

Koch's and Rivers' Postulates Expanded
Noncommunicable chronic diseases can stem from infectious agents

In order to prove an infectious etiology for a disease Koch's postulates require that one isolate a bacterium from a diseased animal or plant and when reintroduced it causes the same disease. Rivers' postulates basically require the same for viral diseases. The introduction of additional approaches, such as polymerase chain reaction (PCR) and antigen and antibody detection using enzyme immunoassays has led to significant expansion of our understanding of microbial involvement in disease states, both acute and chronic. Even these approaches are not able to answer these questions alone. Diphtheria requires that the causative bacterium, *Corynebacterium diphtheriae*, be infected with a virus that confers the ability to produce diphtheria toxin; the fulminant form of hepatitis B requires the presence of both hepatitis B (HBV) and hepatitis D (Δ) viruses. On the other hand, there are cases where more than one "agent" is sometimes found and yet there is no causative relationship, e.g., influenza and *Hemophilus influenzae*. These various factors have made it more difficult to specifically identify some disease etiologies.

We know that HBV and hepatitis C virus (HCV) infections account for most chronic liver disease (CLD) and hepatocellular carcinoma (HCC) cases. Studies associate human papillomavirus (HPV) with at least 90% of malignant lesions and HPV-induced oncoproteins are implicated in the pathway from infection to malignancy.

Microbes also cause nonmalignant chronic diseases. For example, *Borrelia burgdorferi* infections can result in chronic Lyme arthritis. Hence, we now recognize that at least some forms of chronic inflammatory arthritis have an infectious basis rather than being an autoimmune syndrome. *B. burgdorferi* and *B. garinii* infections also induce the chronic central nervous system manifestations of neuroborreliosis.

Molecular biology, particularly PCR, plus advances in immunologic and other techniques, have exposed new causal links by detecting difficult-to-culture and novel agents in chronic disease settings. The identification of *Tropheryma whipplei* as the microbial source of Whipple disease was accomplished using PCR. Improved culture techniques subsequently facilitated propagation of the bacterium. Evidence confirms neurologic and ocular manifestations of this chronic syndrome. PCR analysis identified the viral cause of Kaposi's sarcoma (KS) in HIV-positive gay men. Researchers also linked the KS-associated herpesvirus to classic KS in the absence of HIV infection.

Detecting an infectious agent, its nucleic acid, or other biomarkers of infection in the setting of chronic disease does not prove it caused the disease. Neither does the presence of antibodies to pathogens, since immunoglobulin G indicates previous infection but not necessarily causation. This fact is also true for other ubiquitous infections. For example, peptic ulcer disease only develops in some of the many people infected with *Helicobacter pylori*. In contrast, the inability to detect an agent in the setting of chronic disease does not rule out an infectious etiology. Existing methods may not be sensitive enough to link known agents with chronic disease, or they may be unable to detect as yet uncharacterized novel or emerging microbes. Testing may occur too long after exposure, particularly when years of pathology precede diagnosis of the chronic condition, or if persistent immune response to an already cleared infectious agent accounts for chronic disease.

Bacteria, fungi, parasites, viruses and prions are all implicated as infectious agents causing chronic diseases. As yet unidentified etiologic agents may be described in the future. Might we consider Creutzfeldt-Jacob and other encephalitides as well as Alzheimer's Disease manifestations of chronic "infections"? And psychiatric disorders? Borna Disease Virus is recognized as the cause of Borna Disease. This RNA virus gives rise to a T-cell dependent immune response that causes a fatal neurologic disease in horses and several other mammals. It has been proposed that similar agents may be responsible for some cases of schizophrenia and affective psychoses in humans.

Established causal associations prove that certain infectious agents evoke only one type of chronic pathology, e.g., poliovirus-induced persistent flaccid paralysis. Single agents can also produce multiple distinct syndromes in different organ systems. HBV-associated CLD, HCC, and polyarteritis nodosa, as well as HCV-associated CLD, HCC, mixed cryoglobulinemia, and arthropathy demonstrate this phenomenon. So do three very different outcomes of human T-lymphotropic virus type 1 (HTLV-1) infection: acute T-cell leukemia/lymphoma, tropical spastic paraparesis/HTLV-1-associated myelopathy, and chronic arthropathy. On the other hand, we also know that different organisms can lead to a single common chronic clinical syndrome, e.g., reactive arthritis following *Salmonella*, *Shigella*, *Klebsiella*, or *Chlamydia trachomatis* infections.

Evidence suggests that the endosymbiont bacterium of *Onchocerca volvulus*, *Wolbachia wuchereria*, may stimulate the pathogenic inflammation responsible for river blindness. Could *Wolbachia* also influence in whom *W. bancrofti*-associated lymphatic filariasis develops, potentially opening new therapeutic avenues to prevent this disease? Recently a bacterium has been found that infects a cell's mitochondria. Recognizing that the mitochondrion is the source of a cell's energy we may begin to wonder whether one or more debilitating human diseases has such an etiology.

Infectious agents produce long term effects that include acute infection, persistent active infection, persistent nonreplicating (latent) infection, immune response to an infectious agent that may not commonly be pathogenic, and malignant transformation. Tissue damage or DNA integration explain certain chronic sequelae, but an inflammatory immune response also defines many infectious causes of chronic diseases, including some cancers. Inflammation also drives many chronic conditions that are classified as autoimmune or immune-mediated, e.g., systemic lupus erythematosus, rheumatoid arthritis and Crohn's disease. Innate and adaptive immunity play critical roles in the pathogenesis of these syndromes. Hence, inflammation is a potential link between infectious agents and chronic diseases. Aberrant cellular and humoral responses to infections could be the basis of going from infection to long-term sequelae.