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translating NUTRITION INNOVATION INTO PRACTICE

Translational nutrition is a means of shortening the path between discoveries in nutrition and their application to benefit both society and the food industry.

The global impact of diet-related noncommunicable diseases, such as obesity, diabetes, and cardiovascular disease makes nutrition research urgent. It is imperative to speed up the translation of public health needs for diets that deliver improved health into priorities for nutrition research and, conversely, to apply breakthroughs in research as quickly as possible to help alleviate the global burden of nutrition-related diseases. The timely application of new scientific discoveries or insights into health benefits is a key outcome of the field of study called translational science.

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An Emerging Field

Translational science is a rapidly emerging field that works in two ways: from research to practice and from practice to research. In the former, its purpose is to make new scientific knowledge available and actionable to society. Ideally, scientific research should move rapidly from the laboratory to the benefit of consumers. In the latter, its purpose is to identify research priorities by recognizing the key scientific gaps in nutrition knowledge, crafting research funding priorities to address these gaps, and recruiting research involvement across numerous scientific fields to nutrition-related problems.

Institutes or programs in **translational medicine** have been established at Pennsylvania, Columbia, Washington, and other universities in the United States, in recognition of the need to accelerate the processes by which basic science is applied to improvements in human health—from the detection of risk, through diagnosis, to novel strategies to cure diseases.

Because translational medicine bridges the interface between science and medicine, medical schools and university hospitals are crucial settings where physician-scientists can bridge the gap between medical research and clinical practice. For example, radiologists at the Lucas Center at Stanford University have developed a novel technology to image the patterns and velocity of blood flow through the heart and aorta. Visualization of blood flow can predict when blood vessels may rupture and aid in making decisions for surgical intervention (http://med.stanford.edu/patient_care/translational).

Stanford University is translating this novel technology into improved patient care by implementing it directly into clinical practice. This implementation required the commitment of both scientific researchers to discover and validate the underlying principles and industrial partners that could bring the technologies of NMR imaging into practice.

Translational nutrition is a multidisciplinary endeavor involving nutrition science, food science, and health science, all underpinned by basic life sciences and requiring clear communication. The parallels between the rapidly emerging fields of translational medicine and translational nutrition are numerous, and their successes are complementary.

Nutrition is traditionally a science dedicated to understanding the relationship between diet and health and translating it into solutions for both cure and prevention (Figure 1). Preventing nutrient deficiencies involves many of the basic elements of life sciences research, federal and local regulatory agencies, and the agriculture industry. Many such solutions have been implemented, e.g., the addition of iodine to table salt and the addition of folate to breakfast cereal.

Failure to recognize the complexities of the translational process in nutrition can, however, produce problems, even when relatively mature scientific knowledge is addressed. The essentiality of folic acid was established early in the 20th century; but it was only in 1996 that the potential of low folate status to affect the susceptibility of infants to develop neural tube defects was addressed by fortification of grain products in the U.S. This example and others highlight the challenges and importance of translational science to nutrition: the more complex the relationship is between nutrients, or nutrient imbalances, the more difficult is the implementation of a solution. Also, communication plays an essential part in the acceptance of the solution, and the right communication is not always self-evident.

Examples of Translational Nutrition

The idea that history repeats itself is generally regarded as a truism. Therefore, it is at best unfortunate when people do not use history to avoid making mistakes in the future. Understanding why mistakes have been made in the past, or, conversely, where appropriate actions have led to success, can be a powerful way to generate opportunities for success in the future. Therefore, it is pertinent to explore cases where translational nutrition has been successful and cases where there has been failure to translate effectively.

• **Rapid Translation: *Trans* Fats.** The process of chemical hydrogenation of plant oils to produce stable, functionally superior vegetable fats was developed in the late 19th century and was rapidly industrialized to margarines and shortenings as less-expensive substitutes for the more-expensive animal fats—butter and lard. The presence of *trans* fatty acids—produced by the hydrogenation process—contributed a valuable functionality in oleomargarine and shortenings. Monounsaturated fatty acids with a *cis* double bond are liquid at room temperature, whereas monounsaturated fatty acids with a *trans* double bond are solid fats.

When research began to identify saturated fatty acids and animal fats as contributing to the elevation of plasma cholesterol, the lower proportions of saturated fatty acids in the hydrogenated vegetable fats was marketed as a nutritional advantage. During this period of rapid growth in the use of vegetable shortenings and margarines, no human clinical research was published to challenge the assumption that *trans* fatty acids did not adversely affect blood lipids. Margarines and shortenings were widely assumed to be healthier alternatives to animal fats.

The view of *trans* fatty acids as a positive, or at worst neutral, contributor to blood lipoprotein cholesterol was changed forever when Mensink and Katan (1990) reported that the consumption of *trans* fatty acids by normal humans raised LDL and lowered HDL. An important aspect of this study was that the investigators used experimental oils containing *trans* fatty acids at high concentration. Rather than end a controversy, however, this study ignited one. While nutrition and health scientists called for the removal of *trans* fatty acids from foods, vegetable oil

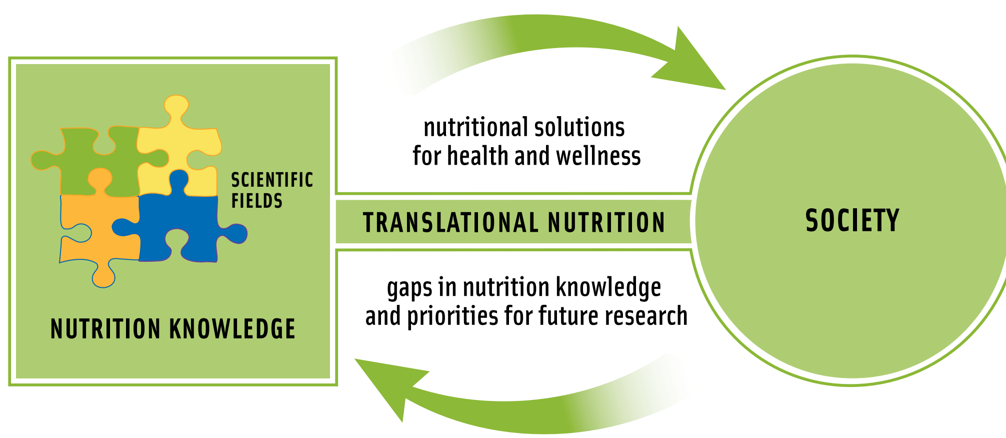


Figure 1. *Nutrition knowledge comes from a variety of scientific disciplines. The art of good translation is in integrating this knowledge, making it accessible to society, and identifying future research that will benefit society.*

manufacturing interests attacked the study as being meaningless because of the disproportionately high content of *trans* fatty acids in the experimental diet.

The controversy could have continued for years but for the study by Zock and Katan (1992) that repeated ostensibly the same clinical trial but at approximately half the *trans* fatty acid content. If the effect of *trans* fatty acids on lipoprotein metabolism required a high intake to be deleterious, then feeding at a lower level would have shown no effect on LDL and HDL. However, the study documented that the effects of a lower *trans* fatty acid intake were linearly related to the prediction of the earlier paper. Clearly, at whatever intake, *trans* fatty acids had an effect on lipoprotein metabolism that could not be discounted.

From that point forward, *trans* fats became the subject of increasing calls for regulation. In 2003, Denmark banned the use of all hydrogenated fats from food products, but made an explicit exception allowing the use of animal fats containing natural *trans* fatty acids, as these were viewed as chemically different. In 2006, mandatory labeling of all *trans* fats irrespective of source went into effect in the U.S. While it is too early to conclude unequivocally, the use of *trans* fats obtained by chemical hydrogenation is rapidly disappearing from the industrial food supply.

• **Slow Translation: Plant Sterols.** Petersen (1951) published the first report that plant sterols lowered plasma cholesterol in chickens. Further studies in the 1950s repeatedly showed cholesterol lowering by plant sterols in chickens, rabbits, and humans. During this time, it was also shown that the initial level of hypercholesterolemia was related to the magnitude of the decrease in serum cholesterol, with greater reductions being associated with higher baseline serum cholesterol levels (Pollack, 1953).

Early food preparations of plant sterols were not very palatable. Many early studies used a powdered form that, although tasteless, was sticky and chalky. In some studies, the plant sterol preparation was provided to volunteers as a suspension or a tablet. However, even as early as the mid-1950s, some researchers incorporated sitosterol into more-appetizing foods such as biscuits (Barber and Grant, 1955; Leonard, 1956) or candy (Fahrenbach et al., 1958).

By the end of the 1950s and in early 1960, a number of patents were issued relating to the preparation and medical use of sitosterol, the first (Beveridge, 1958) interestingly relating to food enriched with plant sterols.

Oster et al. (1976, 1977) demonstrated for the first time that LDL-cholesterol (as well as total cholesterol) was decreased by plant sterols. This finding is relevant because LDL-cholesterol is an important independent risk factor for coronary heart disease.

In 1957, Eli Lilly started marketing *Cytellin*—a strawberry-flavored, red suspension of predominantly beta-sitosterol—in the U.S. Although the drug was not commercially successful, it remained on the market until the 1980s, and no adverse effects were reported. It was nearly 40 years before the food industry made use of this discovery to bring spreads containing plant sterols to the market. Raisio Group (now Raisio plc) introduced *Benecol* margarine with plant sterols in Finland in 1995. *Benecol* was launched in the U.S. in 1999 by McNeil Consumer HealthCare (now McNeil Nutritionals, LLC). In the same year, Lipton, an operating unit of Unilever, launched *Take Control*, a margarine with plant sterols. Both are still marketed in the U.S. (Figure 2). Since then, numerous other plant sterol-enriched products, including Nestle's milk product, *Omega® Plus*, launched last year in Malaysia, have been introduced to the market (Figure 3).

Figure 2. *Margarines containing plant sterols, such as* Benecol *and* Take Control*, are examples of slow translational nutrition, taking a long time from the discovery of the benefits of plant sterols until products appeared on the market.*

Why the Difference?

Why did *trans* fats disappear so quickly from the food supply in response to their cholesterol-raising properties but plant sterols with cholesterol-lowering properties appear so slowly?

Compared with the good-news story about plant sterols, the bad news about *trans* fat was that a vegetable fat (which is generally accepted as being healthier than animal fat) is not only "bad for you" but actually worse than the animal fat it is replacing. By comparison with the plant sterol story, the *trans* fat story is both dramatic news and bad news. According to the proverb that "bad news travels fast" this bad news that *trans* fatty acids have adverse effects on health will quickly become common knowledge—as indeed, it did.

In addition, the production of *trans* fats by industrial hydrogenation provided a visible target and, even more compellingly, one with a financial vested interest. This made the apparent solution, i.e., stop hydrogenation, both immediately possible and philosophically justifiable.

A key factor that explains the slowness of the food industry to take advantage of the knowledge of cholesterol-lowering by plant sterols was industry's lack of participation at the start (i.e., in the 1950s), specifically the following:

• **Lack of Early Commercial Success.** When plant sterols finally became available in food products, there was an expectation that these products would be commercially successful. However, early sales of *Benecol* and *Take Control* were disappointing. U.S. sales of *Benecol* were only $42 million between May 1999 and August 2000, despite $49 million spent on advertising. Sales of *Take Control* were a mere $13 million during 1999, with $15 million spent on advertising (Hicks and Moreau, 2001).

• **Limited Choice of Food Matrix for Carrying Plant Sterols.** From a food manufacturing perspective, margarine was a relatively easy choice of carrier for plant sterols. This is because the plant sterols can be esterified with vegetable oil and incorporated into margarine without changing the physical properties or flavor of the margarine.

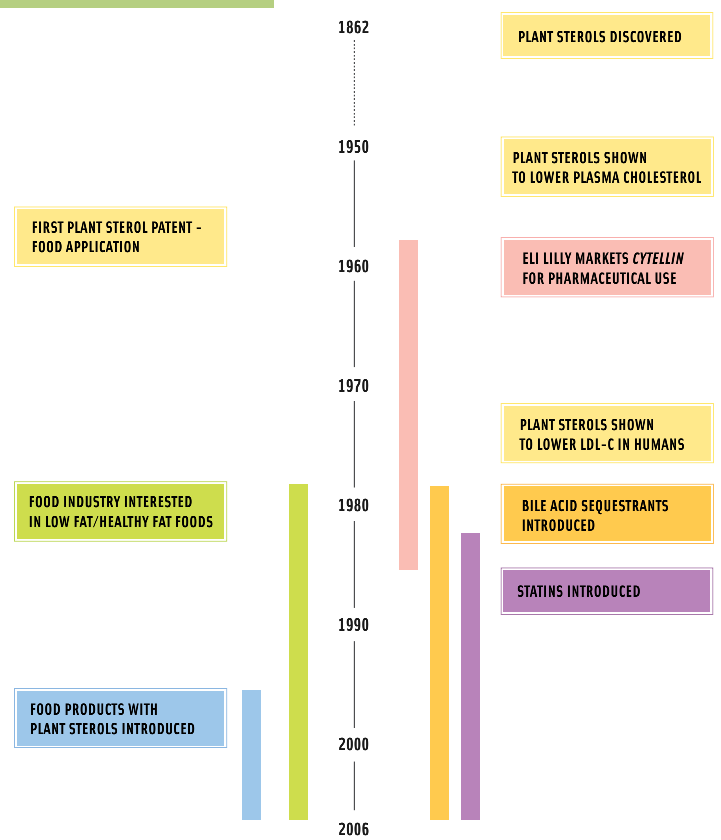
During the 1990s, there were no low-fat foods containing plant sterols. Nestlé achieved success by combining free plant sterols with sorbitan tristearate, and Cargill by developing a micronized form of plant sterols. Cargill's innovation, however, came about 50 years after Tygstrup et al. (1957) first described micronized plant sterols.

• **Competition from Other Food Ingredients.** Consumption of plant sterols is not the only way that consumers can obtain potential heart-health benefits from food. Heart-health benefits are available from a number of everyday foods such as fruits and vegetables, as well as from food ingredients such as oats, whole grains, omega-3 fatty acids, and soy protein. Many consumers are already aware that they can benefit their health by eating foods that are high in these nutrients. However, they require a change in dietary patterns that functional ingredients added to more-familiar products such as margarines do not.

• **Pharmaceutical Success.** In the 1970s and 1980s, new drugs that powerfully lowered LDL-cholesterol were introduced to the market. Consequently, from a medical perspective, the need for foods to deliver cholesterol lowering was not as pressing.

• **Critical Review of the Primary Literature.** By 1967, there were more than 100 publications on the clinical use of sitosterol for cholesterol lowering. Yet, in a review the same year, Abrams and Schwartz (1967) cited only three references, and erroneously wrote that large amounts of sitosterol were needed to lower cholesterol and that treatment must be long term, also making it expensive.»»

Figure 3. *History of plant sterols.*



Before 1990, fewer than 10 review articles touched on the subject of phytosterols and cholesterol lowering. Since 1990, more than 100 reviews have been published on phytosterols and their effects on cholesterol metabolism.

Timely and critical review of the primary literature is becoming a critical step in the translational process.

What Can We Learn from these Cases?

Translational scientists can learn from this recent history by developing an appreciation of the commercial opportunities and barriers to applying science to diet; monitoring new scientific discoveries and evaluating their potential impact on food buying habits and health outcomes; evaluating the potential benefits of novel scientific discoveries relative to the same benefits brought by pre-existing scientific knowledge; anticipating rather than waiting for consumer trends and insights in health; anticipating research in related fields, e.g., breakthroughs in pharmaceutical research; identifying food delivery systems that are compatible with the compounds, their modes of action, and suitability to the benefits and target consumers; critically evaluating the level of evidence and the scientific consensus support; and being aware of the channels through which consumers are educated about nutrition and health.

Benefits of Translational Nutrition

There are numerous benefits of translational nutrition:

• **Speed and Efficacy.** As for medical sciences, nutrition science has been discouragingly slow in translating epidemiological variations in diet-related health into basic research initiatives and similarly slow in translating basic research into public health implementation of these findings into dietary changes in the population.

Early appreciation of the potential for bench studies to bring health benefits could help to speed up all of the multiple steps in bringing innovation into practice. In the case of nutrition, the phytosterols example illustrates the time required using traditional scientific channels to take a basic discovery to a food product with established efficacy. Other examples include long-chain omega-3 polyunsaturated fatty acids and heart attack, probiotics and infant diarrheal disease, etc. In each case, abundant epidemiological data documented the variation in the health condition as a function of diet and illustrated the need to understand the scientific basis of the relationships, to facilitate the matching of diets or food products to appropriate consumers.

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• **Tempering Premature Embracement of New Ideas in Nutrition.** Just as nutrition translation can be used effectively to accelerate scientific application of scientific discoveries, it can also be equally effective in avoiding the premature adoption of new ideas lacking in scientific evidence and consensus.

Some ideas purportedly nutritious are poorly substantiated by science, yet enthusiastic followers of new ideas may appear to be credible, giving rise to "fad" diets or diet "crazes." Consequently, a role for translational nutrition should also be in recognizing where there is insufficient scientific information to support the commercialization of new ideas in nutrition.

• **Reduced Risk of Missed Opportunities.** Translational nutrition provides the opportunity to systematically evaluate the potential of bench discoveries to deliver health benefits and thereby reduce the risk of missing promising applications. Concrete examples of the failure to advance promising medical research findings into practical applications illustrate the opportunity. For example, Ioannidis (2004) reported that of 101 articles published in six prestigious basic research journals between 1979 and 1983, only one had a major

Figure 4. *Translational nutrition for the food industry bridges the gap between nutrition research and business. It fast-tracks the transfer of innovation to consumers and drives forward a strategy for consumer-relevant research.*

impact on clinical practice, with 75% remaining untested in clinical trials. The medical community has taken note, and this is leading to the rising importance of translational medicine.

• **Commercial Opportunities.** Translational nutrition can lead not only to benefits to society but also to those organizations that bring the new knowledge into practical solutions (Figure 4). In the context of nutrition, it is clear that food ingredient manufacturers and food companies have a lot to gain by using translational nutrition to meet consumer needs for health and well-being.

Skills Needed for Translational Nutrition

As stated above, translational nutrition is a multidisciplinary endeavor involving nutrition science, food science, and health science, all underpinned by basic life sciences and requiring clear communication. When successful, this approach will lead to nutrition solutions that could not be readily envisaged using the scientific know-how of any single scientific discipline independently.

If translational nutrition is successful, then consumers should notice more-rapid and better-substantiated advances being made in our scientific understanding of the links between nutrition and health. This in turn should be reflected in more-sophisticated consumer demands on food companies to deliver health benefits.

Leadership in translational nutrition therefore requires an ability to take an integrated view of relevant knowledge, extending from the cell to society. This is not typically how the specialist scientist works. Therefore, a new approach to understanding science is required—one that focuses on integration and application and is delivered through appropriate channels.

Just as there is a lack of scientists trained in translational medicine, there is a lack of scientists trained in translational nutrition. One way to faciltate this training would be for nutrition scientists to have internships/work experience in the agricultural industries such as farming, ingredient manufacturing, food manufacturing, and food retailing. Such on-the-job training is already found in other disciplines such as medicine, engineering, or teaching, where, as part of their training, students spend some time working alongside the professionals.

The translational flow of nutrition information is unlikely to happen by itself. Rather, the failure of current strategies illustrates that this information must be proactively managed, using the skills of scientists who can translate nutrition science into practical outcomes for individuals. **FT**

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