Table 1 Henle-Koch Postulates (1840)

1.	The parasite occurs in every case of the disease in question and under circumstances which can account for the pathological changes and clinical course of the disease.
2.	It occurs in no other disease as a fortuitous and nonpathogenic parasite.
3.	After being fully isolated from the body and repeatedly grown in pure culture, it can induce the disease anew.

Derived from Evans, A. S., *Yale J. Biol. Med.*, 49, 175, 1976.

II. BACKGROUND

Perhaps the most widely known formal conceptualization of epidemiologic analysis, the Bradford Hill postulates, arose from the long-running debate over a question first posed nearly 50 years ago: is there a causal relationship between cigarette smoking and carcinoma of the lung? Early studies by Dorn[1] and later by Doll and Hill[2] stimulated much controversy.

Similar criteria for inferring causality, however, have existed for at least a century and a half. Historically, that early set of causality postulates was developed in 1840 by Swiss anatomist Jakob Henle and elaborated upon by his student Robert Koch, the famed German physician, pathologist, and bacteriologist. Their combined efforts, presented in public lectures by Koch in 1884 and 1890, are known as either the Henle-Koch or Koch postulates (see Table 1).

Even as the Henle-Koch postulates were being promulgated, it was clear that their strict, overly deterministic rules would limit their utility.[3] For example, researchers were unable to transmit some diseases (e.g., typhoid fever, leprosy) to experimental hosts, and unable to isolate and culture any infective agents at all in other diseases. The asymptomatic carrier state violates the second Koch postulate. These limitations resulted, for the most part, from the era's limited scientific technology, incapable of dealing with nonbacterial diseases. The discovery of viruses in 1930 further demonstrated the limitations of the Henle-Koch postulates. American virologist Thomas Rivers showed that the Henle-Koch postulates literally cannot be applied to viruses, which require living tissue for propagation and cannot be grown in pure cultures.

In the 1950s, Robert J. Huebner incorporated Henle-Koch and Rivers in his "Bill of Rights for Prevalent Viruses".[3] His intent was to apply reasoning arising from legal scholarship to scientific research, trying thereby to avoid subjecting microorganisms to guilt by association. Furthermore, he stressed that his suggestions should be regarded not as "postulates" but merely as useful guidelines.

In the last several decades, continued technological innovations, such as electron microscopy, molecular genetics, and immunology, have revealed disease to be a complex interaction among broadly defined agent, host, and environment. As the intricacy of these multifactorial conditions is uncovered, Henle-Koch and its descendants are less and less relevant to the concept of causation.

In 1968, virologist Werner Henle (Jakob's grandson), his wife Gertrude, and German physician Volker Diel claimed that Epstein-Barr virus, or a close relative, caused infectious mononucleosis. They used seroepidemiologic techniques rather than isolating a causative agent or reproducing the disease anew in an animal model.

Table 2 Elements of Immunological Proof of Causation

1. Antibody to the agent is regularly absent prior to the disease and to exposure to the agent (i.e., before the incubation period).
2. Antibody to the agent regularly appears during illness and includes both IgG- and IgM-type antibodies.
3. The presence of antibody to the agent indicates immunity to the clinical disease associated with primary infection of the agent.
4. The absence of the antibody to the agent indicates susceptibility to both infection and the disease produced by the agent.
5. Antibody to no other agent should be similarly associated with the disease unless it is a cofactor in its production.

Derived from Evans, A. S., *Yale J. Biol. Med.*, 49, 175, 1976.

Table 3 Surgeon General's Report (1964)

1. The consistency of the association
2. The strength of association
3. The specificity of the association
4. The temporal relationship of the association
5. The coherence of the association

Derived from Surgeon General, Advisory Committee of the U.S. Public Health Service, PHS Pub. No. 1103, Public Health Service,Washington, D.C., 1964.

Table 4 Bradford Hill Postulates (1965)

1. Strength of association
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

Derived from Hill, A. B., *Proc. R. Soc. Med.*, 58, 295, 1965.

Such studies have resulted in the promulgation of immunological criteria of causation[3] (see Table 2).

While infectious disease research became ever more complex, epidemiology also turned its attention to noninfectious chronic diseases. Clearly, the Henle-Koch postulates are inappropriate to chronic diseases, which have become the primary concern of environmental epidemiology. Recognizing this fact, the 1964 Surgeon General's Report on Smoking included a set of causality criteria[4] (see Table 3).

As noted at the beginning of this section, the Bradford Hill criteria[5] emerged from the extended debate over the causal relationship between cigarette smoking and lung cancer (see Table 4). Supporters of the tobacco industry and others have criticized study design, sampling, research protocols, results, and conclusions of the research; this scrutiny has encouraged epidemiologic researchers to delineate the philosophical and logical underpinnings of causality research.