Back to the Future

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The past predicts the future. Improving health through changing foods and behavior is a continuum that started over four centuries ago.

Diet, Lifestyle, and Disease

A recent article in the *New England Journal of Medicine* (Diabetes Prevention Program Research Group, 2002) reported that diet and lifestyle were twice as effective as pharmaceutical therapy in preventing adult-onset diabetes in a high-risk population. Controlled dietary intervention to reduce caloric intake plus exercise reduced the incidence by 58%.

Type-2 or adult-onset diabetes, formerly called non-insulin dependant diabetes, is a serious and costly disease affecting 8% of adults in the United States. Sixteen to 17 million Americans now have type-2 diabetes, which consumes 10% of the national healthcare budget. Considering that the healthcare budget is a trillion and a half dollars, diabetes is more costly than many other problems combined.

The April 2002 issue of *Science* magazine contained a series of fascinating articles on the puzzle of complex diseases. The article by Walter C. Willett at the Harvard Medical School, Department of Epidemiology and Nutrition, showed that genetic and environmental factors, including diet and lifestyle, contribute to cardiovascular disease, cancer, and other major causes of mortality (Willett, 2002). Not all of these diseases are genetic in origin, many of them—probably the majority—are diet and/or lifestyle or environmental in nature. Lifestyle modifications can significantly reduce the incidence of four major diseases without medication: colon cancer, stroke, coronary heart disease, and type-2 diabetes, which cost us treasure and life productivity. The article also discussed the relationship between HDL cholesterol, the relative risk

of heart attack and alcohol-dehydrogenase genotype. The risk is higher for a person with the slow isozyme form of alcohol dehydrogenase who has more than one drink per day compared to someone who doesn't drink who has the fast form of the isozyme. Therefore, if you know what your genotype is, you can modify your diet to affect your expected clinical outcome—you can reduce your disease risk with a diet/lifestyle intervention. The basis of pharmacogenomics is that everyone responds differently to a drug and, in the same way, people respond differently to alcohol. It is said that one glass of red wine a day will reduce your chance of a heart attack—but, the effect may depend on your genotype.

Historical Perspective

The future of agriculture, food, and medicine lies along this pathway. By knowing our genotype, the content of the food we eat, including micronutrients, and metabolic pathways, we will have a better understanding of how to modify lifestyle to improve our health.

A book on the vitamins was published in the 1920s, when people were beginning to understand that some dietary components are essential. Vitamins are organic molecules that function in a wide variety of capacities within the body and are essential for health. There are two categories: water-soluble and fat-soluble. Polish scientists coined the term vitamin in 1911. In 1933, vitamin D was added to milk, introduced by the Borden Company to prevent rickets. By 1948, all thirteen essential vitamins had been isolated, and most were synthesized. In 1949, the essential amino acids were defined after a long and tortuous discovery process. One publication dates back to 1788, by William Stark who discovered that scurvy was diet-related. Stark, a physician, studied the effects of various dietary regimens upon himself. Keeping accurate records, he induced diseases in himself, and then observed the effects of eating certain foods. He died at the age of 29 with a serious case of scurvy, after depriving himself of vitamin C for a long period of time.

How we understand diet, health, and micronutrients thus has a long history. One manuscript, a treatise on the derivation of rickets, has a publication date of 1651 (in London by the College of Physicians). In 1922, vitamin D was isolated and used to treat rickets. In 1923 it was found that sunlight would substitute for vitamin D, and also could be used as treatment. Through the next 10 or 20 years, vitamin D became a supplement in our food, in butter and cheese and other dairy products, and bread. In 1911 the Morton Salt Company started adding magnesium carbonate to salt to make it flow even when it's raining, and the slogan was adopted in 1914, "When it rains, it pours." In the upper midwest in 1905, physician David Marine, while studying iodine levels in the great lakes, made the correlation between people who drank iodine-deficient water and goiter. He experimented with iodine supplements to treat goiter. Around 1920, iodine was first added as a salt supplement, and the Food and

Figure 1. Nicolai Tulp's treatise *Observationes Medicae*.

Drug Administration, in its early days, approved the language, "This salt provides iodide, a necessary nutrient."

In his book *The Jungle*, Upton Sinclair drew national attention to shocking conditions in the meat-packing industry, which led to the 1906 Meat Inspection Act and greatly improved the quality of meat supply in this country. In 1911, Proctor and Gamble introduced Crisco® for cooking, which, over the years, largely replaced animal fats and butter for cooking foods. It probably was the start of the long, slow trend toward getting saturated fats out of the diet. In 1914, Joseph Goldberger published a book on therapy for pellagra, a B-vitamin deficiency (Goldberger, 1914). He described experiments that would be unethical today: diets of various compositions were given to people in orphanages and prisons to determine who got what disease and then various types of food were supplied to try to correct deficiencies.

The first clinical descriptions of beri-beri were by Dutch physicians, Bontius and Nicolai Tulp, in the seventeenth century. The frontispiece of Tulp's treatise, *Observationes Medicae*, showed an individual with the disease (Figure 1), which is also caused by a deficiency of B vitamins. In the 1800s Christiaan Eijkman made the observation that individuals in Indonesia eating white rice developed lameness. At the same time he was observing chickens, inadvertently fed white rice, which also were lame. When switched to brown rice, which contains B vitamins in the bran, the chickens recovered. His experiments with Indonesians confirmed recovery from beri-beri with brown rice in the diet.

Clearly, clinical experiments on diet and lifestyle intervention go back a long way. In the 1920s, vitamin A was found and named by George Wald, who also discovered its importance for vision, for which he was awarded the Nobel Prize in 1967. During that time, concepts of food safety were changing, and sanitation laws were passed largely as a result of Upton Sinclair's book. Food became safer, water purer, and life spans increased.

In the 1920s, George Whipple did some beautiful experiments on anemia. He took blood from dogs until they were severely anemic, then provided various diets: some were fed corn, some soybeans, some meat and muscle, and others liver. Those fed liver regenerated hemoglobin most rapidly. He determined that hemoglobin will return to normal in 8 weeks, but no more quickly than 8 weeks, whatever the initial level of hemoglobin. There is a certain set regeneration time as long as iron is not limiting in the diet. From this research, we developed iron therapy: eat liver to be healthy. This was a major milestone in understanding how food can affect human health, for which Whipple won the Nobel Prize for physiology and medicine in 1934. In the 1940s, as people went off to war, calcium and iron and vitamins were added as supplements to bread.

In the mid-1920s, Otto Rohwedder launched the bread-slicing machine after many setbacks. In 1928 the Peter Pan peanut butter company observed that the introduction of sliced bread greatly increased the consumption of peanut butter.

In 1929, when Popeye cartoons were introduced, spinach consumption dramatically increased, particularly among children.

Clarence Birdseye, born in the 1880s, attended Amherst and majored in biology but never finished. Instead he took a job as a naturalist in the Arctic. While fishing there, he observed that fish froze instantly on the ice and, when thawed, tasted just as good as fresh. He started Birdseye Frozen Foods, and, little by little, learned that many of the micronutrients and proteins are stable when kept frozen. The effects of Birdseye's discovery are probably among the most profound of the twentieth century.

Diet and Health

In the 1920s, a publication described heart disease as the leading cause of death in the United States. In 1953, Ancel Keyes showed the correlation between coronary heart disease and diets high in animal fats.

An article in the May 2002 issue of *Science* magazine discussed how green tea can reduce fatty accumulation in the liver, and therefore reverse some of the chronic effects of alcoholism (Anon, 2002). For the past few years claims have been made that green tea prevents cancer and cardiovascular disease, and an article in the May 2002 edition of *General Dentistry* suggested that green tea can prevent oral cancers (Hsu, 2002).

There was a meeting in May, 2002, at the NIH—"Conjugated Linoleic Acids, Research, Current Status, and Future Directions"—sponsored by many of the major divisions of the NIH: nutrition research, diabetes and digestive kidney diseases, national heart/lung, national cancer, and the office of dietary supplements. The CLAs are a group of several linoleic acids called octadecanoic acids, which are essential fatty acids. They are present in animal products; dairy cows that graze on grass have 500% more CLAs in their milk than do cows given other types of feed. Conjugated linoleic acids may be among of the most potent cancer-fighting substances in our diet. They may delay the onset of adult diabetes, and have also been shown to reduce body fat in people who are overweight. So, this isn't only just a crop issue, it's an animal issue as well.

It appears that CLAs may be involved in gene regulation. In the future, foods may be designed to "dial up" a level of gene expression, depending on our genotype and disease.

Genomics and Health

The understanding of one plant genome leads to a similar understanding of many others. Likewise, a simple understanding of a genome of one vertebrate can lead to a similar understanding in many others. Recently, the genome of rice was published, providing information about barley, oats, sorghum and corn, and even grass in your front yard. When you study the fruit-fly genome, it tells you about 40% or 50% of the human genome. The same applies with worms like *Caenorhabditis elegans*.

It doesn't take a genius to figure out that the various citrus fruits not only share a common genetic backbone, but are nearly identical. Understanding one teaches you nearly everything about the other. Understanding the fruit fly teaches us about the mouse.

We are rapidly approaching a time when we will understand the food genomes, and what's in our milk, and how animal metabolism produces beneficial compounds like CLAs. We will understand also how genes that encode antioxidants, vitamins, and other constituents are regulated. With an integrated approach, we will better understand how supplements and functional and medical foods affect disease.

The Future

And we are rapidly approaching a time when farming with an "F" will also be done with a "Ph," but foods for health will go beyond that. Food can be manipulated in many ways using traditional technologies as well as by genetic engineering. Infectious disease is an important component of food safety, and Francisco Diaz, a professor of food science in the University of Minnesota College of Agricultural, Food and Environmental Sciences, has found that dietary changes directly before slaughter dramatically reduce the carriage rate of *Escherichia coli*.

There is also a political side to this. If you are in a policy position and suggest eating less red meat, you can be sure that animal commodity groups will be on your telephone tomorrow morning. If you say eat less sugar, sugar-beet growers will be on the telephone. And if you recommend applying more fertilizer to increase crop yields, someone from the Gulf of Mexico will say, "What about my dead zone?" It's a complicated issue, with profound implications for the future. It will probably be possible to eliminate much of the major economic and suffering diseases with changes in food and lifestyle. The questions that we must face are: "Can we do it?" "Should we do it?" "What will be the consequences of our actions?"

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