Microbial Origins of Chronic Diseases

Lisa M. Gargano and James M. Hughes

Division of Infectious Diseases, Department of Medicine, School of Medicine, Emory University, Atlanta, Georgia 30322; email: lgargan@emory.edu, jmhughe@emory.edu

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Abstract

Chronic diseases such as cardiovascular disease and cancer are among the leading causes of death worldwide and have been on the rise over the past decade. Associations between microbial agents and development of chronic diseases have been made in the past, and new connections are currently being assessed. Investigators are examining the relationship between infectious agents and chronic disease using new technologies with more rigor and specificity. This review examines microbial agents' links to and associations with cardiovascular diseases, cancer, neurodegenerative diseases, renal diseases, psychiatric disorders, and obesity and addresses the important role of the human microbiome in maintenance of health and its potential role in chronic diseases. These associations and relationships will impact future research priorities, surveillance approaches, treatment strategies, and prevention programs for chronic diseases.

INTRODUCTION

Microbiome: the totality of the community of microbes and their genetic elements in a particular environment, in this case on the human body

Chronic disease: a long-lasting condition that can usually be controlled but may require lifelong treatment

CVD: cardiovascular disease

Noncommunicable disease (NCD): a medical condition or disease that is not transmissible from person to person

Human interactions with microbes are variable and complex. In recent years, our understanding of human-microorganism interactions has fundamentally changed because we have learned that infectious agents can cause chronic illnesses and have begun to understand the important role of the human microbiome in health and disease. We are learning that infectious agents can cause chronic illnesses that were not thought to be related to infectious processes.

Chronic diseases are the most common, costly, and preventable health problems in the United States, exacting an extraordinary toll. Chronic diseases are the leading causes of death and disability, causing 7 of 10 deaths each year. Cardiovascular disease (CVD) and malignancies account for more than 50% of all deaths annually (90). In 2005, 133 million Americans had at least one chronic illness. The economic cost is estimated at $1.3 trillion annually; of this amount, lost productivity totals $1.1 trillion (33). Obesity has become a major health concern; more than one-third of adults and almost 17% of youth between the ages of 6 and 19 are obese (100). About one-fourth of those with chronic conditions have one or more daily activity limitations (5).

Chronic diseases are not limited to the developed world; developing countries increasingly suffer from high levels of morbidity and mortality. Deaths from noncommunicable diseases (NCDs) increased by 9 million between 1990 and 2010, accounting for 2 of every 3 deaths worldwide by 2010 (34.5 million) (76). In 2010, 8 million people died from cancer, a 38% increase from 2 decades ago (**Figure 1**) (76). CVDs rose by 31.2%. In 2008, more than 25% of all deaths attributed to NCDs occurred before the age of 60; 90% of these premature deaths occurred in low- and middle-income countries (141). Premature deaths in persons under age 60 accounted for 13% of NCD deaths in high-income countries, 25% of NCD deaths in upper-middle-income countries, and 28% in lower-middle- and low-income countries. In low-income countries, the proportion of premature NCD deaths under age 60 was 41%, 3 times the proportion in high-income countries (141). Based on current trends, by the year 2020 these diseases could account for 73% of all deaths and 60% of the total disease burden (143). Nearly 50% of chronic disease deaths are attributable to CVDs; obesity and diabetes are also showing worrying trends, affecting a large proportion of the population and appearing earlier in life.

Many chronic diseases do not result from infection; some are genetic, others result from environmental toxins, others result from the interaction of multiple behavioral and other risk factors, and others are of unknown cause. Infectious agents can cause chronic disease in several ways. Inflammation triggered by infections or by immune response to infections can lead to chronic disease, such as *Chlamydia* infection and CVD (64). The initial stages of infection can also cause permanent, lifelong deficits or disabilities (e.g., permanent paralysis from poliovirus infection) (99). Infection can indirectly predispose a person to chronic illness (e.g., maternal infection predisposing offspring to psychiatric disorders) (99). The identification of infection as a trigger for chronic disease is very important because it may allow earlier laboratory diagnosis and treatment of the disease and provide important prevention opportunities. This review focuses on selected examples of discoveries of connections between infectious agents and chronic diseases: We first review established connections, then consider more recent data relevant to emerging connections, and then review recent data suggesting some potential connections (**Table 1**). We also address the role the human microbiome may play in chronic diseases and discuss public health implications and issues for future consideration.

ESTABLISHED CONNECTIONS

Cancer is the second leading cause of death in adults in the United States (19). The first clear demonstration of virus-induced cancer was seen in the discovery of the role of Rous sarcoma virus

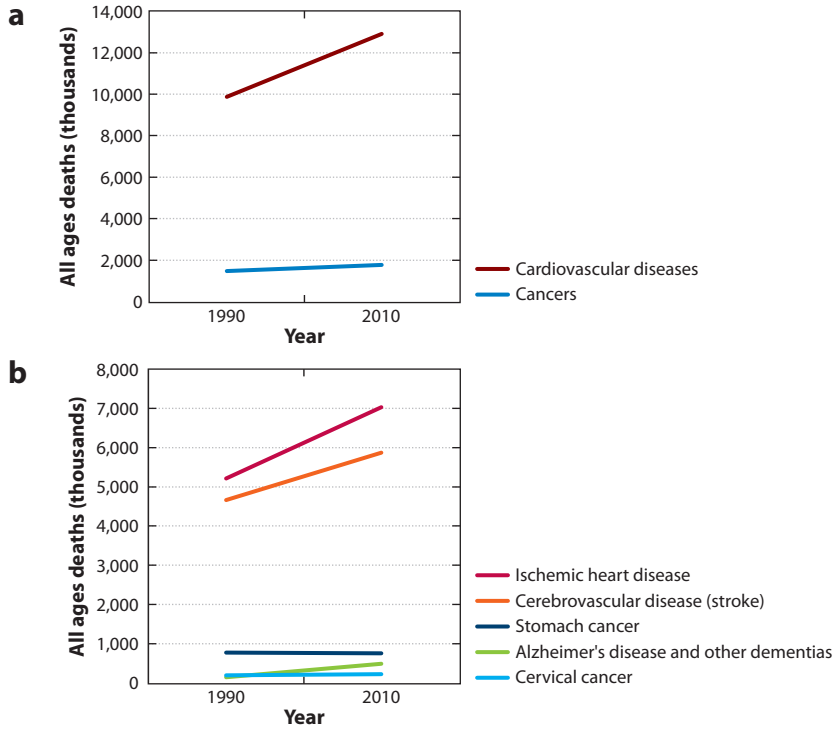

Figure 1

Changes in global deaths from 1990 to 2010. (*a*) Number of deaths from chronic diseases. Cardiovascular diseases include ischemic heart disease and cerebrovascular disease. Cancers include stomach, liver, cervical, Hodgkin's disease, bladder, and nasopharynx. (*b*) Changes in selected specific chronic disease global deaths from 1990 to 2010 (76).

in cancer in chickens (52). It has become clear in the past three decades that many human cancers are caused by viruses. Associations between infectious agents and cancer of the gastrointestinal tract, liver, cervix, and skin have suggested that additional cancers may have an infectious origin (41). Of the 12.7 million new cancer cases in 2008, the population attributable fraction (PAF) for infectious agents was 16.1%, accounting for 2 million cases (14). The PAF was 22.9% in less developed countries compared with 7.4% in more developed countries. *Helicobacter pylori*, hepatitis B (HBV) and hepatitis C (HCV) viruses, and human papillomavirus (HPV) accounted for 1.9 (95%) of the 2 million cancer cases (14).

H. pylori was identified in 1982 by Warren and Marshall who found that the organism was present in patients with chronic gastritis and gastric ulcers, conditions that were not previously believed to have a microbial cause. They also linked *H. pylori* to the development of duodenal ulcers and gastric cancer (139). However, more than 80% of infected individuals are asymptomatic, and Warren and Marshall postulated that the organism may play an important role in normal gastric ecology (139). Of 650,000 cases of gastric cancer attributed to *H. pylori* in 2008, 470,000 (72%) occurred in less developed regions (31) (**Figure 2**). In a large cohort study assessing the link between HBV and liver cancer, more than 22,000 government workers were monitored starting in 1974 in Taiwan; risk of liver cancer was 60 times higher in chronically HBV-infected persons than in non-HBV carriers (9).

HBV: hepatitis B virus

HCV: hepatitis C virus

HPV: human papillomavirus

Table 1 Selected infectious determinants of chronic diseases

Infectious agent(s)	Chronic disease(s)
Established connections	
Helicobacter pylori	Gastric cancers/peptic ulcer disease
Hepatitis B/C virus	Liver cancer
Human papillomavirus	Cervical cancer
Schistosoma haematobium	Bladder cancer
Epstein-Barr virus	Burkitt lymphoma, nasopharyngeal carcinoma
Kaposi-associated herpesvirus (HHV-8)	Kaposi's sarcoma, primary effusion lymphoma
Emerging connections	
Adenovirus 36	Obesity
Porphyromonas gingivalis (periodontitis)	Stroke, myocardial infarction, atherosclerosis
Chlamydia pneumoniae	Cardiovascular disease
Human papillomavirus	Nongenital cancers
Potential connections	
Prenatal influenza infection	Psychiatric disorders
Acute diarrhea	Gastrointestinal conditions
West Nile virus	Chronic renal disease

Acute hepatitis is a viral infection characterized by inflammation of the liver, jaundice, and gastrointestinal symptoms. Populations with a high prevalence of hepatitis also have a high prevalence of cirrhosis and liver cancer (13, 99). HBV has caused epidemics in parts of Asia and Africa and is endemic in China (140). About one-third of the world's population has been infected, including 350 million chronic carriers (142). In 2010, China had an estimated 120 million people chronically infected with HBV, followed by India and Indonesia with 40 million and 12 million, respectively (142). An estimated 600,000 people die every year of complications from HBV infection (142). An estimated 130–200 million people worldwide are chronically infected with HCV (50). HCV, identified in 1989 (56), persists in the liver in about 85% of those infected and can now be treated

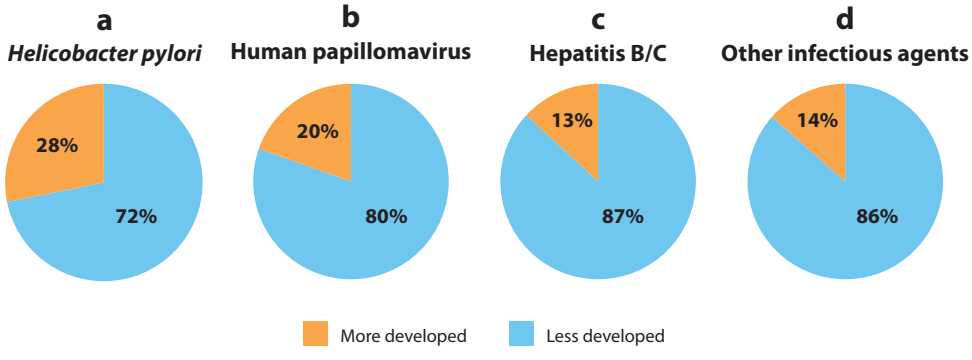

Figure 2

Distribution of all new cancers in 2008 attributable to infection by country development status. (*a*) *Helicobacter pylori*; (*b*) human papillomavirus; (*c*) hepatitis B/C; (*d*) other infectious agents. Percent of disease attributable to infection in 2008 (31).

effectively with medications, but no vaccine is available. HCV infection is the leading cause of liver transplantation in the Western world (113). Of 609,000 cases of liver cancer attributed to HBV and HCV and HCV-associated non-Hodgkin's lymphoma in 2008, 528,000 (87%) occurred in less developed regions (**Figure 2**) (31).

Identification of sexual activity as a risk factor for cervical cancer led to laboratory and epidemiologic research attempting to identify an infectious agent. In the 1980s, data emerged suggesting human papillomavirus (HPV) as the cause of cervical cancer. More than 30 types of HPV are transmitted through sexual contact. HPV types 6 and 11, called low-risk, cause genital warts. Persistent infection with high-risk HPV types 16 and 18 cause precancerous lesions and invasive cancer (118). Most HPV infections in young females are transient; 70% resolve in 1 year and 90% in 2 years (44). However, when an infection due to an oncogenic type persists, there is a high risk of precancerous lesions of the cervix, which can progress to invasive disease. This process usually takes 10–15 years, providing many opportunities for detection and treatment of the precancerous lesion and prevention of the disease. Progression to invasive cancer can almost always be prevented when standard prevention strategies are applied, but the lesions may require surgical intervention. Of 680,000 cases of cancers attributed to HPV in 2008, 485,800 (80%) occurred in less developed regions (**Figure 2**) (31).

Schistosoma haematobium, a trematode found in the Middle East, India, and Africa, causes urinary schistosomiasis. Studies have shown the relationship between *S. haematobium* infection and the development of squamous cell carcinoma of the bladder (68). Evidence supporting the association between urinary schistosomiasis and bladder cancer includes the geographical correlation between the two conditions, the distinctive patterns of gender and age at diagnosis, the pathology of schistosome-associated bladder cancer, and studies in experimentally infected animals (88).

Epstein-Barr virus (EBV) infects >90% of the world's population. Although most humans coexist with the virus without serious sequelae, a small proportion develop tumors (131). In 1958, Burkitt described a common cancer primarily affecting children in specific regions of Africa (16). EBV was first identified in 1964 by observation of virus-like particles in a cell line that had been established from a biopsy obtained from a Burkitt's lymphoma patient (39). Sera from patients with the lymphoma had much higher antibody titers to EBV than did controls without the lymphoma. The subsequent detection of EBV DNA in Burkitt's lymphoma and experimental production of lymphomas in nonhuman primates established EBV as the first virus clearly implicated in the development of a human tumor (39).

Human herpesvirus 8 (Kaposi-associated herpesvirus) was identified in 1994 as the cause of Kaposi's sarcoma (KS), a common cancer in AIDS patients (14, 23); body cavity lymphoma (21); and most cases of multicentric Castleman's disease (102). KS occurs when someone infected with KSHV becomes immunocompromised because of HIV infection, medical treatment, or advancing age.

EMERGING CONNECTIONS

Adenovirus 36 and Obesity

Adenovirus 36 (Ad-36), one of more than 50 human adenovirus serotypes (83), has been associated with obesity in experimental animals and epidemiologic studies. Adenoviruses cause up to 10% of upper respiratory infections in children and adults and can also cause conjunctivitis, tonsillitis, middle ear infections, croup, and gastroenteritis (137). Ad-36 was first associated with obesity in chickens (34); subsequent studies in animals found a similar association, with up to 100% of infected animals developing obesity relative to uninfected counterparts (116). Human studies have observed correlations between Ad-36 antibodies and increased adiposity; one study found

Seronegative: laboratory test results showing the absence of a specific antibody in serum

triple the likelihood of obesity in individuals with Ad-36 antibodies compared with seronegative individuals (13). Twin studies also support the association; infected twins tend to be obese more frequently than do their uninfected siblings (6a). Additional adenoviruses (Ad-37, Ad-5) may also be associated with obesity (133).

In one study, chickens were exposed to Ad-2, Ad-31, or Ad-37; researchers measured food intake and tracked weight for three weeks before measuring visceral fat, total body fat, serum lipids, and viral antibodies. Chickens inoculated with Ad-37 had much more visceral fat and body fat compared with chickens infected with Ad-2, Ad-31, or the control group, even though they did not consume more calories. The Ad-37 group was heavier than the other three groups, but the difference was not statistically significant (133).

Periodontitis: inflammatory disease affecting the tissues that surround and support the teeth (periodontium); caused by microorganisms that adhere to and grow on tooth surfaces

Seropositive: laboratory test results showing the presence of a specific antibody in serum

CP: *Chlamydia pneumoniae*

Periodontitis and Effects Outside the Mouth

Periodontitis is caused by microorganisms that adhere to and grow on tooth surfaces, eliciting an aggressive immune response. Periodontitis has been linked to increased inflammation elsewhere in the body, as indicated by elevated levels of C-reactive protein and interleukin-6 (5–7). Periodontitis is associated with an increased risk of stroke (107, 108), myocardial infarction (MI) (109), and atherosclerosis (10, 11, 38, 43, 144). In a study in Finland of 893 subjects free of CVD at baseline, *Porphyromonas gingivalis* seropositivity was associated with an increased risk of stroke during a 15-year follow-up period; compared with seronegative subjects, men and women seropositive for *P. gingivalis* had an odds ratio (OR) [95% confidence interval (CI)] of 1.63 (1.06–2.50) and 2.30 (1.39–3.78) for stroke, respectively (107). Another study assessed serum antibodies to major periodontal pathogens for their association with risk of MI; a high *P. gingivalis* IgA antibody titer predicted MI independently of classic cardiovascular risk factors. The risk for MI increased by increasing quartiles of antibody levels (109). In those over age 60, positive serology was also associated with impairments of long-term delayed memory and calculation abilities (66, 96).

Cardiovascular Disease and *Chlamydia pneumoniae*

CVD deaths account for the highest proportion of total deaths in the United States (20). In 2010, ischemic heart disease was the leading cause of mortality (13.3%) worldwide (76). Although principal risk factors for CVD are hypertension, diabetes, and behavioral factors, *C. pneumoniae* (CP) infection has been associated with an increased risk of CVD. CP is a cause of respiratory infections including pneumonia (93). The observation that individuals with IgG antibody to CP were at increased risk of subsequently developing an MI suggests that CP plays a role in CVD (13). Studies have found twice the prevalence of CP antibody in individuals with CVD compared with individuals without CVD (94). Furthermore, live CP and CP-specific T-cells have been detected in coronary and carotid atherosclerotic plaque (87, 146) but not in neighboring healthy tissues (60, 70, 78). Early clinical trials of antibiotics found a modest-to-moderate benefit (on the order of 20–30% event reduction) in CVD and acute coronary syndromes (6). A large trial with more than 7,000 participants found only a 7%, nonsignificant reduction in the incidence of the primary end point (composite of death, MI, hospitalization for unstable angina, or need for repeat revascularization at 3 years). However, post hoc analyses suggested a possible benefit during and shortly after treatment (that is, a 33% reduction in risk of death or MI at 6 months, $p = 0.03$), but it was not sustained over the observation period (6). Negative outcomes might be explained by inadequate study size or design or by an ineffective antibiotic regimen; Gieffers found that CP-infected circulating monocytes were refractory to azithromycin (48).

The potential role of CP is supported by studies showing that CP can directly infect coronary artery endothelial cells and aortic smooth muscle cells (47). However, some argue that CP induces

nonspecific inflammation that may be associated with atherosclerosis. Moreover, CP infection does not cause atherosclerosis in animals, although it may accelerate disease progression and result in plaque activation (17, 57). The mechanism could involve either direct action on plaques or signaling by inflammatory mediators (17).

HNSCC: head and neck squamous cell carcinomas

HPV and Nongenital Cancers

Although HPV infects stratified epithelial cells of the skin, oral cavity, and anogenital tract (42), its role in head and neck cancer is less clear than in cervical cancer. Although head and neck squamous cell carcinomas (HNSCC) account for only 3–4% of all cancer diagnoses in North America and Europe, HNSCC is the sixth most common malignancy worldwide (32, 61). Tobacco and alcohol have long been recognized as HNSCC risk factors, but the possibility that HPV also has an etiological role was suggested in 1983 (126).

HPV is found in 23–35% of all HNSCC biopsies worldwide, and similar to cervical cancer, HPV-16 infection has been associated with 68–87% of HPV-positive head and neck cancer cases worldwide (69, 89). The epidemiology of head and neck cancer has changed over the past four decades. In the United States, the incidence of tobacco-associated head and neck cancer has declined, likely owing to a decrease in tobacco use, whereas the incidence and prevalence of HPV-related HNSCCs have increased (24, 45, 115, 123). In addition, a recent report found that HPV infection was associated with a higher risk of laryngeal carcinoma, with HPV-16 especially associated with the increased risk (73). The authors concluded that further studies are needed to verify the relationship between HPV infection and laryngeal cancer.

POTENTIAL CONNECTIONS

Infections and Psychiatric Disorders

Although schizophrenia can cluster in families, in many cases no genetic link is apparent (30). The earliest studies of the possible association of prenatal infection and schizophrenia used ecologic data, namely influenza epidemics in populations, to define exposure status (84). Initial studies provided evidence consistent with an association between second-trimester exposure to influenza epidemics and schizophrenia in offspring (85, 98). However, subsequent investigations, some of which were larger with more complete case ascertainment, failed to replicate the association (40, 125). Although similar studies of other infectious agents have suggested potential relationships with schizophrenia, the associations have generally been weak (84). More recently, investigators have attempted to confirm maternal infection by analyzing maternal serum stored for 30–40 years until offspring had developed schizophrenia. This study found an association, as documented by positive influenza antibody titers, between schizophrenia spectrum disorders and maternal influenza during the first trimester of pregnancy that approached statistical significance ($p = 0.08$) and during the first half of pregnancy that was of borderline significance ($p = 0.052$) (15). Such studies have limited sample sizes, and storage and stability of samples may be questionable. If the association between maternal influenza and schizophrenia holds in additional studies, maternal influenza infection could be an important risk factor for schizophrenia because of the annual occurrence of seasonal influenza epidemics.

Two studies conducted on women pregnant during the 1957 influenza epidemic provided some evidence of an association between influenza infection and development of bipolar disorders in offspring (18, 80). These studies had several limitations, including diagnosis based on case notes, no differentiation of the manic-depressive from the depressive disorder, small sample sizes, and

BDV: Borna disease virus

risk of exposure misclassification (101). A recent nested case-control study of a birth cohort from 1959 to 1966 of women receiving obstetric care from Kaiser Permanente documented maternal influenza infection by medical record review of clinical diagnosis of pregnant women treated for influenza in the Kaiser system. Researchers found a nearly fourfold increase in risk of bipolar disorder in offspring of mothers who developed physician-diagnosed influenza at any time during pregnancy (101).

Borna disease virus (BDV) is a neurotropic virus. Although the BDV causes Borna disease in horses and other animals, recent findings have suggested that BDV may play a role in some human neurological and psychiatric conditions including bipolar disorder and depression. The epidemiology and consequences of human infection have been controversial since the first serologic studies suggested a role for BDV in bipolar disorder in 1985 (114). Most reports implicating BDV in human disease have focused on neuropsychiatric disorders including unipolar depression, bipolar disorder, and schizophrenia. Isolation of infectious virus is rarely reported. Infection is more frequently diagnosed by serology or polymerase chain reaction of peripheral blood mononuclear cells or tissues. Serologic studies have revealed antibodies to BDV in subjects with selected neuropsychiatric disorders with a prevalence of 0–93% versus 0–15% of normal controls. Serological assays differed among the studies, and the wide range of prevalence rates could reflect differences in assay sensitivity and specificity (119). A recent study reported the absence of an association of psychiatric illness with antibodies to BDV or with BDV nucleic acid in serially collected serum and white blood cell samples from a study population of 198 matched pairs of patients and healthy controls (52 schizophrenia/control pairs, 66 bipolar disorder/control pairs, and 80 major depressive disorder/control pairs) (55).

Acute Diarrhea and Gastrointestinal Conditions

Infectious diarrhea is a global public health problem with high morbidity and mortality in children under five and the elderly. Although most of the burden of these infections falls on the developing world (76), acute infectious diarrhea is a frequent cause of outpatient visits and hospitalizations throughout the developed world. Recent evidence suggests that these infections may also contribute to the pathogenesis of many chronic health problems. The most important risk factor identified to date for the development of irritable bowel syndrome (IBS) is acute gastrointestinal infection. Studies have suggested that infections with nontyphoid *Salmonella* spp., *Campylobacter* spp., and *Shigella* spp., as well as certain viruses and protozoa, are a risk factor for postinfective IBS (35, 36, 111, 120, 124). A recent small study found an increased risk following *Clostridium difficile* infection (37). Evidence for an association between acute infections and first onset or relapses of inflammatory bowel disease (IBD) is controversial (46, 49, 62, 106, 128).

Celiac disease is a chronic inflammatory enteropathy caused by intolerance to gluten. Recent epidemiologic studies indicate that celiac disease is a common disorder, and its clinical similarity to IBS has been recognized (135). Given the potential for infections to act as a trigger, efforts have been made to identify an infectious association. To date, there is no compelling evidence for such an association beyond an observation of increased risk following neonatal infections (135).

Infectious Origins of Alzheimer's and Cognitive Impairment

Approximately 5 million Americans have Alzheimer's disease; ~5% of people over 65 and 50% of those over 85 are estimated to have the disease (4). The potential roles of behavioral risk factors and microbial agents including CP and herpes simplex-1 virus (HSV-1) are being examined. An association between CP and neurodegenerative disorders was first suggested by statistical analysis

and some empirical associations (13). In addition to CP's ability to persist in tissues and cross the blood-brain barrier, the organism activates endothelial cells and causes inflammation and progression of pathophysiology associated with Alzheimer's disease (59). One study found that 90% of postmortem brain samples from late-onset Alzheimer's disease patients tested positive for CP (7).

HSV-1 antibodies have been highly correlated with Alzheimer's diagnosis. The overall prevalence of HSV-1 infection in the United States was 62% between 1999 and 2004 (145). More than 70% of the population is infected by age 50 (72). A cohort study followed more than 500 elderly people for 14 years and found hazard ratios of 2.55 in participants with previous HSV-1 infection compared with controls (72). A 2011 study demonstrated that in cell culture fluorescently tagged HSV-1 particles damaged nerve cells in ways similar to that observed in Alzheimer's disease specimens (25). A large multiethnic cross-sectional study that included 1,625 people with an average age of 69 years found that people who had higher antibody titers against cytomegalovirus, HSV-1, and HSV-2 were 25% more likely to have a lower cognition score than were those with the lowest levels (65). This study did not find a link between CP and cognitive abilities (65). Caution is necessary when assessing the infectious origin of neurodegenerative disease because most studies have been cross-sectional, and conflicting evidence supports a potential role for different agents (77).

West Nile Virus and Chronic Renal Disease

West Nile virus (WNV) has become endemic in the United States; more than 1.7 million people are estimated to have been infected since 1999 (75). A study using a golden hamster model indicated that renal disease could result from acute experimental infection with WNV (129). After clinical recovery from acute WNV infection, animals developed chronic kidney infection with histopathological changes in renal tissue and virus detectable for up to eight months (97). Three studies have found the virus in the urine of human WNV patients (8, 91, 132). Previous reports have found that 9% of hospitalized WNV patients developed acute renal failure at the time of initial infection (92). Another study assessing mortality of WNV patients several years postinfection found that 21% of deceased WNV patients had documented renal failure as a contributing or an underlying cause (74). A recent study found evidence of chronic renal disease in 40% of survivors, the majority of cases (83%) appearing four to nine years after infection (97). In multivariate analysis, only neuroinvasive WNV disease was independently associated with chronic renal disease (97).

THE ROLE OF THE MICROBIOME IN CHRONIC DISEASES

Humans are colonized by residential microbes including bacteria, archaea, fungi, eukaryotes, and viruses (134). Each anatomical niche possesses its own mixture of microbial populations (27). The microbiome composition evolves over a person's life. The Human Microbiome Project launched in 2007 by the National Institutes of Health "aims to characterize microbial communities found at several sites on the human body, including nasal passages, oral cavities, skin, gastrointestinal tract, and urogenital tract, and to analyze the role these microbes play in human health and disease" (95). In 2012 this research consortium mapped the normal microbial makeup of healthy humans to allow researchers to put changes in the microbiome into context and understand what role it plays in disease development (95).

Increasing evidence supports the concept of a rich, complex, dynamic, and individual-specific microbial interaction with humans (105). The microbiome is important to immune system development in the first 2–3 years of life. Studies suggest that practices such as delivery by caesarean section (C-section) versus vaginal birth and formula use versus breastfeeding affect the composition of microbial communities that assemble in the infant gut (104). In addition, antibiotic use

in mothers before C-section and in infants, children, and adults impacts the microbiota (63). In fact, a number of disorders discussed in this review may be associated with a disturbed or altered microbiome in infancy. A microbiological examination of almost 1,000 stool samples from 1-month-old infants demonstrated that a high abundance of *Escherichia coli* was associated with the subsequent development of eczema, whereas infants colonized with *C. difficile* were at higher risk for eczema, recurrent wheezing, allergic sensitization, and atopic dermatitis (103). Infants delivered vaginally typically possess higher abundance of certain *Bifidobacterium* and *Bacteroides* species, which have been associated with beneficial health effects, including downregulation of inflammatory responses (29, 67, 79). In contrast, infants delivered by C-section exhibit a different GI bacterial community, dominated by *Staphylococcus* spp., *Streptococcus* spp. (1, 138), and *C. difficile* (104), which are associated with an increased risk of allergic disease development (117). A meta-analysis demonstrated a 20% increase in risk of development of asthma and allergies in children delivered by C-section compared with those delivered vaginally (130). The working hypothesis is that induction of immune system maturation in these infants may be delayed, rendering them more susceptible to disease later in life.

CD: Crohn's disease

Infectious disease: a condition caused by a pathogenic microbe that may or may not be transmissible from person to person

The interplay between the microbiome and disease is arguably most well studied in the field of IBD [Crohn's disease (CD) and ulcerative colitis (UC)]. Early childhood antibiotic exposure has been associated with significantly increased risk for CD many years after antibiotics were given (54, 58, 81, 121, 122, 136). However, as in any observational study, causality cannot be inferred. Confounding (e.g., prescribing antibiotics to children with intestinal symptoms of as yet undiagnosed IBD) would also be a possible explanation. In addition, several studies are limited by recall bias, lack of controls, incomplete antibiotic documentation, or inclusion of exposures occurring between IBD symptom onset and diagnosis.

Microbial diversity is significantly diminished in CD (82). Gut microbiome population structures of CD or UC patients differ from that of healthy patients but are similar in pattern across all patients with each disease but are unique for each disease (110). A study of twins discordant for UC found that those affected had significantly reduced diversity but increased proportions of Actinobacteria and Proteobacteria (71). Compared with controls, CD patients have an overrepresentation of *E. faecium* and several Proteobacteria (86).

Manichanh et al. (82) reported a decreased abundance of Bacteroidetes in obese humans that increases upon caloric restriction and weight loss. In one study, antibiotic use before six months of age was significantly associated with development of obesity (2). This and other early studies provide support for the idea that alterations of the microbiota could contribute to obesity (28, 112).

A recent study has highlighted the role of the intestinal microbiome in the production of the proatherosclerotic metabolite trimethylamine *N*-oxide (TMAO) following ingestion of lecithin (in eggs) and the reduction of plasma TMAO levels following broad-spectrum oral antibiotic therapy. An elevated plasma TMAO level was associated with increased risk of a major adverse cardiovascular event independent of other risk factors (127).

PUBLIC HEALTH IMPLICATIONS

The division of epidemiology into separate disciplines focusing on infectious diseases and chronic diseases is potentially problematic. As the understanding of the role of microbial agents in chronic diseases has increased, this segregation has led to neglect of issues at the interface. Appreciation of the role of infectious agents in some chronic diseases has provided a unique opportunity to develop and implement new effective prevention and treatment strategies. HBV vaccine provides greater than 90% protection to infants, children, and adults immunized before virus exposure. A study in South Korea assessed the effect of nationwide HBV vaccination on liver cancer mortality in a

population under 20 years of age. Following HBV vaccine introduction in 1985, HBV vaccination was recommended mainly for government employees, members of the military, and students on a voluntary basis. The national vaccination program for infants and children was launched in 1995. Comparing age-specific mortality rates of liver cancer before and after the national vaccination program was initiated, researchers found a significantly reduced liver cancer mortality rate in 2002–2006 compared with the period 1991–1994 (RR 0.30, 95% CI 0.21∼0.44). After program implementation, HBV prevalence declined from 6∼8% to 2∼3% (51).

HBV vaccination at birth became standard policy in Taiwan in 1984. A 20-year follow-up study in Taiwan collected data on nearly 2,000 children and adolescents with a diagnosis of early-stage liver cancer. Among children ages 6–19, there were only 64 cases among 37,709,304 person-years in the vaccinated group, compared with 444 among 78,496,406 person-years in the unvaccinated group, an age- and sex-adjusted relative risk of 0.31, $p < 0.001$. Of those who developed cancer despite vaccination, many were not given all recommended doses. The risk of developing hepatocellular carcinoma for vaccinated cohorts was statistically significantly associated with incomplete HBV vaccination; for those who received fewer than 3 doses of HBV vaccine, the OR was 4.32 (95% CI = 2.34–7.91) (22). A recent 30-year outcome analysis of the national hepatitis B immunization from Taiwan found a continuous decline in age- and sex-adjusted rate ratios of chronic liver disease and hepatocellular carcinoma mortality and hepatocellular carcinoma incidence for birth cohorts born after the implementation of the program (26).

HPV vaccine, introduced in the United States in 2006, is currently recommended for both boys and girls ages 9–27 years. In clinical trials performed in 15–25-year-old women, the vaccine demonstrated excellent protection from persistent infection against HPV, with high antibody titers persisting up to 4.5 years (53). A recent study from Australia showed that the incidence of genital warts declined by more than 90% in adolescent and teenage girls in the first 4–5 years following introduction of HPV vaccine. Genital warts occurred more than 70% less often among women 21–30 years old, compared with the 3–4-year period before the vaccine became available (3). Future studies will assess the effectiveness of the vaccine against cervical cancer. As our understanding of the role of microbial agents in chronic disease increases, development of new prevention tools, including vaccines, will aid the fight against chronic diseases. For example, antimicrobial agents may have a role in preventing CVD or in preventing and managing obesity.

ISSUES FOR FUTURE CONSIDERATION

Comprehensive and coordinated efforts will be needed to enhance the discovery and understanding of the links between microbial agents and chronic diseases. Interdisciplinary research is needed to further elucidate the mechanisms by which infectious agents cause chronic diseases. This will be even more important in the future as new infectious agents continue to be identified using state-of-the-art laboratory methods (113a). Increased efforts are needed to identify and support applied research activities, including longitudinal studies, development of more sensitive and specific diagnostic tests, and exploration of contemporary research areas such as systems biology and genetics to address and clarify associations between infectious agents and chronic diseases.

Efforts to improve public health in developing countries are shifting their emphasis from infectious and other childhood diseases to chronic conditions in adults (143). As indicated by the high burden of malignancies of infectious origin in less developed regions of the world (31, 76), this increased emphasis is important and timely. Understanding of the epidemiology of identified infectious agents, such as CP and AD-36, that could cause or contribute to chronic disease in developing countries is lacking. Relevant data will need to be collected and provided to public health officials in these countries to inform their policy development. Interdisciplinary teams including

behavioral, environmental, and veterinary scientists in addition to clinicians, epidemiologists, and laboratory researchers will be needed to better understand the interplay among environment, genetics, microbial agents, and behavioral factors in the causation of chronic diseases.

CONCLUSIONS

The chronic health consequences of exposure to microbial agents should be considered in global burden of disease assessments to inform policy discussions and to emphasize the potential benefit of reducing these infectious diseases among high-risk populations through primary and secondary prevention programs. Epidemiologic associations must be supported by evidence to suggest plausibility and a likelihood that the link is causal in nature. The need to assess these associations and relationships will impact future research priorities, surveillance approaches, treatment strategies, and prevention programs for chronic diseases.

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