

Commentary I

Interaction and evolution in epidemiology

Dr. Rothman is professor of epidemiology at the Department of Epidemiology and at the Division of Preventive Medicine, Department of Medicine, Boston University School of Medicine

Zhang et al. (2004) have traced the evolution of epidemiologic concepts through the “fossil record” of selected textbooks, one of which is my 1986 book, *Modern epidemiology* (Rothman 1986). I would like to report that it feels better to be the author of a fossil than to be a fossil oneself, however fine that distinction may be – but some might argue with my premise.

Paradoxically, history seems to shorten as time progresses. When I began to study epidemiology at Harvard at the tail end of the 1960s, the text that we used was the 1960 book *Epidemiologic methods* by MacMahon, Pugh & Ipsen. Today this text is more than 40 years old, considerably older than Greenwood’s (1935) text was in the 1960s. Although not on the list of Zhang et al. (2004), *Epidemiologic methods* was a clear and incisive compendium of cutting edge epidemiologic concepts. It was superseded in 1970 by a substantial revision, *Epidemiology: principles and methods*, authored by MacMahon & Pugh. The 1970 revision is on the list of books described by Zhang et al. (2004).

At about the time that the MacMahon & Pugh 1970 text was published, I was beginning to search for possible thesis topics for my doctoral dissertation in epidemiology. In my searching I came across a 1965 paper by Keller & Terris entitled “The association of alcohol and tobacco with cancer of the mouth and pharynx”. Both alcohol and tobacco have causal effects on mouth cancer. These effects were mutually confounded because the two exposures were correlated. In their 1965 paper, Keller & Terris considered confounding between alcohol and tobacco, but did not address the question of possible interaction between the two causes. It was the issue of biologic interaction that first drew me into a concerted inquiry into epidemiologic concepts and methods.

The 1960 book by MacMahon, Pugh & Ipsen makes no mention of interaction, but by 1970, MacMahon had added a reference to Lancelot Hogben’s description of the interaction

between genes and environment (quoting Hogben’s 1932 William Withering Memorial Lectures of the University of Birmingham, which were published in 1933 as *Nature and nurture*). Even so, the topic of interaction had barely been broached by epidemiologic teachers and writers. To conceptualize interaction, to proceed to evaluate it from epidemiologic data, and to distinguish it from other multivariable issues, required a synthesis of diverse epidemiologic topics, many of which were themselves in their early stages of development. These topics included causation, effect estimation, confounding, study design and analytic methods. Layered over these subjects was a fog of confusion caused by the fact that in statistics, the term “interaction” was often used in a sense that did not correspond to a singular, meaningful concept of biologic interaction.

Although I ultimately chose a different project for my epidemiology doctoral thesis, I did proceed to collaborate with Andrew Keller and to write a paper (1972) in which we proposed that interaction should be measured as a departure from additivity of effects, and in which we discussed the quantification of the risk of mouth cancer attributable to the interaction between alcohol and tobacco. My subsequent pursuit of this topic prepared me for *Modern epidemiology*, which I began to write a decade after the collaboration with Keller.

Today, knowledge of the core issues that drew me into the field of epidemiology has grown far beyond the more primitive levels of several decades ago. The field has also surged from having but a handful of textbooks to scores of useful texts. The hindsight provided by Zhang et al. (2004) in their review of selected epidemiology textbooks clarifies how many of the fundamental concepts have crystallized during the century in which epidemiology came of age.

Kenneth J. Rothman

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Address for correspondence

Prof. Kenneth J. Rothman
715 Albany Street
Boston, MA 02118 USA
e-mail: KRothman@bu.edu



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