis
Yersinia pestis [pneumonic plague]
Corynebacterium diphtheriae
Encephalitozoon spp., *Enterocytozoon bieneusi*, *Septata intestinalis* [microsporidiosis]
Cryptosporidium spp.
Acanthamoeba spp.
Trypanosoma cruzi
Cyclospora cayetanensis
Plasmodium spp.
Coccidioides immitis

cur when antibiotic resistance develops in known agents, or when public health and sanitary measures for infections that were previously thought to be controlled deteriorate.[1]

Pathology is key to the detection and surveillance for emerging and reemerging pathogens. Yet there is a dearth of infectious disease pathologists in the United States and elsewhere in the world, and the use of the autopsy, a prime pathological tool, is on the wane. This article explores the historical linkages between the disciplines of infectious diseases and pathology, and suggests that infectious disease pathology as a subspeciality be strengthened and training programs be initiated.

The Threat of Emerging Infections

A critical factor in the amplification of emerging infections as a global health threat has been a pervasive sense of complacency toward infectious diseases in general by health professionals and policymakers. This attitude has led to serious breakdowns in public health surveillance systems, prevention programs, and disease control efforts.[1,10,11] The breakdown in the capabilities of the public health and clinical care systems to deal effectively with the problem of emerging and reemerging infections has had such wide-reaching impact that the subject was addressed in three recent reports from the National Academy of Science's Institute of Medicine.[12–14] The first report, published in 1987, described the limited capacity in the United States for the diagnosis, treatment, and control of infections acquired in tropical countries. These threats include Lassa, Ebola, and Machupo hemorrhagic fevers, drug-resistant malaria, and infections by penicillinase-producing *Neisseria gonorrheae*.[12] The second report of the Institute, published in 1988, addressed the disarray of the U.S. public health system.[13] The third report, issued in 1992, emphasized the ongoing threat to both domestic and global health from emerging infections, as most recently illustrated by the international responses to the epidemics of plague in India and Ebola virus infection in Zaire.[14]

A survey by the World Health Organization in 1993 demonstrated that virology laboratories around the world are not fully prepared to recognize emerging viruses, or even known viral pathogens, that do not commonly occur in their respective geographic areas.[15] Only 56% of the 34 laboratories surveyed had the capability to diagnose yellow fever, and fewer than half were able to diagnosis hantaviruses (44%), Japanese encephalitis (47%), Rift Valley fever virus (41%), or California encephalitis (18%). In the United States, the nation's surveillance system has declined to the level that it has been estimated that several thousand cases would have to occur for a community-wide outbreak of a diarrheal illness in an urban area to be detected by public health authorities.[11]

In addition to the renewed interest focused on emerging infections from international, federal, state, and local health services and universities, there has been increasing concern from the public and the media. This concern has arisen, in part, because of heightened attention to several recent infectious disease outbreaks. In 1993, contamination of a municipal water supply with *Cryptosporidium* resulted in the largest recorded waterborne outbreak in the history of the United States, affecting an estimated 403,000 persons in Milwaukee, WI.[16] The same year, commercially prepared hamburgers contaminated with *Escherichia coli* 0157:H7 caused a multistate outbreak of hemorrhagic colitis and hemolytic-uremic syndrome, which resulted in the deaths of at least four children.[17] Other emerging and reemerging infections that have been recent targets of media at-

tention include the bacterial agents of necrotizing fasciitis, dramatized in the lay press as "flesh-eating bacteria," toxic shock syndrome, hantavirus, and antibiotic-resistant strains of pneumococci, enterococci, and *Mycobacterium tuberculosis*. The most recent example is the outbreak of Ebola hemorrhagic fever, which occurred in Zaire in early 1995,[18] and which received worldwide media coverage. The focus of the media on international epidemics of pneumonic plague in India, cholera in Latin America and Africa, and diphtheria in Russia, and even the recent proliferation of books and movies depicting outbreaks of emerging and tropical infections, may have helped to dispel the notion of our safety from infectious diseases in the United States.[19,20]

Contributions of Pathology to Emerging Infections

Expertise in pathology, in all of its components and subspecialties, is critical to a strong national public health program for the surveillance, diagnosis, treatment, and control of emerging infections. There are numerous examples of important contributions from pathologists to our understanding and management of emerging infections, in spite of the small numbers of pathologists with infectious disease training. The hantavirus outbreak that occurred in the southwestern United States in 1993 is a recent example of a multispecialty coordinated effort among local, university, and government physicians and scientists in which pathologists played an important role in recognizing the syndrome and in characterizing a new viral agent. The early recognition of this outbreak by the Office of the Medical Investigator in Albuquerque, NM, underscores the potential role of forensic pathologists in identifying emerging infections and disease outbreaks.

Dr. Sherif Zaki of the Centers for Disease Control and Prevention and colleagues have recently summarized their results of the characterization of the pathological spectrum of illness produced in 44 fatal cases of infection with this newly described hantavirus, termed Sin Nombre virus.[21] Their description of the production of diagnostic reagents to this virus; subsequent anatomic localization of virus by using a combination of viral RNA amplification, immunohistochemistry, and immunoelectron microscopy; and, finally, correlation of these data with serological and clinical findings are a superb example of the contributions made by infectious disease pathology as part of a multidisciplinary approach to investigation of emerging infections and disease outbreaks.

Because of this success, when the Ebola hemorrhagic fever outbreak was discovered in Kikwit, Zaire, in 1995, one goal of the site investigation team was to obtain autopsy tissues for subsequent pathological analysis. These specimens are helping to provide valuable clues for understanding mechanisms of transmission and pathogenesis of this lethal filovirus infection. Complementing these pathological studies of emerging infections in humans are experimental pathology investigations that use a variety of animal models, including nonhuman primates. Using these methods, veterinary pathologists have made substantial contributions to our understanding of the pathogenesis of such agents as Japanese and Venezuelan equine encephalitis, and Ebola, Marburg, and Lassa hemorrhagic fever viruses (Figure 1).[22,23]

Anatomic pathologists have also made substantial contributions to our understanding of the natural history of patients infected with the human immunodeficiency virus (HIV) (Figure 2). The recognition of the medical significance of the protozoan agents producing microsporidiosis in patients with acquired immunodeficiency syndrome (AIDS) provides another example of a closely coordinated effort among epidemiologists, clinicians, and pathologists. Three new species of microsporidia have been described that infect immunocompromised patients with AIDS–*Enterocytozoon bieneusi* in 1985, *Encephalitozoon hellem* in 1991, and *Septata intestinalis* in 1993.[24] Collaborations among governmental, university, and private sector pathologists have been instrumental in defining these agents as new species, in developing diagnostic methods and treatment algorithms, and in improving our understanding of disease progression and systemic dissemination.[25–27]

In addition to microsporidiosis, pathologists have been instrumental in defining the spectrum of other opportunistic agents that infect AIDS patients, including mycobacterial disease, coccidioidomycosis, cryptosporidiosis, bacillary angiomatosis, and viral pathogens such as cytomegalovirus and other herpesviruses (Figure 2).

Pathologists have also made important contributions to the understanding of non-opportunistic infectious diseases. Whipple's disease[28] and cat scratch disease[29] provide examples of important clinical entities in which the causative microbial agents were first characterized by anatomic pathologists long before the etiological agents were identified by microbiological or molecular analysis. At the community and university level, pathologists are often among the first health care providers to encounter infectious

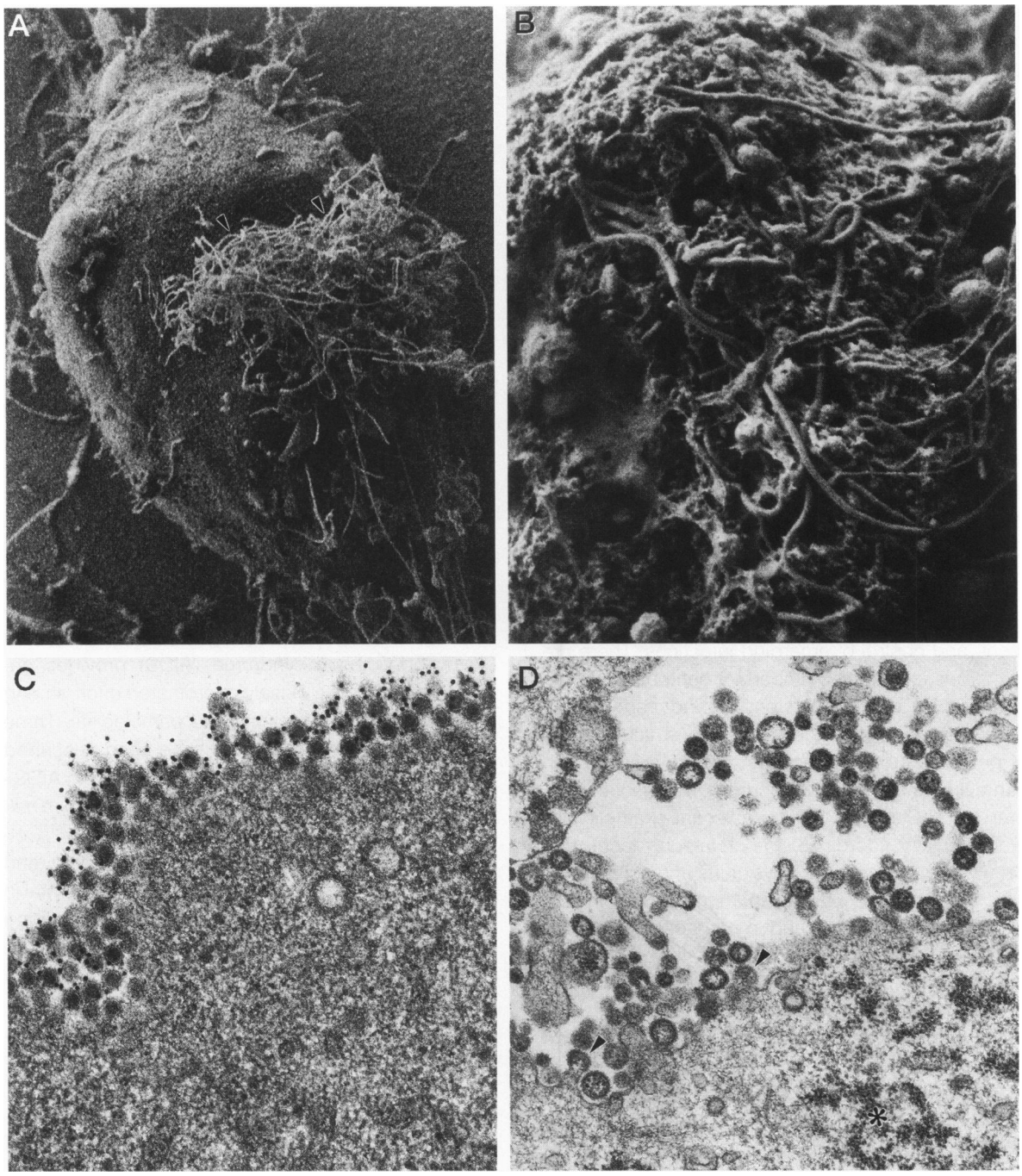

Figure 1. *Ultrastructural photomicrographs of three important emerging viral pathogens responsible for recent human outbreaks.* (**A**) *Scanning electron micrograph of Vero cell infected with Ebola-Zaire virus. Note large aggregate of Ebola virions* (arrowheads) *projecting from surface of cell. Original magnification* × *9500.* (**B**) *Scanning electron micrograph of spleen from rhesus monkey experimentally infected with Ebola-Zaire virus shows degenerate macrophage covered with Ebola virions. Original magnification* × *32,000.* (**C**) *Thin section through Vero cell infected with Venezuelan equine encephalitis (VEE) virus demonstrating positive gold-labeling of virions along plasma membrane after incubation with rabbit antisera raised against a VEE 1A virus. Original magnification* × *107,000.* (**D**) *Thin section of Lassa virus in Vero cell culture. In addition to numerous virions in extracellular spaces, virions are seen budding from plasma membrane* (arrowheads), *and viral inclusion material is present in cytoplasm* (*). *Original magnification* × *58,500. (Photographs courtesy of Thomas W. Geisbert and Nancy Jaax, DVM, Pathology Division, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Maryland).*

disease outbreaks, novel infectious agents, or new manifestations of preexisting infections.

Despite the many significant achievements made by pathologists in recognizing and managing emerging infections, the field of pathology remains largely oriented toward neoplastic diseases, and has not yet identified infectious disease diagnosis as an important component of anatomic pathology training

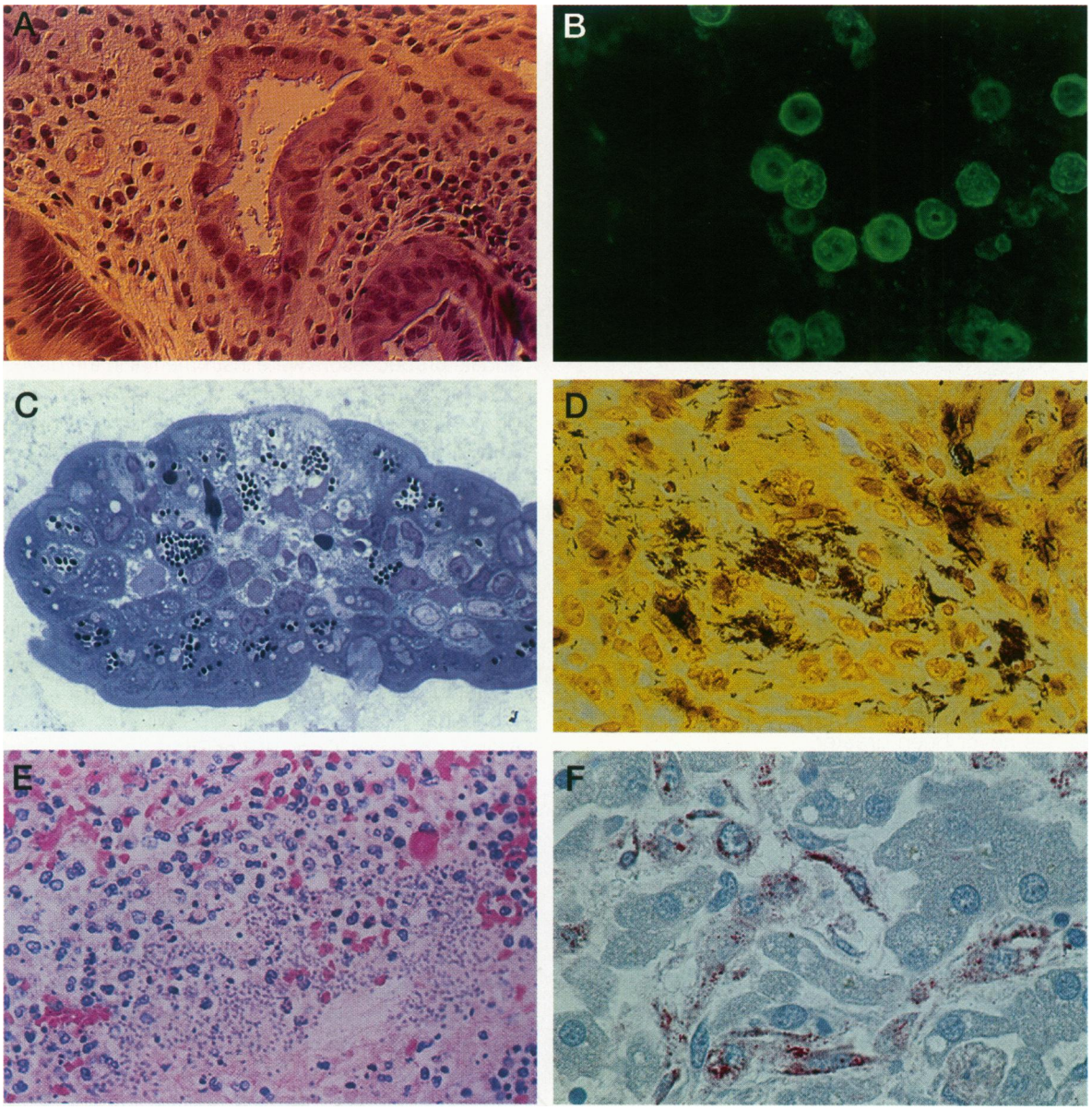

Figure 2. A–C: *The morphological features of three emerging parasitic infections.* (A) *Developing stages of* Cryptosporidium parvum *on the luminal surface of a small intestinal gland. H&E, Nomarski interference contrast, original magnification* ×*400.* (B) *Thick-walled cysts of* Acanthamoeba castellanii *in a cutaneous ulcer from a patient with disseminated fatal infection. Fluorescent antibody to* A. castellanii, *original magnification* ×*400.* (*Photograph courtesy of Govinda S. Visvesvara, Ph.D., Centers for Disease Control and Prevention, Atlanta, GA*). (C) *Intestinal microsporidiosis, showing numerous intracytoplasmic spores in epithelial and mesenchymal cells. The causative agent of this infection,* Septata intestinalis, *was first identified in 1993. Plastic-embedded semithin section, toluidine blue; original magnification* ×*400.* D *and* E: *Emerging bacterial infections.* (D) Bartonella (*formerly* Rochalimaea) henselae *is the etiological agent of bacillary angiomatosis and cat scratch disease. This skin biopsy from a patient with AIDS and bacillary angiomatosis shows the typical clumped and tangled appearance of the bacteria in infected tissues. Steiner stain; original magnification* ×*400.* (E) *Section of lung from fatal human plague, showing pneumonia and hemorrhage associated with numerous* Yersinia pestis *bacilli. Giemsa,* ×*400.* (F) *Dengue fever is an important emerging viral infection which is a major threat to health in the American region. This liver section shows dengue antigens localized to sinusoidal lining cells using an immunoalkaline phosphatase method and monoclonal antibody to dengue virus. Naphthol fast red substrate with hematoxylin counterstain; original magnification* ×*158.* (*Photograph courtesy of Sherif R. Zaki, M.D., Ph.D., Centers for Disease Control and Prevention, Atlanta, GA*).

and research, even in the face of the current threats posed by microbial agents.

The Autopsy and Emerging Infections

The gradual decline of the autopsy as an investigative tool and method of quality assurance has recently received much attention. Unfortunately, efforts by many physicians to reverse this trend have been largely unsuccessful, and autopsy rates (average 10% nationally) remain extremely low in most hospitals and academic centers.[30–32] Within the field of infectious diseases, underuse of the autopsy has occurred in spite of literature doc-

Table 2. *Partial List of Infectious Diseases Discovered or Clarified by Autopsy since 1950 (Modified from Hill and Anderson[30])*

Pneumocystis pneumonia
Legionnaire's disease
Whipple's disease
Viral hepatitis
Spongiform encephalopathy [Creutzfeldt-Jacob disease]
Progressive multifocal leukoencephalopathy
Acquired immunodeficiency syndrome
Microsporidiosis
Congenital infections (eg, toxoplasmosis, cytomegalovirus)
Disseminated fungal diseases

umenting its value in diagnosing clinically occult or undetected infections, assessing antemortem modalities of therapy, and providing a greater understanding of pathogenesis of disease.[30,31] Autopsy-based studies have been instrumental in the discovery or understanding of many infectious diseases (Table 2).[30] With the advent of the AIDS pandemic, and newly emergent and reemergent infections, the necessity for autopsy-based studies has never been greater.

Autopsy-based studies have been especially invaluable in defining the spectrum of HIV-related infections and proximate causes of death in patients from differing geographic cohorts. Investigations using a combined clinical and autopsy approach on a cohort of 247 West African patients with AIDS in Côte d'Ivoire have found that the three major causes of death–tuberculosis, toxoplasmosis, and bacteremia–can all be potentially prevented or treated.[33] Additional autopsy data from HIV-infected patients in Côte d'Ivoire have demonstrated important differences between AIDS in West Africa and developed nations. For example, in West Africa *Pneumocystis* pneumonia accounts for only 2% of deaths[33]; infections caused by the atypical mycobacteria have a 7% prevalence and account for no deaths[33]; nocardiosis has an unusually high prevalence[34]; and non-Hodgkin's lymphomas are significantly less frequent.[35]

Good candidates for thorough future autopsy studies of emerging infections, incorporating classical methods of examination with molecular pathological techniques, include evaluation of unexplained deaths occurring in young persons, patients dying with fever of unknown origin, and deaths involving idiopathic encephalitis, respiratory failure, meningitis, gastroenteritis, and myocarditis.

Development of Infectious Disease Pathology: the Armed Forces Institute of Pathology

Pathologists have figured prominently in the field of infectious disease for many decades, and their contributions to our understanding of the epidemiological, clinical, and pathological aspects of microbial disease are too numerous to discuss in this brief commentary. Because of the close association between tropical and infectious diseases and the military, the Armed Forces Institute of Pathology (AFIP) and its predecessors were instrumental in the development of infectious disease pathology as a discipline in the United States. The establishment of the Army Medical Museum by Surgeon General William A. Hammond in 1862 provided for the collection of ". . . all specimens of morbid anatomy, both medical and surgical, which may have accumulated since the commencement of the rebellion in the various U.S. hospitals. . .".[36] By 1871, most of the 1150 specimens in the medical collection pertained to typhoid fever, other dysenteric conditions (including the intriguing entity "Chickahominy diarrhoea"), and febrile camp diseases. After the Civil War, a young military physician, Capt. Walter Reed, was appointed as director of the Pathological Laboratory of the Army Medical Museum, and subsequently as its curator from 1893 to 1902. These appointments resulted in three brilliant years of scientific achievement for Dr. Reed from 1898 to 1900, during which time he increased the understanding of transmission of typhoid fever and discovered the method of transmission of yellow fever. Interest in infectious disease pathology was rekindled at the Army Medical Museum during World War I, especially with the widespread epidemics of influenza and pneumonia that affected the troops. The first postwar curator of the museum, Col. Charles F. Craig, was well known for his studies of filariasis, dengue fever, dysentery, and malaria. He was instrumental in reducing the prevalence of malaria among army personnel, and after his retirement, he became chairman of the Department of Tropical Medicine at Tulane University.[36]

At the onset of World War II, the medical community and, in particular, the military, were faced with the problem of diagnosing exotic tropical and infectious diseases acquired by armed forces personnel stationed throughout the world. Because the pathological aspects of these diseases were largely unknown to American pathologists, Dr. Sophie Spitz, a young staff pathologist at the Army Institute of Pathology, prepared comprehensive study sets from tissues sent to the institute from tropical installations

for use by military pathologists. After the seminar of the American Society of Clinical Pathologists in 1944 entitled "Pathology of Tropical Diseases," Dr. Spitz and Col. James E. Ash, the curator of the Army Medical Museum and an experienced tropical disease pathologist, prepared their classic textbook that illustrated the pathological features of 90 tropical diseases.[37] This was based upon tissues from autopsies and surgery from patients with infectious and tropical diseases that were collected from combat areas, channeled through a medical laboratory in the theater of action, and forwarded to the Medical Museum. After World War II–and change of name from the Army Institute of Pathology to the AFIP–a separate Division of Geographic Pathology was created in 1961. The distinguished infectious disease pathologist, leprologist, and medical mycologist, Dr. Chapman H. Binford, was appointed as the first Director. During this period, Dr. Hans Smetana performed his well-known studies on the histopathology of experimental yellow fever. Dr. Binford was succeeded as Director by several noted experts in tropical and infectious disease pathology, including Dr. Howard Hopps and, in 1970, Dr. Daniel H. Connor. Together, Drs. Binford and Connor published in 1976 the successor volume to the original work of Drs. Ash and Spitz.[38] This textbook became the definitive reference in the field of infectious disease pathology. The Division of Geographic Pathology of the AFIP has added much to our knowledge of the pathology in infectious diseases, including Hansen's disease, filariasis, Buruli ulcer, and leptospirosis, to name a few. Individuals from other divisions of the AFIP have also produced significant pathological findings in infectious diseases, eg, Dr. Willam Manion on Chagas' disease and Dr. F. K. Mostofi with schistosomiasis. Although the AFIP has been the preeminent center for the diagnosis of infectious and tropical diseases, and many pathologists and laboratory scientists from both the United States and abroad have studied there, there has never been a formal or recognized postgraduate training program in infectious disease pathology established at this institute or, in fact, elsewhere in the world.

Current Status of Infectious Disease Pathology in the United States

The pathology of infectious diseases constitutes a major component of the pathology practices in departments that serve the increasing numbers of patients receiving organ transplants or chemotherapy for neoplastic diseases, persons with AIDS and other immunodeficiency conditions, immigrants, travelers, burn and postoperative patients, and the indigent. Nevertheless, infectious disease pathology is not generally recognized within the pathology community as a bona fide subspecialty. For example, there is no subspecialty board examination. The field is represented by a single organization, the Binford-Dammin Infectious Disease Pathology Society, founded in 1984. Despite the pandemic of AIDS and heightened awareness of emergent infections, no journal is dedicated to the pathology of infectious diseases, and manuscripts in this field must compete for publication in the most prestigious peer-reviewed pathology journals with larger numbers of papers in neoplastic diseases, immunology, and cell biology.

The most serious problem is that no formal training program for infectious disease pathology currently exists in the United States, or elsewhere in the world. As a consequence of this lack of training opportunities, there is a severe deficiency of young, well-educated pathologists with infectious disease expertise.[39] With the retirement of the previous generation of infectious disease pathologists, where will the medical community find the experts necessary to provide pathology support for detecting and addressing emerging and reemerging infections and investigations of outbreaks of illness of unknown etiology in the future?

It is critical that pathologists are seen as essential members of any organized program to detect and rapidly respond to emerging and reemerging infections. The dearth of infectious disease pathologists is not just a problem for academic centers or government institutions. It is a national health care problem that potentially affects our national capability for a rapid response to the certainty of new infectious threats to public health. This shortage of pathologists with infectious disease expertise impairs the surveillance of infectious diseases; integration of programs to monitor, control, and prevent vector-borne, nosocomial, and emerging pathogens; and development and maintenance of diagnostic and reference reagents for the identification and typing of emerging and reemerging infections.

Recommendations for the Strengthening of Infectious Disease Pathology

How can pathologists resolve the many years of neglect of this subspecialty area and find solutions to assure the public at large, and medical community in particular, of a supply of physicians trained in infec-

Table 3. *Core Skills Necessary for the New Generation of Infectious Disease Pathologists*

Field	Skills
Anatomic pathology	Light and electron microscopic recognition of infectious agents in cytological, biopsy, and autopsy tissues using routine and special staining methods
Clinical laboratory microbiology	Virology, bacteriology, parasitiology, mycology Serology, immunology
Immunopathology and molecular biology	Polymerase chain reaction; in situ polymerase chain reaction In situ nucleic acid hybridization Immunofluorescence, immunohistochemistry, immunoelectron microscopy
Experimental pathology	Tissue culture techniques Comparative pathology of infectious diseases in animal models
Infectious diseases	Natural history Differential diagnosis Pathogenesis Host response
Public health	Epidemiology and biostatistics

tious disease pathology to support diagnosis, teaching, and research into the emerging and reemerging infections of the future? A possible start to address these issues would be the development of a formal training program in Infectious Disease Pathology. Some of the core skills necessary for the new generation of infectious disease pathologists, summarized in Table 3, include expertise in clinical medicine, epidemiology, anatomic pathology, medical laboratory microbiology, and molecular pathology. Establishment of a core program in human infectious disease pathology is an important objective in the strategic planning document of the Emerging Infections Working Group of the Centers for Disease Control and Prevention.[1] Because suitable faculty members are concentrated in governmental and academic centers, one model might be a collaborative, or joint, training program using established infectious disease pathologists from university and governmental institutions located in the same region or city. These types of relationships already exist and are successful in other areas of postgraduate medical training.

The threats of emerging and reemerging infections are clear, and the pathology and infectious disease communities must decide whether they wish to meet the upcoming challenges to public health and patient care with a cadre of well-trained infectious disease pathologists, or to allow the existing expertise in this subspecialty to continue to erode.

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