*Commentary*

# HIV necessary though not sufficient for AIDS

*Man's mind cannot grasp the causes of events in their completeness, but the desire to find those causes is implanted in man's soul. And without considering the multiplicity and complexity of the conditions any one of which taken separately may seem to be the cause, he snatches at the first approximation to a cause that seems to him intelligible and says: "This is the cause!"*

Leo Tolstoy
*War and Peace*, 1869

Does HIV cause AIDS? Does an infectious agent or high cholesterol cause heart disease? Does Epstein-Barr virus (EBV) cause lymphoma? Prevention of chronic diseases – cancers, cardiovascular diseases, autoimmune disorders – continue to stump public health leaders partly because of contradictory scientific findings regarding infectious agents, genetics, diet and behavioural issues. One might consider interactions of risk factors or cofactor theories when studying the etiology of chronic diseases (see table 1).

In the 19th century, John Snow, Ignaz Semmelweis, Louis Pasteur, Robert Koch, and other clinicians and researchers developed and conclusively proved the germ theory of disease causation. The acceptance of the "single agent, single disease" concept led to the sciences of infectious diseases and microbiology, and to the prevention, control, and even elimination of many previously baffling and devastating illnesses. In the 20th century, Peyton Rous, Alfred Evans, and others proposed multifactorial causes of cancers and other diseases (Rous 1965; Evans and Muller 1990; Dahlquist

**Table 1.** Hypotheses – Etiology of selected diseases.

| Featured infectious agent(s) | Disease | Cofactor(s) |
|---|---|---|
| EBV | Non-Hodgkin's lymphoma | PCBs, pesticides, hair dyes |
| EBV | Burkitt's lymphoma | Malaria, nitrosamines |
| EBV | Nasophyaryngeal cancer | HLA genotype |
| Enteroviruses | Type 1 diabetes mellitus | Genetics, nitrosamines, breastfeeding |
| HBV and HCV | Hepatocellular carcinoma | Aflatoxin, alcohol, *Schistosoma japonicum* |
| HHV-6 | Multiple sclerosis | Other viruses, neurotoxic agents |
| HHV-8 | HIV-Related Kaposi's sarcoma | HIV, nitrite inhalants |
| HHV-8 | Other forms of KS | Immunosuppressants, diet |
| HPV-16, 18 | Cervical cancer | Smoking, tar-douches, wood/coal-burning cooking, HSV-2, *Chlamydia trachomatis* |
| HPV-5, 8, 17 | Skin cancers | Sunlight, radiation, genetics |
| Influenza B/VZV | Reye's syndrome | Salicylates, enzyme deficiencies |
| Bacteria | | |
| *Chlamydia pneumoniae* | Coronary artery disease/Stroke | Genetics, diabetes, HBP, obesity, cholesterol, CMV |
| *Helicobacter pylori* | Stomach cancer | Alcohol, smoked fish, dietary nitrosamines, genetics |
| *Mycobacterium tuberculosis* | Reactive tuberculosis | HIV, substance abuse, diabetes, silicosis, immunosuppressants, malabsorption, ESRD |

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; ESRD, end stage renal disease; HBP, hypertension; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigens; HPV, human papillomavirus; HSV-2, herpes simples virus 2; KS, Kaposi's sarcoma; PCBs, polychlorinated biphenyls; VZV, varicella zoster virus.

*et al* 1991; Ferrara *et al* 2000; Haverkos *et al* 2000; Donati and Jacobson 2002; Ming *et al* 2002). Intellectual curiosity and open-mindedness are needed in the 21st century to identify the interactions among multiple factors associated with chronic diseases.

Co-carcinogenesis is not a new concept. Peyton Rous and colleagues explored such an interaction in the 1930s and consistently produced squamous cell skin cancers after exposing rabbit ears to tars and Shope papillomavirus (Rous and Kidd 1938). These experiments led to the concept of "initiation and promotion" as an etiology for cancer.

The mechanisms by which salicylates, varicella zoster virus (VZV)/influenza B viruses, and genetic errors of metabolism interact to produce Reye's syndrome are still not clear. However, publicizing the association of aspirin with this syndrome during the febrile prodrome led to a marked decrease in its occurrence (Rennington *et al* 1986). This public health success story resulted from epidemiologic investigations considering a multifactorial cause of disease.

The natural history of AIDS begins with gradual onset of immune dysfunction due to HIV infection and is followed by one or several latent or newly acquired infectious cofactors, such as *Pneumocystis carinii* and *Mycobacterium tuberculosis* that produce disease. The striking epidemiology of AIDS-related Kaposi's sarcoma (KS) suggests that HIV, HHV-8, and one or more additional factors associated with the "gay" lifestyle act in concert to produce the sarcoma (Osmond *et al* 2002). The possibility that cofactors may be "co-responsible" for other HIV-related illnesses, such as wasting syndrome, lymphomas, and lipodystrophies, should be entertained.

Leo Tolstoy may have pointed clinical scientists in the right direction. In this age of specialization, identifying the interaction of pathogens represented by different scientific disciplines will be difficult. However, delineating the web of causation of chronic diseases could lead to effective strategies for prevention and treatment of diseases that appear uncontrollable today.

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*Note*: The opinion and assertions herein are the author's private views and not to be construed as official or reflecting the views of the Food and Drug Administration.