Classic examples of vitamin deficiency diseases are scurvy, rickets, beriberi, and pellagra. However, evidence over the past several decades clearly shows that suboptimal intakes of some vitamins and minerals may contribute to risk for some chronic diseases, including major causes of mortality and morbidity such as cardiovascular disease, cerebrovascular disease, cancer, osteoporosis, and hypertension. On the other hand, consuming excess amounts of vitamins and minerals may be deleterious in some circumstances. At the opposite end of clear deficiency is overt toxicity, but there could also be adverse effects in a range that does not produce clear toxicity, but that in the long-term, could be deleterious to health in more subtle ways.

This chapter will provide an overview of the major established or highly suspected associations between vitamins and minerals and the development and prevention of major chronic disease states. Unlike the establishment of a clear deficiency state and reversal of the condition, such as vitamin C to cure scurvy, studying the relationship between the range of vitamins and minerals and chronic diseases is fraught with many difficulties. Thus, the relationships are likely to generate less consensus and more scientific controversy. Nonetheless, a large body of evidence is currently available for many of the relationships, and sensible recommendations to optimize benefit while minimizing risk can be made. However, as science and research evolve, and the strength of evidence for a specific relationship waxes and wanes, these recommendations will also evolve. In addition, new relationships are likely to be discovered, and these could alter existing recommendations.

In the first part of this chapter, the major research approaches utilized in this field will be summarized, and the major strengths and limitations will be addressed. Then, specific nutrient-disease relationships will be discussed. This chapter will only examine vitamins and minerals for which there are a sufficient amount of human data for effects of long-term, suboptimal intakes and a major health consequence. The classic vitamin deficiency syndromes will not be reviewed. The focus will be on studies in which apparently healthy individuals are followed, and the influence of specific vitamins and minerals is studied before a disease occurs. Whether these nutrients influence the course of an existing disease will not be addressed in this chapter. In the final section, recommendations will be made.
Research Approaches

Three factors make study of vitamin/mineral and chronic disease difficult to conduct and interpret. First, chronic diseases typically develop over a long time period. For example, colorectal cancer may develop 40 years or more after the initial carcinogenic insult. In contrast, for the classical vitamin deficiency diseases, reversal of the conditions occurs a very short time after the administration of the active compound. Secondly, chronic diseases involve multiple factors. Unlike scurvy, which is only caused by vitamin C deficiency, chronic diseases have multiple factors involved, which often interact. Moreover, nutrients tend to interact with other nutrients and factors, and thus may be beneficial or deleterious only under specific conditions. For example, a specific nutrient may only be relevant for individuals who have a certain behavior, such as those who smoke cigarettes or drink alcohol, or who are deficient in another nutrient, or who have a genetic susceptibility. The importance of a particular factor may vary across populations depending on the constellation of co-factors.

To establish a benefit of a nutrient, human studies are required. Animal studies may in some cases be quite complementary in understanding mechanisms and biologic plausibility, but metabolic differences among species, and sometimes even among individuals within the same species, make it infeasible to base recommendations strictly on animal data. While many subtleties exist in the design and conduct of human studies of nutrient-disease associations, two critical distinctions are most important to consider. First, it is important to note whether the study is based on a randomized design or is observational, and second, among observational studies, whether the study design is prospective or retrospective. In principle, causality of an association can only be established using a randomized design, in which the exposure of interest or a placebo is randomly assigned to study subjects. Thus, if an association is observed, it can be attributed strictly to the compound, assuming adequate statistical power and execution of the study. In observational studies, we observe an association between a certain factor and an outcome, for example, vitamin C and cancer risk, but because the vitamin C is based on the subjects’ self-selected diet, confounding factors could potentially account for the association. Well-designed observational studies are those that are designed to best account for confounding factors. One of the important factors that influences reliability in observational studies is whether information is collected prospectively or retrospectively relative to the disease outcome. If the disease has occurred prior to collection of exposure information, as in a case-control study, the likelihood for biased and unreliable results is typically increased.

Although in principle, randomized controlled studies are the gold standard, these studies are expensive and difficult to conduct. In fact, chronic diseases are known to have a relatively long period for development, and most randomized trials conducted are typically only over a period of several years. Thus, if an observational study that assessed diet for a 20-year period provides an apparently conflicting answer from a randomized trial conducted over a 3-year period, the differences in results could be because the results from the observational study are biased, or that the randomized trial was not conducted for a sufficient time. Of course, many other factors could have