# History and Impact of Nutritional Epidemiology[1–3]

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**ABSTRACT**

The real and important role of epidemiology was discussed, noting heretofore unknown associations that led to improved understanding of the cause and prevention of individual nutritional deficiencies. However, epidemiology has been less successful in linking individual nutrients to the cause of chronic diseases, such as cancer and cardiovascular disease. Dietary changes, such as decreasing caloric intake to prevent cancer and the Mediterranean diet to prevent diabetes, were confirmed as successful approaches to modifying the incidence of chronic diseases. The role of the epidemiologist was confirmed as a collaborator, not an isolated expert of last resort. The challenge for the future is to decide which epidemiologic methods and study designs are most useful in studying chronic disease, then to determine which associations and the hypotheses derived from them are especially strong and worthy of pursuit, and finally to design randomized studies that are feasible, affordable, and likely to result in confirmation or refutation of these hypotheses. *Adv. Nutr. 5: 534–536, 2014.*

As large databases from epidemiology studies become more available and papers using their large amount of information proliferate, there is a tendency for conclusions of those papers to achieve the status of answers rather than as the lead point for prospective studies to confirm or refute the associations suggested by epidemiologic methods. In this setting, it seemed appropriate to review the contributions that epidemiology made to the knowledge base in nutritional sciences to better understand the role of the plethora of papers in nutritional epidemiology that now fill our journals.

Dr. Alpers introduced the session by explaining the above rationale for the session. He pointed out that randomized controlled trials (RCTs) are the gold standard in clinical research and that these would be preferred for nutritional studies. However, there are difficulties in using foods or nutrients as interventions in RCTs. These difficulties include having the wrong proportion of food intake assigned to the diet, testing the wrong dose of nutrient, getting the duration of intervention wrong, intervening too late to alter the natural history of the disease under study, and not being able to correct for confounding factors, among which are lifestyle biases, genes, environmental effects on genes, or nonnutrient constituents of foods. For these and other reasons, data on the effect of diets or nutrients in chronic disease are dependent on observational studies to produce associations and derive hypotheses for additional testing. Such studies can be very useful, but when individual nutrient intervention were used to confirm hypotheses, the results did not in general confirm the implications from the associations identified in observational studies. Confirmation was found using whole diets or dietary patterns (e.g., Mediterranean) or whole food classes (e.g., whole grains), but the individual nutrients responsible for the confirmed observations found with food are not known. This symposium includes talks that use examples from the history of the field of nutritional epidemiology to demonstrate when epidemiology led to considerable advances but also to note the areas in which this methodology was not so successful and to exercise caution in the interpretation of the resulting associations.

Dr. Carpenter was unable to attend, but his talk was interpreted by Dr. Bier, who spoke on the "Historical Role of Epidemiology in Identifying Essential Nutrients." He expanded on Dr. Carpenter's selected example of the successful use of epidemiology in the discovery of the cause and prevention of beriberi. In his historical exposition, Dr. Carpenter chose to highlight the less well known story of Hamilton Wright, who studied beriberi in Malaya, then a British colony. Wright recognized that Malaya was an optimal location to study beriberi because the country was

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inhabited by 3 Asian populations whose different environmental conditions and habits might provide clues to the origin of the disease. He noted that, although Chinese brought in to work in the tin mines commonly developed beriberi, native Malays and Tamils imported from Sri Lanka did not. However, when imprisoned in a multiracial prison, all were similarly susceptible to the disease. Among other differences identified in the free-living populations, he realized that the Chinese ate "Siam" (white) rice and the Tamils ate "Bengal" (parboiled) rice. However, based on his medical training, including the recently appreciated germ theory of disease, and the limits of nutritional knowledge at the time, Wright persisted in his belief that the disease was caused by an unknown organism that entered the body by mouth with subsequent gastrointestinal production of a toxin responsible for the signs and symptoms of beriberi. Shortly thereafter, Dr. W. L. Braddon realized that Wright's interpretation was mistaken and that the disease was a dietary disease. He recognized the importance of the fact that the Chinese ate Siam rice and that parboiling (Bengal) rice afforded protection against beriberi. He further appreciated that, although Malays ate Siam rice, it was often consumed freshly after winnowing. Thus, although he realized that beriberi was dietary in origin, he interpreted his findings as an indication of a toxin present in the rice. Understanding how to prevent the disease required a prospective experiment, then performed by Walter Fletcher, the senior physician at the Insane Asylum in Kuala Lumpur, where a beriberi outbreak had just occurred. Dr. Fletcher did not believe Dr. Braddon's hypothesis, so he decided to test it by feeding inmates in 1 building Siam-style rice and in another building parboiled rice, cooked in the Tamil way. He found that 18 of 120 individuals fed Siam-style rice died compared with 0 of 120 fed Tamil rice. Fletcher rightly attributed the advantage as showing that white rice was deficient in a "dietetic value." The irony of these findings was that, because of the poor medical communications of the time, the British experiments took place after earlier studies nearby in Asia already demonstrated the essential role of nutrient-deficient rice in the pathogenesis of the disease. In Japan, Kenehiro Takaki appreciated that kakké (beriberi) was the consequence of a rice diet, although he attributed the problem to protein deficiency, and Christiaan Eijkman in Indonesia, after an exhaustive series of experiments to eliminate alternative explanations possible from the observational data, came to the realization that the rice pericarp "silver skin" contained something essential for health. Although he did not identify the factor as thiamine, he shared in the Nobel Prize for this work that progressed from the observations on ingested rice to an identification of the source of the material that treated the disease. Dr. Bier concluded by noting that epidemiologists, clinical scientists, and chemists in this discovery process acted as collaborators, not rivals, but that the unraveling of the dilemma took time and studies in the field had to be designed to answer the hypothesis first established by epidemiologists.

Dr. Donald McCormick followed by speaking on the role of epidemiology in decision making for food fortification, using examples of many micronutrients. He initiated the discussion by noting that food fortification has clear benefits for certain portions of the population and, as examples, used folate addition to foods to aid pregnant women in preventing deficiency and lowering the incidence of neural tube defects in the fetus and vitamin D added to milk to prevent rickets. However, he noted the increasing tendency for the false expectation that food fortification at amounts higher than needed to prevent deficiency might decrease nondeficiency diseases. These expectations are often initiated by epidemiologic studies. The data with folate supplements and their role in preventing colorectal cancer are mixed, showing an inhibitory effect in individuals who are folate deficient but a promoting effect on the progression of established neoplasms. Similarly, the benefit suggested for vitamin D by epidemiologic studies in conditions as diverse as cancer and heart disease has yet to be confirmed by prospective RCTs. When there is no evidence of deficiency, current RDA amounts of intake should suffice for most people. However, the difficulty in defining and agreeing on a biochemical definition of the deficiency state continues to plague the field of micronutrients (e.g., vitamins B-12 and D) and led to additional confusion about how to translate the findings from epidemiologic studies into prospective trials that will provide definitive answers.

Dr. Anthony Miller then addressed the role of epidemiology in identification of foods and nutrients that influence the risk of cancer. He first discussed study designs beginning with correlative/ecologic studies. They further include case-control studies in which biases need to be recognized and cohort studies in which recognition of misclassification is important. Finally, intervention studies designed to confirm observed associations from the first 2 study types often use surrogate endpoints to detect premalignant changes, but when cancer is the endpoint in a study of finite length, the length of follow-up and timing in regard to natural history becomes very important. A number of non-interventional studies were reviewed initially, demonstrating that increased total calories were associated with increased risk of cancer but showing rather little specificity for specific macronutrients or food components. Although some studies demonstrated a reduced risk with increased intake of fiber or vegetable and fruit, other studies did not confirm these associations. The best associations continue to reflect cancer risk that is increased by higher caloric intake or decreased risk when following a total diet, such as the Mediterranean diet. Interventional studies, exemplified by β-carotene and vitamin A supplementation, mostly failed to reduce risk. The current period of increased interest in genetics was discussed, noting that multiple single-nucleotide polymorphisms in genes were tested for their association with cancer risk and that small effects were seen that need replication. These may indicate individual susceptibility, but in addition, these studies tend to ignore the effects of dietary factors. Thus, the role of cancer prevention by dietary

change may have been downgraded in the recent literature. Dr. Miller concluded that improved calibration of nutrient intake improved our recognition of associations but that misclassification of dietary intake (e.g., red meat, fiber) impaired our ability to detect causal associations, if they truly exist. He also concluded that the effects of dietary patterns need to be pursued and that we not be misled or sidetracked by genetic associations, each of which may account for only a small portion of the cancer risk in a population-based study. This is important, because cancer risk seems to be increasing as a function of increased weight/obesity, but it is not certain whether this is all due to increased caloric intake or whether individual dietary components play a role.

Dr. Paul Jacques in his discussion of "The Relevance of Nutritional Epidemiology in the 21st Century" provided additional historical examples of successful confirmation of observational hypotheses with a focus on foods and dietary patterns and noted 1 future direction for the discipline. He reviewed the data on an association between ingestion of whole wheat and favorable health outcomes in diabetes and cardiovascular disease and the resulting interventional studies that confirmed the benefit of ingesting whole-grain foods. He followed this with the data on the Mediterranean-style dietary pattern, again confirmed by interventions on the incidence of diabetes and cardiovascular disease. These examples demonstrated the consistency between the evidence provided by the observational studies and intervention trials. However, as reviewed in cancer outcomes by Dr. Miller, clear epidemiologic data on the role of individual nutrients is more difficult to obtain. Thus, Dr. Jacques noted that 1 direction for the future of nutritional epidemiology was to use metabolomics to identify metabolites (not nutrients) associated with the individual foods and dietary patterns and by quantifying their potential to uncover diet–disease relations in populations. He concluded that, although traditional approaches continue to provide valuable knowledge about the cause of chronic diseases, new technologies will be essential to maximize the impact of epidemiology in the future.

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