

ARE ALL DISEASES INFECTIOUS?

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Bennett Lorber, MD, DSc

The complex interactions between microorganisms and human hosts include the well-known, traditional infectious diseases and the symbiotic relation we have with our normal flora. The media have brought to the public's attention many newly described infectious diseases, such as Ebola virus hemorrhagic fever, that were not part of common medical parlance a decade ago. While flooding us with interesting and often dramatic reports of so-called emerging infectious diseases, the media have largely ignored a more fundamental change in our appreciation of human-microorganism interactions: the discovery that transmissible agents may play important roles in diseases not suspected of being infectious in origin. A well-known example is ulcer disease; other examples include neurodegenerative disease, inflammatory disease, and cancer. These fascinating instances of host-pathogen interaction open new prospects for the prevention of disease through immunization.

The interactions between microorganisms and humans are complex and wondrous. On the one hand, they may result in human illness or death, as in bacterial meningitis or viral hemorrhagic fever. On the other hand, they may be truly symbiotic, as in the case of the flora that coat our mucous membranes to produce such nutrients as vitamin K and suppress colonization by pathogens.

Extraordinary changes have occurred in our appreciation of human-microorganism interactions (1). Not the least of these changes is the recognition of new infectious diseases. With just a few moments' reflection, one can call to mind an impressive list of diseases and pathogens that were not part of common medical parlance a decade ago (Figure). Since smallpox was consigned to history almost 20 years ago, the weight of new afflictions has tipped the balance. National newsmagazines have eagerly and excitedly reported on many of these so-called emerging diseases, and these diseases have been the subject of bestselling books, movies, and television docudramas. Last year saw the advent of a new medical journal devoted to emerging infectious diseases (2).

In almost every instance, these newly recognized diseases were thought to be of infectious origin before they were proven to be so, because the clinical picture suggested that likelihood. Almost without exception, these newly described entities are acute self-limited illnesses that have fever as a hallmark, and many mimic known infectious diseases. For example, human ehrlichiosis is a febrile illness that follows a tick bite and is similar to Rocky Mountain spotted fever (3). Although we have been flooded with interesting and sometimes dramatic reports of emerging infectious diseases and antimicrobial-resistant bacteria, the media have largely ignored a quieter revolution that has been taking place in our understanding of human-microorganism interactions: the discovery that transmissible agents are responsible for diseases that were never suspected of being infectious in origin. Examples include ulcers, neurodegenerative diseases, vasculitides, and cancer (Table 1). In some instances, the pathogen is truly causal, a *sine qua non* for disease development. In other cases, it may trigger an immune reaction that leads to illness or function as a risk factor for disease.

HOW DO WE KNOW A DISEASE IS INFECTIOUS?

The first to prove that a disease was caused by a particular organism was Robert Koch (46), who showed the bacterial origin of anthrax in 1876. Koch found that mice could be infected with matter obtained from diseased domestic animals, that disease could be transmitted from mouse to mouse through a series of inoculations, and that features of the disease were seen at each transfer. He cultivated bacteria by putting infected pieces of spleen into drops of sterile serum, and he observed and photographed bacteria in the culture medium through his microscope. After serially transferring cultures eight times, he inoculated a healthy animal. This inoculation produced the characteristic disease in the animal, from which Koch reisolated the organism. These experiments fulfilled criteria proposed 36 years earlier by Henle (46) as necessary to establish a causal relation between a specific agent and a specific disease. These criteria are now known as the Koch postulates (Table 2). Because routine methods sometimes fail to grow a pathogen, the Koch postulates may not be fulfilled; an infectious origin is then presumed because a given disease responds to antimicrobial agents. This leap of logic is fraught with hazards. For

example, many will recall that antibiotic-related colitis due to *Clostridium difficile* toxin (47) was originally thought to be caused by *Staphylococcus aureus* because 1) uncontrolled studies during the peak era of staphylococcal nosocomial infections found *S. aureus* in stool specimens and 2) patients responded to oral vancomycin, a nonabsorbable, antistaphylococcal agent (48).

Modern technology has made it possible to establish the association of a specific infectious agent with a disease without fulfilling the Koch postulates. Whipple disease is a case in point. Diagnosis of this disorder is usually established by small-bowel biopsy tissue that shows pathognomonic periodic acid-Schiff staining matter in macrophages. Electron microscopy has clearly shown bacteria in these macrophages, and the disease responds to antimicrobial agents. However, attempts to grow the organism in the laboratory have failed.

The answer to this problem came from molecular biology. In 1992, Relman and associates (49), building on the work of Wilson and coworkers (50, 51) from a year earlier, used a polymerase chain reaction (PCR)-based detection method to amplify 16S ribosomal RNA sequences from tissue. They identified the Whipple bacillus as a bacterium that was related to actinomycetes but was genetically distinct enough to be given its own genus designation. Relman and associates proposed the name *Tropheryma whippelii* for this organism. This PCR technique has subsequently been used as a diagnostic tool (52) to identify the Whipple bacillus in such extraintestinal sites as the eye (53) and the mononuclear cells of the peripheral blood (54). It has also been used to establish a novel *Bartonella* species as the etiologic agent of cat scratch disease, bacillary angiomatosis, and peliosis hepatis (55).

PEPTIC ULCER

The best known example of an infection that was not suspected of being one is that of ulcers. In 1983, at the Royal Perth Hospital in Australia, Marshall and Warren successfully cultured a spiral bacterium from human gastric mucosa and showed an association between the presence of this organism and gastric inflammation (5). Their discovery forced revision of the view that bacteria could not survive in stomach acid and revolutionized our understanding of upper gastrointestinal illnesses. The bacterium, *Helicobacter pylori*, lives on gastric epithelium and attaches to specific receptors. It causes one of the most common of all bacterial infections (4, 5). About 40% of persons in developed countries are infected with *H. pylori* by adulthood and once acquired, infection persists for life if untreated.

The evidence that *H. pylori* is an important cause of gastritis and peptic ulcer disease and is a risk factor for gastric carcinoma is now overwhelming (4, 5). *Helicobacter pylori* also appears to play a role in the development of the so-called maltomas, which are low-grade B-cell lymphomas of lymphoid tissue associated with gastric mucosa (5, 42). It is detected in more than 90% of gastric maltomas, and eradication of it results in regression of these tumors (42).

Our understanding of ulcer pathogenesis is incomplete. The role of acid must be elucidated, as must the reason why some persons infected with *H. pylori* develop ulcers and some do not. Nevertheless, discovery of *H. pylori* has revolutionized ulcer treatment through the realization that antimicrobial agents can cure ulcers related to the organism and, by eradicating it, prevent ulcer recurrence.

DEMENTIA AND PARALYSIS

Scrapie, a disease of sheep and goats named for the unique tendency of afflicted animals to scrape off their coats by rubbing against inanimate objects, is one of a group of diseases called "spongiform encephalopathies." This term derives from the histologic findings in the brain that are characteristic of these conditions. All of these diseases are fatal. They were originally thought to be neurodegenerative, and some were thought to be hereditary, but they are now known to be caused by transmissible agents (7, 9). The other animal diseases in this group include transmissible mink encephalopathy, chronic wasting disease of mule deer and elk, feline spongiform encephalopathy, and bovine spongiform encephalopathy (also known as mad cow disease).

Mad cow disease was first identified in 1986 when cows in Great Britain began to acquire an illness that was characterized by apprehension and lack of coordination and eventually led to death (9). The source of this new epidemic was traced to a food supplement that included bone meal and neural tissue taken

from dead sheep. More than 130 000 cattle have been stricken to date. There is great concern that humans may have fallen ill from having eaten tainted beef (56).

The first human spongiform encephalopathy to be described was kuru, which has been seen only among the Fore highlanders of Papua, New Guinea. Many will remember that kuru was first described in 1957 by Gajdusek (57), who noted that afflicted Fore tribesmen developed a strange illness marked first by ataxia, then by dementia, and eventually by death. Evidence suggested that kuru was acquired through ritual cannibalism; the Fore tribe honored their dead by eating their brains. With the cessation of cannibalism, kuru has disappeared (57).

Four types of human spongiform encephalopathy are currently recognized (9): **Creutzfeldt-Jakob disease, Kuru, Gerstmann-Sträussler disease, and fatal familial insomnia**. The most important of these, Creutzfeldt-Jakob disease, occurs worldwide, typically as a sporadic disease with onset in the seventh decade of life; 10% to 15% of cases appear to be inherited. A few cases are iatrogenic, and the disease has been transmitted through dura mater grafts, corneal transplants, neurosurgical instruments, and the injection of cadaveric-derived human growth hormone. Experimental studies have shown that scrapie, Creutzfeldt-Jakob disease, and kuru can be transmitted by injecting extracts of diseased brains into the brains of healthy animals. The incubation period is measured in years and even decades.

In the early 1970s, Prusiner (7, 9) began a series of laboratory investigations showing that the agents of spongiform encephalopathies are tiny bits of protein that contain no nucleic acids. This observation was initially met with much skepticism because it was contrary to the main dogma of molecular biology: that all reproducing and transmissible agents require genetic material made of nucleic acids. Prusiner coined the term "prion" for these "proteinaceous infectious particles" that are responsible for transmissible and inherited disorders as well as sporadic disease.

This discovery marked a revolutionary change. It was newly recognized that neurodegenerative diseases with no evidence of inflammation could be caused by transmissible agents, and a new construct for thinking about the molecular requirements for transmissibility was developed.

GUILLAIN-BARRE SYNDROME

The Guillain-Barré syndrome, the most common cause of acute neuromuscular paralysis, was associated with antecedent gastrointestinal and respiratory illnesses through case-control studies in the 1960s and 1970s. Clinically associated illnesses have included mononucleosis, chickenpox, mumps, hepatitis, and mycoplasmal infection; many viruses have been implicated through serologic studies. An association between the Guillain-Barré syndrome and infection with the bacterium *Campylobacter jejuni* was recently described, and more than 20 reports and case series have documented this association in the past 10 years (10, 11).

At the onset of symptoms of the Guillain-Barré syndrome, 20% to 30% of patients have documented positive results on stool cultures for *C. jejuni* (10). Serologic evidence of *C. jejuni* infection is often documented in many patients with negative cultures, and antiganglioside antibodies have been associated with campylobacteriosis even in the absence of the Guillain-Barré syndrome (11). The Guillain-Barré syndrome subsequent to *C. jejuni* infection is associated with axonal degeneration, slow recovery, and severe residual disability (58).

ACUTE FACIAL NERVE PARALYSIS

Another acute neuroparalytic problem, **acute facial nerve paralysis**, has been associated with infectious diseases, including syphilis and the Ramsay Hunt syndrome due to varicella-zoster virus. We recently learned that the spirochete *Borrelia burgdorferi* can produce acute facial paralysis, Bell's palsy, as a common neurologic manifestation of early Lyme disease (12). However, the cause of most cases of Bell palsy remained obscure until early this year (13), when a strong association with herpes simplex virus type 1 (HSV-1) was made. With PCR analysis, HSV-1 genomic sequences were found in endoneurial fluid from the facial nerve or from muscle innervated by the facial nerve in patients with Bell palsy; the virus was not present in controls.

ACUTE RENAL FAILURE

That infectious agents could be among the many causes of acute renal failure was brought home to U.S. physicians when some 3000 cases of a febrile illness with renal failure occurred among United Nations troops involved in the Korean Conflict. Hemorrhagic fever with the renal syndrome, as it is now called, is caused by infection with one of several hanta viruses (15). These viruses produce asymptomatic, lifelong infections in rodents and are transmitted to humans through inhaled rodent excreta.

Most cases of the hemolytic uremic syndrome occur in children younger than 10 years of age; in this group, it is the most common cause of acute renal failure (17). In 1982, two outbreaks of acute bloody diarrhea were linked to ingestion of poorly cooked hamburgers by patrons of fast-food restaurants. These outbreaks were ultimately shown to have been caused by *Escherichia coli* O157:H7, an uncommon organism that produces a Shiga-like verotoxin (16-18). Many cases of bloody diarrhea caused by this *E. coli* serotype have subsequently been reported, and most are linked to ingestion of poorly cooked ground beef. Most interesting is that about 10% of infected persons younger than 10 years of age develop the hemolytic uremic syndrome, and it appears that as many as 75% of cases of the syndrome in the United States are complications of intestinal infection with *E. coli* O157:H7 (16-18).

ARTHRITIS

Physicians have long known that so-called reactive arthritis (spondyloarthropathy) follows intestinal infection with *Salmonella typhimurium* and *Yersinia enterocolitica* or urethral infection with *Chlamydia trachomatis* (28). Although live bacteria have not been convincingly shown in inflamed joints, recent studies have reported finding bacterial antigens and nucleic acid in intrasynovial cells by immunofluorescence and molecular hybridization (28).

The cause of rheumatoid arthritis remains unknown. In the past, a causal role for several agents, including mycoplasmas, was suggested, but convincing data are lacking. In September 1995, Tilley and colleagues (29) reported a 48-week, double-blind, placebo-controlled trial that showed a beneficial effect for the antibiotic minocycline in rheumatoid arthritis. This intriguing study harks back to an earlier observation. In 1947, Brown treated patients who had rheumatoid arthritis with crystalline chlortetracycline hydrochloride and, in 1949, reported favorable results at the 7th International Congress on Rheumatic Diseases (59). Unfortunately for Brown and the progress of tetracyclines as antiarthritic agents, the beneficial effects of cortisone in the treatment of arthritis were introduced at the same meeting. The effect of tetracycline paled beside that of steroids, and the salutary effects of antibiotics on rheumatoid arthritis were largely ignored for almost 50 years.

VASCULITIS

It has been known for some time that patients occasionally develop polyarteritis nodosa a few months after having had hepatitis B infection. About 15% to 25% of patients with polyarteritis nodosa (even those without a history of hepatitis B infection) can be shown to have immune complexes containing hepatitis B antigens in the circulation and in involved tissues (19).

In 1985, a group from the Mayo Clinic (23) reported that trimethoprim-sulfamethoxazole had a beneficial effect in patients with Wegener granulomatosis. Reports of efficacy followed during the next few years from at least three groups. For example, a 1988 report (24) stated that 10 patients who had been treated with trimethoprim-sulfamethoxazole alone starting in 1984 had had an excellent response and that 9 of the 10 were in complete remission. In contrast to these glowing reports, workers from the National Institutes of Health (60) claimed that only 1 of 9 patients treated with trimethoprim-sulfamethoxazole in a so-called ongoing, prospective, open study had prolonged improvement. Therefore, the jury is still out on the effect of trimethoprim-sulfamethoxazole for Wegener granulomatosis.

In 1994, a group from the Netherlands (61) studied a cohort of 71 patients with Wegener granulomatosis and found that those who were chronic nasal carriers of *S. aureus* were more likely than those who were not nasal carriers to have relapses. Relapses were not related to diagnosed infections, and investigators are now studying whether eradication of carriage affects relapse rates.

Mixed cryoglobulinemia has recently been linked to a viral origin. When serologic testing for hepatitis C virus (HCV) and the ability to test for the HCV genome using PCR technology became available, the role of HCV infection in mixed cryoglobulinemia became clear. The first report (21) came from an Italian group in 1991. This group found that 91% of 45 patients with mixed cryoglobulinemia had antibodies to HCV. Subsequent studies in Italy (20), France (22), and the United States (21) showed evidence of HCV infection in a large percentage of patients. Other investigators showed that the HCV RNA levels of some antibody-negative patients were higher in cryoprecipitates than in plasma (62), suggesting that some immune complexes contained HCV antigens and that HCV plays a part in the pathogenesis of cryoglobulinemia. Antiviral treatment may have a role in the treatment of mixed cryoglobulinemia. A 1992 report (62) showed that 2 patients had a dramatic clinical response to interferon- α , characterized of the disappearance of palpable purpura and of renal dysfunction.

The cause of giant cell arteritis remains unknown. A study published in 1995 (25) reported the incidence of giant cell arteritis in Olmstead County, Minnesota, over a 40-year period. This study documented that the incidence of giant cell arteritis had a cyclic pattern that peaked about every 7 years and an overall frequency that increased steadily over time. This was a totally new observation. Although the observed periodicity does not prove an infectious origin, it is compatible with one. The data need to be confirmed in other populations.

(HERE SEE WORK OF JADIN RICKETTSIA IN SOUTH AFRICA)

INFLAMMATORY BOWEL DISEASE

Because its clinical and histopathologic features are similar to those of ileocecal tuberculosis, investigators have long suspected that Crohn's disease has an infectious origin. Sporadic reports of case clustering of Crohn's disease among family members and close friends support this idea.

Mycobacterium paratuberculosis causes Johne disease, a chronic, granulomatous enterocolitis of ruminants that does not respond to antimycobacterial treatment. In 1984, Chiodini (6) recovered M. paratuberculosis from the tissues of three patients with Crohn's disease; he later cultured identical isolates from Crohn's disease tissues at five centers on three continents. Mycobacterium paratuberculosis has been isolated from fewer than 15% of patients with Crohn's disease, but it is rarely found in tissue from patients with ulcerative colitis or from controls. Interest in M. paratuberculosis as an etiologic agent has recently been renewed because the organism has been detected more frequently using PCR. In 1992, Sanderson (6) found M. paratuberculosis DNA in 65% of Crohn's disease samples, 4% of ulcerative colitis samples, and 13% of control samples. An even higher percentage of samples positive for M. paratuberculosis has been found in children with Crohn's disease.

It was recently suggested that Crohn's disease is caused by a persistent infection of vascular endothelial cells due to a viral-induced, focal granulomatous vasculitis. Wakefield (6) visualized paramyxovirus-like structures in nine of nine patients with Crohn's disease. Measles antigen and messenger RNA were localized to granulomas and endothelial cells by immunohistochemistry and in situ hybridization.

{ALSO WEGENER'S GRANULOMATOSIS, MOST LIKELY}

DIABETES

Several observations support a link between infection and insulin-dependent diabetes mellitus (26). Enteroviruses have been found in the pancreas of patients with recent-onset insulin-dependent diabetes. After infection with certain enterovirus strains, susceptible mice develop insulin-dependent diabetes. Insulin-dependent diabetes also has a seasonal incidence similar to that of enteroviral infections: Enteroviral infections peak in the late summer and early autumn, and insulin-dependent diabetes peaks in autumn and early winter.

Several seroepidemiologic studies have linked insulin-dependent diabetes with antibodies to enteroviruses. For example, a 1995 report (27) of a case-control study supported an association between IgM antibodies to enteroviruses and new onset of insulin-dependent diabetes in older children.

CORONARY ARTERY DISEASE

Implication of an infectious origin of atherosclerosis would open the potential for preventing heart attacks with a vaccine. Several reports have shown a relation between cytomegalovirus infection in transplant recipients and early coronary artery vasculopathy (30, 31). Cytomegalovirus antigens have been shown in atheromatous plaques in these patients.

Another infectious agent has been implicated in the pathogenesis of coronary artery disease in persons with normal immune function. In 1988, Saikku and colleagues (32) showed that men with acute myocardial infarctions were more likely than age-matched controls to have elevated serum antibody levels to *Chlamydia pneumoniae*. In a follow-up study that was part of a large prospective study of risk reduction for coronary artery disease involving more than 4000 patients (32), these authors showed that elevated serum levels of antibodies to *C. pneumoniae* were associated with the development of coronary artery disease, as were circulating immune complexes containing chlamydial lipopolysaccharides. The study addressed the concern that myocardial infarction may have activated a latent chlamydial infection. These data were supported by a study (33) from the United States. In 1993 (34), PCR and immunocytochemistry were used to show *C. pneumoniae* in coronary artery atheromas in approximately one half of study patients. Electron microscopy showed that typical pear-shaped *C. pneumoniae* elementary bodies were present in 6 of 21 atheromatous plaques, providing further evidence that *C. pneumoniae* may be involved in atherosclerosis and coronary artery disease.

CANCER

The most recent type of cancer to be linked to an infectious agent (Table 1) is Kaposi sarcoma, the most common neoplasm in patients with the acquired immunodeficiency syndrome (AIDS). An infectious origin for Kaposi sarcoma has been suggested by epidemiologic studies showing that patients with AIDS who are bisexual or homosexual are 20 times more likely to develop Kaposi sarcoma than are heterosexual patients with AIDS (43). Kaposi sarcoma occurs more frequently than would be expected in homosexual men who do not have human immunodeficiency virus (HIV) infection. In these persons, it behaves in the same manner as classic Kaposi sarcoma (43), supporting the theory that Kaposi sarcoma may be caused by sexual transmission of an infectious agent.

In 1994, Chang and colleagues (63) used a technique that had been described a year earlier (64) that enables investigators to find and amplify unique DNA sequences in tissue. This technique can find foreign (nonhuman) DNA and differentially amplify it, leaving the host DNA behind. This application is a brilliant use of PCR technology. Chang and colleagues found unique DNA sequences in Kaposi sarcoma lesions in 25 of 25 patients with AIDS. These sequences were shown to be nonhuman and similar, but not identical, to genes of the Epstein-Barr virus and herpesvirus saimiri (whose natural host is the squirrel monkey). These DNA sequences identified a totally new herpesvirus—the eighth to be discovered.

Was this new virus an etiologic agent or did it just preferentially colonize Kaposi sarcoma lesions in immunosuppressed patients? To answer this question, the novel herpesvirus DNA was looked for (43) in Kaposi sarcoma lesions from patients with AIDS, patients with classic Kaposi sarcoma, and patients with Kaposi sarcoma who were homosexual but HIV negative. Also studied were patient tissues not involved with Kaposi sarcoma lesions and control tissues from healthy persons. A strong association was seen between Kaposi sarcoma lesions and the newly described herpesvirus. Viral sequences from the three types of Kaposi sarcoma were more than 98% identical (43), suggesting that all were caused by the same agent. It appears that a new human herpesvirus is the cause of Kaposi sarcoma.

Other investigators (44) looked for this new herpesvirus DNA in lymphomas from patients with and without AIDS. Of 193 patients with lymphoma who were studied, the so-called Kaposi sarcoma-associated herpesvirus was found in only 8 patients, all of whom had a body cavity-based lymphoma. These 8 samples also contained the Epstein-Barr virus genome. The Kaposi sarcoma-associated herpesvirus sequences were 40 to 80 times more abundant in lymphoma cells than in Kaposi sarcoma cells. This same virus has since been shown in patients with Castleman disease (45) and in the lymphomatous pleural effusion (65) of an HIV-negative elderly man without Epstein-Barr virus infection.

CONCLUSIONS

A quiet scientific revolution has been taking place, showing that infectious agents can be the causes of, precipitating factors for, or risk factors for various diseases that were not previously thought to be caused by transmissible agents, thereby expanding our understanding of human-microorganism interactions. Are all diseases infectious? Of course not. But who would have guessed 20 years ago that ulcers could be eradicated with antibiotics, that spongiform encephalopathies were caused by transmissible agents composed only of tiny bits of protein, or that an unknown herpesvirus was the cause of Kaposi sarcoma? We have every reason to believe that science will show still more infectious causes for degenerative, inflammatory, and even hereditary diseases. Although this prospect is sobering, the opportunity for disease prevention through immunization is exciting to contemplate. Developments in this area are eagerly anticipated.

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Requests for Reprints: Bennett Lorber, MD, Section of Infectious Diseases, Temple University Hospital, Broad and Ontario Streets, Philadelphia, PA 19140.