Nutrition and Cancer, 66(6), 1077–1082

ISSN: 0163-5581 print / 1532-7914 online
DOI: 10.1080/01635581.2014.927687

Routledge
Taylor & Francis Group

COMMENTARY

Untold Nutrition

T. Colin Campbell
Division of Nutritional Sciences, Cornell University, Ithaca, New York, USA

Nutrition is generally investigated, and findings interpreted, in reference to the activities of individual nutrients. Nutrient composition of foods, food labeling, food fortification, and nutrient recommendations are mostly founded on this assumption, a practice commonly known as reductionism. While such information on specifics is important and occasionally useful in practice, it ignores the coordinated, integrated and virtually symphonic nutrient activity (wholism) that occurs *in vivo*.

With reductionism providing the framework, public confusion abounds and huge monetary and social costs are incurred. Two examples are briefly presented to illustrate, the long time misunderstandings (1) about saturated and total fat as causes of cancer and heart disease and (2) the emergence of the nutrient supplement industry. A new definition of the science of nutrition is urgently needed.

Nutrition has long been viewed through the lens of reductionism, which focuses on parts instead of the whole. The vast majority of experimental studies have focused on individual nutrients, their structural identities, their mechanisms of action and their effects on specific outcomes. This strategy has served the purpose of sharpening the message about functions of individual nutrients but, far too often, these findings are not synthesized into a whole food context.

The activities of individual nutrients—often determined in laboratory (in vitro) experiments—are substantially modified upon consumption. Nutrients interact with each other and with other chemicals in food, both during intestinal digestion and absorption and after, during their metabolism and tissue distribution. Nutrient functions also vary with nutrient dose and these relationships, however defined they may be under static conditions, can readily change within microminutes of time. The proportion of nutrients digested, absorbed, transported, metabolized, and stored or excreted during these stages constantly changes. Collectively, these varying activities affect ultimate function that makes it virtually impossible to know how much of a nutrient in food, itself only an estimate, is needed at the functional site.

Even though estimates of dose-response behaviors for individual nutrients may be useful under many circumstances, they are limited to the conditions of the observational period, especially when nutrients are evaluated in isolation. In spite of these limitations, we still conduct experimental research and inform ourselves about nutrition by assuming activities of individual nutrients. The nutrient composition of foods is described and displayed as the amounts of individual nutrients and health claims often focus on the kind, amount, and presumed functions of individual nutrients, as in food labeling, food fortification, and health claims. This myopic focus on individual nutrients rather than food, which may be called reductionism, is costly, both in dollars spent and in lives lost. I will cite two prominent examples of reductionism (among many) to illustrate the problem created by assuming that single nutrients, upon consumption, act independently.

The first is the vitamin supplement industry, now running at $32 billion annually, according to a 2011 industry report (1). Its modern day history started in the mid-1980s after it got a marketing boost in 1976 with the Proxmire Amendment of the food and drug regulations. This legislation permitted food companies to sell vitamins and minerals without a doctor's prescription (2). The industry also got a scientific boost from the publication of the 1982 National Academy of Science (NAS) report on Diet, Nutrition and Cancer (3) that set goals of using a lower fat diet (<30%) and the consumption of more fruits, vegetables, and grains based on their nutrient contents. Although this NAS expert committee based their goals in reference to the nutrient contents of foods, they explicitly cautioned that these goals applied to whole foods, not to the individual nutrients contained therein, as in nutrient supplements. Still, the emerging vitamin supplement industry at that time ignored the warning and claimed otherwise, landing them in a 3-year administrative court hearing before the U.S. Federal Trade Commission. Being a witness on behalf of the NAS to those hearings, I saw firsthand the intense, well-funded effort by the industry to argue that the NAS goals referred to individual nutrients, thus supporting their efforts to develop nutrient supplements for the marketplace (4). Now, 20–30 years later, a large number of randomized clinical trials

Submitted 20 May 2014; accepted in final form 21 May 2014.
Address correspondence to T. Colin Campbell, Jacob Gould Schurman Professor Emeritus of Nutritional Biochemistry, Division of Nutritional Sciences, Cornell University, Ithaca, NY 14850. Phone: 607-533-9156. E-mail: tcc1@cornell.edu

have been undertaken to test the efficacy of these supplements and the results have been found wanting (5–9)

Summaries, which mostly represent meta-analyses of more than 100 trials and hundreds of thousands of experimental subjects, overwhelmingly show no long-term benefit for vitamin supplements, along with worrisome findings that certain vitamins may even increase disease occurrence for diabetes (5, 9), heart disease (6, 7), and cancer (7). Supplementation with omega-3 fats also was said to have no long-term benefits, even posing increased risk for diabetes (8, 9). More worrisome is the fact that these findings, first appearing more than 10 years ago, have had no discernible effect on their market. The public desire for quick fixes through pills (i.e., reductionism) is overwhelming, especially when money can be made. The activities of individual nutrients observed in carefully controlled research conditions will not necessarily be the same, at least quantitatively, when these nutrients are consumed in the form of whole food.

A second example of nutritional reductionism has a lifetime of many decades. Total dietary fat (as well as dietary cholesterol and saturated fat) has long been considered a major cause of cardiovascular disease (10, 11) and some cancers (12–14), culminating in major policy recommendations to reduce its intake (3, 15, 16). This conviction has had major implications far beyond what may be known to the casual observer. This story began about a century ago with experimental animal studies that mistakenly and mysteriously concluded that fat was a primary cause of these diseases. Some, but not all, of this early research, conducted by German and Russian scientists, certainly indicated that dietary fat elevated serum cholesterol and arteriosclerotic lesions [as reviewed by Kritchevsky (17)], but these findings were somewhat equivocal and inconsistent until the 1920s when it was shown that protein was a much more important cause of atherosclerosis than dietary fat (18–20). These 1920s studies also showed that serum cholesterol was not the cause of heart disease and, further, that dietary cholesterol had little or no effect on serum cholesterol (19).

Somewhat later, additional insight emerged when it was animal-protein [especially casein (21, 22) but also lactalbumin (23)] not plant-based protein that increased serum cholesterol and enhanced development of early heart disease. This casein effect was substantial, being about 5 times greater than the soy protein effect (21, 22). A substantial cholesterol-lowering effect of soy protein also was shown in human studies (24), and subsequently in still more human studies, as reviewed by a soy industry consultant (25). Eventually, this cholesterol-lowering effect of soy was judged to be an acceptable claim by the FDA in 1999 (26).

When it was shown that soy protein decreased serum cholesterol in rabbits by 70-80% (21, 22) [as reported by Kritchevsky (23)] and in humans by as much as 30–40% (27), it was called a cholesterol-lowering (hypocholesterolemic) effect by soy, a marketable idea. But this observation also could just as easily have been said to be a cholesterol-increasing (hypercholesterolemic) effect of animal protein (especially casein). In doing so, the soy protein effect would have been considered an indication of a natural, healthy condition promoted by plant proteins in general, whereas the casein effect would have indicated an unnatural, unhealthy condition. Therefore, during that history, it is animal protein that should have been labeled as the main cause of increased serum cholesterol and heart disease, not total fat, animal fat, and/or cholesterol.

A very similar story can be told for the association of dietary fat with cancer, especially cancers of the breast (28) and colon (29). Dietary fat as a cause of cancer became a leading hypothesis at a conference in Miami, Florida, and published in the November 1975 issue of *Cancer Research*. Also, the previously mentioned NAS 1982 report on diet, nutrition and cancer (3) suggested as their first-listed goal a reduction of dietary fat to 30% of total calories. Thereafter, several other public policy reports also made similar recommendations to decrease fat consumption (15, 30–32).

The association of fat with breast cancer in population-based studies was especially impressive (Fig. 1) (33). However, this oft-cited paper (33) also showed that this association of total dietary fat with breast cancer (Fig. 1A) was explained by the consumption of saturated fat (Fig. 1B) (typically found in animal-based foods), not polyunsaturated fat (Fig. 1C) (typically found in plant-based foods). Essentially the same dietary fat associations exist for colon and prostate cancers as well (34).

I find these opposing associations of animal and plant fat diets with breast cancer (Fig. 1A–1C) to be especially revealing. Animal fat—thus also total fat—is highly correlated with animal protein ($r = 0.94$), according to a large database on food and health for different countries (35). This impressive association therefore suggests that dietary animal protein could be an equally important cause of cancer, similar to the conclusion drawn for the association of animal protein with heart disease discussed above. And because chronic degenerative diseases typically common to Western industrially developed countries are substantially correlated with each other (29, 36, 37), this interpretation is likely to apply to these other diseases as well. An association of protein with cancer is consistent with experimental animal reports from the 1940s and 1950s showing animal protein to promote development of cancers of various sites (38–40).

Similarly, in a long series of laboratory animal experiments in my laboratory, the animal-based protein, casein, proved to be a powerful promoter of primary liver cancer initiated either by a powerful chemical carcinogen (41–48) or by a viral carcinogen (49, 50). Increasing dietary casein above recommended protein levels (~10% of diet calories) dramatically promotes tumor formation (~100% of experimental animals) (41), whereas switching to diets containing low dietary protein (~10% of diet calories) reverses cancer development (~0% of experimental animals) (42, 48). A series of many experiments

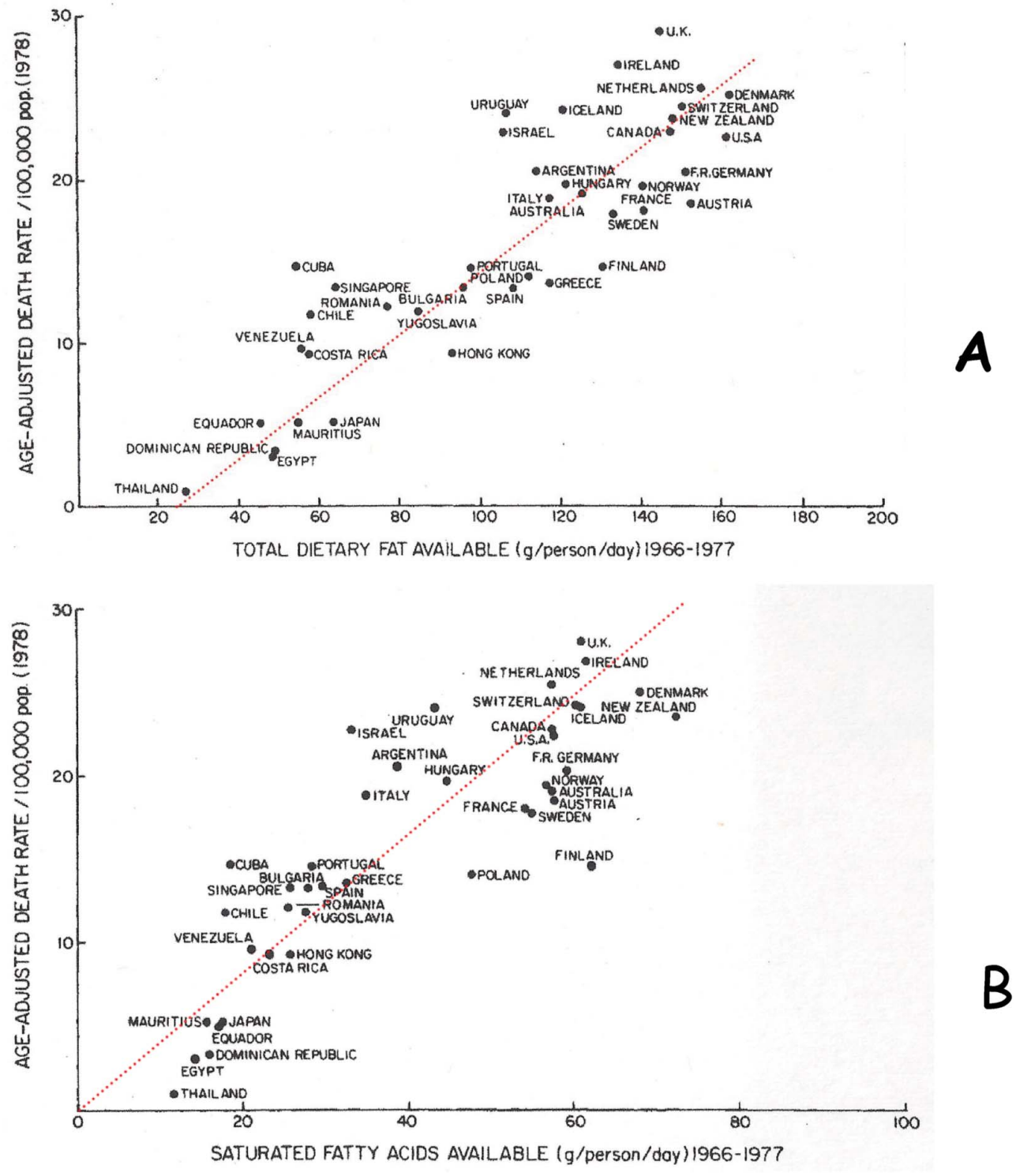

FIG. 1. Correlations of age-adjusted breast cancer mortality with total dietary fat (A), saturated fat (B) and polyunsaturated fat (C). Regressions are eyeball, based on authors findings that total fat (A) and saturated fat (B) were significantly correlated with breast cancer mortality while polyunsaturated fat (C) was not correlated. This figure is reprinted from Carroll et al. (33). From Carroll KK, Braden LM, Bell JA, and Kalamegham R: Fat and cancer. *Cancer* 58, 1818–1825, 1986. Copyright © 2006 by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc. (*Continued*)

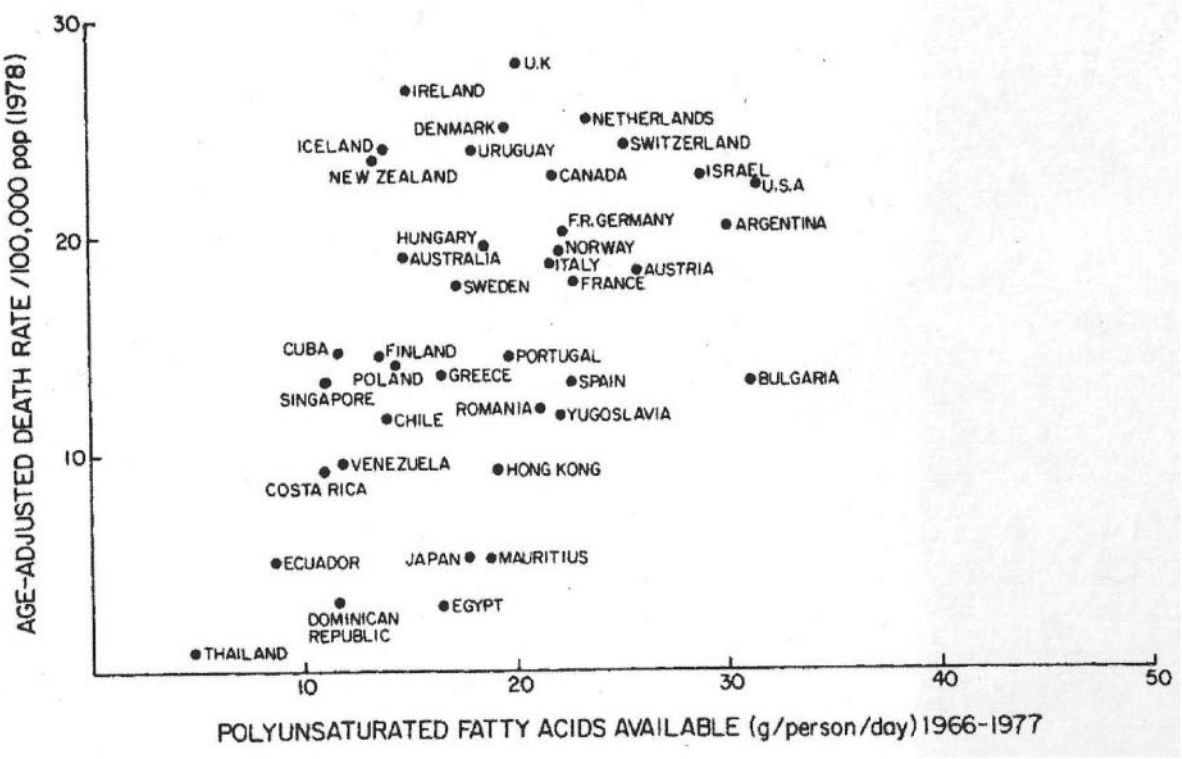

FIG. 1. (Continued)

on this protein effect illustrated a multimechanistic and highly integrated network of metabolic reactions converging to produce the outcome (42, 44, 51–59). This evidence is more than sufficient to qualify casein, when fed in excess of the recommended level of protein (i.e., the RDA equivalent) as the most significant chemical carcinogen ever identified—either this is the conclusion or the expensive, highly reductionist government-sponsored bioassay program for determining chemical carcinogens (60) as important causes of human cancer should be abandoned.

In short, an important role for animal-based protein in cancer causation has long been overshadowed in favor of the false hypothesis that it was total fat and especially animal-based fat (mostly saturated fat) that causes these diseases (28, 33).

Searching for specific nutrients as independent causes of heart disease, cancer, and related diseases has been a routine assumption and practice of long standing, which causes more confusion than clarity. First, it is the combined, integrated effects of all nutrients that is far more relevant than the independent effects of individual nutrients. Second, in the examples cited here, although it is acceptable to choose a few nutrients as indicators of a total diet (as with antioxidants or dietary fiber indicating plant-based foods or saturated fat favoring animal-based foods), choosing saturated fat either as a primary causal factor or as an indicator of a high risk dietary pattern has proven to be very misleading.

It is not that fat or protein or other individual nutrients do not have independent and direct-acting properties that could contribute to increased or decreased disease risk. This is important information provided by reductionist research. But this information should not be used out of its context. It should be used to help explain the larger environment of which it is a part and to which it contributes.

Early during the history of heart disease, a choice was made in favor of fat instead of protein as a (or "the") principle cause of this disease. This choice has survived for almost an entire century, becoming embedded in our collective consciousness. The correct choice should have been animal-based protein, not as a single nutrient causing heart disease or cancer but, more importantly, as a marker of a diet that causes these diseases.

This is a highly significant and relevant observation because diets ever richer in animal protein-based foods also are ever more deficient in plant-based foods. This exchange assumes, of course, that total food or calorie consumption is mostly a zero-sum game. Plant-based foods in the whole food form are far, far richer in antioxidants, complex (natural) carbohydrates, and vitamins while also having lower and more appropriate concentrations of protein and fat. This dietary pattern sets up a broad and worthy hypothesis involving very complex causes (e.g., plant-based foods) and outcomes that offer a frame of reference for interpreting detailed and

mechanistic findings of reductionist research. These detailed findings inform us of the biochemical properties of the participating nutrient parts, which either support or deny such a broad hypothesis, thus helping us to understand the healthful properties arising from the wholeness of food and dietary lifestyles.

I believe that focusing on the properties of isolated nutrients beyond their whole food context is more akin to pharmacology; considering whole foods containing countless nutrient-like substances that act within a natural context describes nutrition; and limiting our thinking to out-of-context parts considers only the threads of a tapestry, not the tapestry itself.

Trying to understand nutrition from a perspective of its parts as if they were acting independently explains why nutrition is so confusing for so many people, professionals included. Within this scenario, choosing which specific nutrients or nutrient combinations are responsible for hypothetical cause-effect relationships offers a long list of choices whose interpretive analyses are likely to be much more subjective. Without a biologically plausible context, we risk becoming entrapped in trying to understand the meaning of nutrient parts instead of the whole diet, or even the whole dietary lifestyle. Nutrition, if and when it is understood as a wholistic (spelling intended) phenomenon, only then can its real meaning be understood and applied.

REFERENCES

1. Lariviere D: Nutritional supplements flexing muscles as growth industry. *Forbes*, 2013 Apr 18. Available from: http://www.forbes.com/sites/davidlariviere/2013/04/18/nutritional-supplements-flexing-their-muscles-as-growth-industry/.
2. Anonymous: *CODEX and Dietary Supplements. Frequently Asked Questions*. (2010).
3. Committee on Diet Nutrition and Cancer: *Diet, Nutrition and Cancer*. National Academy Press, Washington, DC, 1982.
4. United States Federal Trade Commission: *Complaint Counsel's Proposed Findings of Fact, Conclusions of Law and Proposed Order* (Docket No. 9175). Report No. 9175 Washington, DC: United States Federal Trade Commission, 1985.
5. Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, et al.: Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer:systematic review. *Brit Med Journ* **332,** 752–760, 2006.
6. Morris CD and Carson S: Routine vitamin supplementation to prevent cardiovascular disease: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Internal Med* **139,** 56–70, 2003.
7. U.S. Preventive Services Task Force: Routine vitamin supplementation to prevent cancer and cardiovascular disease: recommendations and rationale. *Ann Internal Med* **139,** 51–55, 2003.
8. Kaushik SV, Mozaffarian D, Spiegelman D, Manson JE, and Willett W: Long-chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus. *Am J Clin Nutr* **90,** 613–620, 2009.
9. Djousse L, Gaziano JM, Buring JE, and Lee I-M: Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. *Am J Clin Nutr* **93,** 143–150, 2011.
10. Keys A: Coronary heart disease in seven countries. *Circulation* **41** (Suppl.), I1–I211, 1970.
11. Keys A: The diet/heart controversy. *Lancet*, 844–845, 1979 Oct 20.
12. Carroll KK: Experimental evidence of dietary factors and hormone-dependent cancers. *Cancer Res* **35,** 3374–3383, 1975.
13. Higginson J: Present trends in cancer epidemiology. *Proc Can Cancer Conf* **8,** 40–75, 1969.
14. Wynder EL and Shigematsu T: Environmental factors of cancer of the colon and rectum. *Cancer* **20,** 1520–1561, 1967.
15. National Research Council & Committee on Diet and Health: *Diet and Health: Implications for Reducing Chronic Disease Risk*. National Academy Press, Washington, DC, 1989.
16. Select Committee on Nutrition and Human Needs, U.S. Senate: *Dietary Goals for the United States, 2nd ed*. Washington, DC: U.S. Government Printing Office, 1977.
17. Kritchevsky D and Czarnecki SK: Dietary protein and experimental atherosclerosis: early history. In *Animal and Vegetable Proteins in Lipid Metabolism and Atherosclerosis: Vol. 8. Current Topics in Nutrition and Disease*, Gibney MJ and Kritchevsky D (eds.). Alan R. Liss, Inc., New York, NY, 1983, pp. 1–7.
18. Newburgh LH and Clarkson S: Production of athersclerosis in rabbits by diet rich in animal protein. *JAMA* **79,** 1106–1108, 1922.
19. Newburgh LH and Clarkson S: The production of arteriosclerosis in rabbits by feeding diets rich in meat. *Arch Intern Med* **31,** 653–676, 1923.
20. Clarkson S and Newburgh LH: The relation between athreosclerosis and ingested cholesterol in the rabbit. *J Exp Med* **43,** 595–612, 1926.
21. Meeker DR and Kesten HD: Experimental atherosclerosis and high protein diets. *Proc Soc Exp Biol Med* **45,** 543–545, 1940.
22. Meeker DR and Kesten HD: Effect of high protein diets on experimental atherosclerosis of rabbits. *Arch Pathology* **31,** 147–162, 1941.
23. Kritchevsky D, Tepper SA, Czarnecki SK, Klurfeld DM, and Story JA: Effects of animal and vegetable protein in experimental atherosclerosis. In *Current Topics in Nutrition and Disease: Vol. 8. Animal and Vegetable Proteins in Lipid Metabolism and Atherosclerosis*, Kritchevsky D and Gibney MJ (eds.). Alan R. Liss, Inc., New York, NY, 1983, pp. 85–100.
24. Sirtori CR, Noseda G, and Descovich GC: Studies on the use of a soybean protein diet for the management of human hyperlipoproteinemias. In *Current Topics in Nutrition and Disease: Vol. 8. Animal and Vegetable Proteins in Lipid Metabolism and Atherosclerosis*. Kritchevsky D and Gibney MJ (eds.). Alan R. Liss, Inc., New York, NY, 1983, pp. 135–148.
25. Messina M and Messina V: The role of soy in vegetarian diets. *Nutrients* **2,** 855–888, 2010.
26. U.S. Food and Drug Administration: *Soy Protein and Coronary Heart Disease*. Washington, DC: Food and Drug Administration, Health & Human Services, 1999.
27. Sirtori CR, Agradi E, Conti F, Mantero O, and Gatti E: Soybean-protein diet in the treatment of type II hyperlipoproteinemia. *Lancet* **1,** 275–277, 1977.
28. Carroll KK, Gammal EB, and Plunkett ER: Dietary fat and mammary cancer. *Can Med Assoc Journ* **98,** 590–594, 1968.
29. Wynder EL: The epidemiogy of large bowel cancer. *Cancer Res* **35,** 3388–3394, 1975.
30. United States Department of Health and Human Services: *The Surgeon General's Report on Nutrition and Health*. Superintendent of Documents, U.S. Government Printing Office, Washington, DC, 1988.
31. World Cancer Research Fund/American Institute for Cancer Research: Food, Nutrition, and the Prevention of Cancer: A Global Perspective. American Institute of Cancer Research, Washington, DC, 1997.
32. World Health Organization: *Diet, Nutrition and the Prevention of chronic Diseases: Report of a Joint WHO/FAO Expert Consultation*. Geneva, Switzerland: World Health Organization, 2003.
33. Carroll KK, Braden LM, Bell JA, and Kalamegham R: Fat and cancer. *Cancer* **58,** 1818–1825, 1986.

34. Rose DP, Boyar AP, and Wynder EL: International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, and per capita food consumption. *Cancer* **58,** 2363–2371, 1986.
35. Armstrong D and Doll R: Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* **15,** 617–631, 1975.
36. Campbell TC, Chen J, Brun T, Parpia B, Qu Y, et al.: China: from diseases of poverty to diseases of affluence. Policy implications of the epidemiological transition. *Ecol Food Nutr* **27,** 133–144, 1992.
37. Rose DP: Dietary factors and breast cancer. *Cancer Surveys* **3,** 671–687, 1986.
38. Hawrylewicz EJ: Fat-protein interaction, defined 2-generation studies. In *Dietary Fat and Cancer*, Ip C, Birt DF, Rogers AE, and Metlin C (eds.). Alan R. Liss, Inc., New York, NY, 1986, pp. 403–434.
39. Hawrylewicz EJ, Huang HH, Kissane JQ, and Drab EA: Enhancement of the 7,12-dimethylbenz(a)anthracene (DMBA) mammary tumorigenesis by high dietary protein in rats. *Nutr Reps Int* **26,** 793–806, 1982.
40. Hawrylewicz EJ, Huang HH, and Liu J: Dietary protein enhancement of N-nitroso-methylurea-induced mammary carcinogenesis, and their effect on hormone regulation in rats. *Cancer Res* **46,** 4395–4399, 1986.
41. Madhavan TV and Gopalan C: The effect of dietary protein on carcinogenesis of aflatoxin. *Arch Path* **85,** 133–137, 1968.
42. Appleton BS and Campbell TC: Effect of high and low dietary protein on the dosing and postdosing periods of aflatoxin B1-induced hepatic preneoplastic lesion development in the rat. *Cancer Res* **43,** 2150–2154, 1983.
43. Appleton BS and Campbell TC: Dietary protein intervention during the post-dosing phase of aflatoxin B1-induced hepatic preneoplastic lesion development. *J Natl Cancer Inst* **70,** 547–549, 1983.
44. Dunaif GE and Campbell TC: Relative contribution of dietary protein level and Aflatoxin B_1 dose in generation of presumptive preneoplastic foci in rat liver. *J Natl Cancer Inst* **78,** 365–369, 1987.
45. Schulsinger DA, Root MM, and Campbell TC: Effect of dietary protein quality on development of aflatoxin B1-induced hepatic preneoplastic lesions. *J Natl Cancer Inst* **81,** 1241–1245, 1989.
46. Youngman LD: *Recall, memory, persistence, and the sequential modulation of preneoplastic lesion development by dietary protein*. M.S. Thesis, Cornell University, Ithaca, NY, 1987.
47. Youngman LD: The sustained development of preneoplastic lesions depends on high protein diets. *Nutr Cancer* **18,** 131–142, 1992.
48. Youngman LD and Campbell TC: Inhibition of aflatoxin B1-induced gamma-glutamyl transpeptidase positive (GGT+) hepatic preneoplastic foci and tumors by low protein diets: evidence that altered GGT+ foci indicate neoplastic potential. *Carcinogenesis* **13,** 1607–1613, 1992.
49. Cheng Z, Hu J, King J, Jay G, and Campbell TC: Inhibition of hepatocellular carcinoma development in hepatitis B virus transfected mice by low dietary casein. *Hepatology* **26,** 1351–1354, 1997.
50. Hu J, Cheng Z, Chisari FV, Vu TH, Hoffman AR, et al.: Repression of hepatitis B virus (HBV) transgene and HBV-induced liver injury by low protein diet. *Oncogene* **15,** 2795–2801, 1997.
51. Adekunle AA, Hayes JR, and Campbell TC: Interrelationships of dietary protein level, aflatoxin B_1 metabolism, and hepatic microsomal epoxide hydrase activity. *Life Sci* **21,** 1785–1792, 1977.
52. Bell RC, Golemboski KA, Dietert RR, and Campbell TC: Long-term intake of a low-casein diet is associated with higher relative NK cell cytotoxic activity in F344 rats. *Nutr Cancer* **22,** 151–162, 1994.
53. Bell RC, Levitsky DA, and Campbell TC: Enhanced thermogenesis and reduced growth rates do not inhibit GGT+ hepatic preneoplastic foci development. *FASEB J* **6,** 1395, 1992.
54. Hayes JR, Mgbodile MUK, Merrill AH Jr, Nerurkar LS, and Campbell TC: The effect of dietary protein depletion and repletion on rat hepatic mixed function oxidase activities. *J Nutr* **108,** 1788–1797, 1978.
55. Horio F, Youngman LD, Bell RC, and Campbell TC: Thermogenesis, low-protein diets, and decreased development of AFB1-induced preneoplastic foci in rat liver. *Nutr Cancer* **16,** 31–41, 1991.
56. Mgbodile MUK and Campbell TC: Effect of protein deprivation of male weanling rats on the kinetics of hepatic microsomal enzyme activity. *J Nutr* **102,** 53–60, 1972.
57. Nerurkar LS, Hayes JR, and Campbell TC: The reconstitution of hepatic microsomal mixed function oxidase activity with fractions derived from weanling rats fed different levels of protein. *J Nutr* **108,** 678–686, 1978.
58. Preston RS, Hayes JR, and Campbell TC: The effect of protein deficiency on the in vivo binding of aflatoxin B_1 to rat liver macromolecules. *Life Sci* **19,** 1191–1198, 1976.
59. Youngman LD and Campbell TC: High protein intake promotes the growth of preneoplastic foci in Fischer #344 rats: evidence that early reemodeled foci retain the potential for future growth. *J Nutr* **121,** 1454–1461, 1991.
60. National Toxicology Program: *Report on Carcinogens*, 12th ed. US Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC, 2011.