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PERSPECTIVE

Crystal Ball series

Crystal Ball: Walter Willett

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I've been privileged to know, learn from, and work with many wonderful and amazing people throughout my personal and professional life, and the broad area of nutrition is a thread that connects many of them. The Willett family has been dairy farming in Michigan for about 140 years. My father built on this tradition to become a reproduction physiologist and to head the Rockefeller Research Center on dairy genetics in Madison, Wisconsin. Thus, I spent my early years on a research farm and learned how to milk a cow and count motile sperm before I was five. We moved back to Michigan when I was eleven when my father took a faculty position at Michigan State University in the Dairy Department, but unfortunately he died shortly thereafter of a brain tumor. As the oldest of four children, I had responsibility for a large vegetable garden and participated in multiple 4-H vegetable clubs (4-H is an organization for rural youth). I won many blue ribbons for vegetables at our county fair, and one year also won the Michigan contest in vegetable grading sponsored by the National Junior Vegetable Growers Association. The reward was a trip to the national convention in Florida and tours of Florida agricultural systems; this was a great experience as I had not had a chance to travel outside the Midwest before.

Because Michigan State University was close by, I enrolled there and initially majored in physics, in part inspired by a neighbor who was head of that department who also became a surrogate father. I enjoyed math and the rigor of physics, but felt it was too constraining as I had a sense of adventure and wanted to be engaged in a wider world. However, what I learned in my physics studies has continued to be valuable because much of that field is about measurement, assessing measurement error, and careful observation; all of this is at the core of what I have done subsequently. From physics, I transferred to food science in the Agriculture school at Michigan State, which I enjoyed as it connected multiple strands of science with food and global issues. Among the faculty members who challenged my thinking was Georg Borgstrom, who wrote *The Hungry Planet*, which already in the 1960's described the unsustainable stresses that food systems were putting on ecosystems.

Becoming increasingly interested in the connection between food and health, I enrolled in medical school at the University of Michigan. There I took advantage of opportunities to become engaged in nutrition-related projects. Some of this was as a research subject; to save money, four classmates and I rented a four-person apartment and rotated one person to live in the metabolic ward at the University where we were paid two dollars a day to consume controlled diets. Also, I spent one elective period in Tanzania as a visiting medical student; I hugely enjoyed the experience and vowed to return for a longer stay. For another elective, with supervision by faculty members of the University's School of Public Health, a classmate and I conducted a mini-health and nutrition survey in the Potawatomi Indian community in the northern part of Michigan [1]. This was a formative experience in several ways, including that we used a food frequency questionnaire for dietary assessment, previously described by Drs. Stefanik and Trulson in the Department of Nutrition at Harvard School of Public Health. I was impressed that we could collect a substantial amount of dietary data with great efficiency. Also, we found that members of this community had about four times the rate of type 2 diabetes as the general US population. This finding fueled my long-term interest in understanding the reason for this high risk; we suspected the surplus commodity foods distributed to the community might have some role. My medical school years were also at the height of the Viet Nam War, and with classmates we formed a Viet

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Nam study group, held teach-ins, and participated in multiple anti-war activities as our country was clearly conducting an immoral, deceitful, and destructive activity.

For internship and residency in internal medicine I joined the Harvard Medical Service of Boston City Hospital as this combined top level medical science with a commitment to serve a large urban, disenfranchised community. This was a challenging but tremendous experience, and I came to know leaders in medicine and epidemiology who would become mentors and colleagues, and were people who had a larger picture of the determinants of health beyond the tradition medical model. Because of the Viet Nam War, I became a conscientious objector after internship and worked in a neighborhood health center in Boston as an alternative to going to Viet Nam. Because clinic hours were mostly evenings, I was able to complete a Masters of Public Health during the daytime with a focus in nutrition, and I learned much from some of the towering figures in that field such as Fred Stare, Mark Hegsted, and Jean Meyer. After returning to Boston City Hospital to complete internal medicine residency and to marry my wife, Gail, I accepted a faculty position at the University of Dar es Salaam in Tanzania. There I taught community health, which included everything from nutrition to sanitation and infectious disease control. I conducted the first randomized trial documenting that treating ascariasis could promote growth of young children. Again, I found food frequency questionnaires could be a practical way to gain insights into the diets of rural families and could readily be embedded in nutrition surveys. During the three years in Dar es Salaam, we also gained colleagues and friends who remained part of our circle until today.

The close connections between environmental factors and human health were vividly clear in Tanzania, and the power of epidemiology to understand these links and potential prevention strategies led me back to Harvard to pursue a doctoral degree in that field. Frank Speizer had just started the Nurses' Health Study (NHS), and I joined his group for a thesis on smoking and coronary heart disease. At about the same time, largely based on variations in cancer rates across countries, a hypothesis developed that dietary fat was the primary cause of breast and other major cancers in Western countries. This became widely accepted and was a major pillar of recommendations to consume low fat/high carbohydrate diets. The NHS population of over 121,000 women was an obvious opportunity in which to test this hypothesis because the participants were medically knowledgeable and highly motivated to participate in long-term research. The missing element was a dietary assessment method that could distinguish women by their fat intake and be administered repeatedly over time in a large population. After several rounds of pilot testing, in 1980 we mailed to cohort members a self-administered semi-quantitative food frequency questionnaire (SQFFQ) with particular focus on type and amount of fat (*trans* fatty acids were also becoming suspect). Simultaneously we launched a detailed validation study of the questionnaire among about 200 participants. In the validation study, dietary fat assessed by the questionnaire correlated reasonably well with intake assessed by repeated weighed diet records [2], and we later showed that the percent of energy from fat calculated from the questionnaire predicted biomarkers sensitive to fat intake [3]. Thus, the dietary assessment methods would provide a test of the fat-cancer hypothesis. Because many individuals change their diets over time and food manufacturers modify their products, particularly sources of added fats, we continued to repeat dietary assessments every four years and also simultaneously updated our food composition databases, including our own fatty acid analyses of commonly consumed foods. Over time we made small adjustments in the SQFFQ to accommodate new hypotheses and changes in the food supply, and we also continued to conduct studies to evaluate the validity of dietary assessment methods. In the most recent evaluation we compared the ability of the three main dietary assessment methods (two weeks of weighed diet records, the SQFFQ, and repeated 3–4 days of 24-h recalls) to predict biomarkers of diet [4]. Although prohibitively expensive and burdensome for large cohort studies, the weighed diet records had the highest correlation, but the SQFFQ performance was similar to one week of weighed diet records and superior to the 24-h recalls. This confirmed the choice of food frequency questionnaires as the primary method for large cohort studies, although the additional use of biomarkers and short-term intake assessments can provide additional information for some aspects of diet. We have seen the importance of repeated assessments of intake with long-term follow-up; had only baseline dietary data been available, we could have missed important findings. In addition to the NHS cohort, we added 52,000 male health professionals to study diet and health issues in men and another 116,000 younger nurses to study diets earlier in life in relation to breast cancer and other outcomes. Importantly, several dozen large cohort studies of diet and health have been developed in other countries building on similar approaches. What we have learned about this research approach has been incorporated in three editions of *Nutritional Epidemiology* [5].

Several thousand papers on diet and health have emerged from our cohort studies, which represents the work of many colleagues and trainees. Among the findings has been that dietary fat does not predict risk of breast cancer or other major health outcomes [6]: this has been confirmed in other studies and has contributed to the elimination of recommendations in the US and elsewhere to reduce total fat intake and instead to focus on the type of dietary fat. An

important specific finding was the strong relation between intake of *trans* fat and risk of coronary heart disease [7], supported by controlled feeding studies documenting adverse effects on blood lipids [8], leading to bans on partially hydrogenated oils in many countries. This example also provides a useful paradigm on how the combination of observational studies with disease endpoints and controlled feeding studies with risk factor endpoints can provide a high level of certainty regarding causality, sufficient for making recommendations and formulating policy. Other major research areas have include the importance of carbohydrate quality [9, 10], sugar-sweetened beverages [11], protein sources [12], and empirical evaluation of dietary guidelines [13–15].

A Crystal Ball

Like the universe after the big bang, the field of nutrition is expanding explosively in many different directions, and just where this will take us is far from clear. Dietary assessment and nutritional epidemiology will remain key elements, although we have learned much about the etiology and prevention of major diseases over the last several decades. For every relationship, many details about dose-response and temporal relationships need to be determined. Also, we are now only beginning to examine the effects of diet early and late in the life cycle. We have had great success in extending life expectancy by prevention of cardiovascular disease and cancer, with the result that dementia and other neurodegenerative diseases have become increasingly important; dietary factors appear to have major potential for prevention but this needs much additional work.

One direction nutrition is taking is mechanistic, taking advantage of remarkable technological advances in genomics, metabolomics, proteomics, and microbiome analysis. We will surely learn from studies using these methods, but the degree to which they modify dietary approaches or improve human health is not yet clear. Enthusiasm for genetics as a powerful method to predict disease risk was clearly overly exuberant; for diabetes and heart disease we can do far better by having someone stand on a scale and ask about their smoking, diet, and physical activity. In some cases, the use of genetics for Mendelian randomization approaches can be useful, but this can also be entirely misleading. Although there is currently great enthusiasm for "personalized nutrition" based on genetic analyses, this is not likely to have major impact on diets or health because genetic variants have not turned out to be few and strong, but rather highly numerous, across many genes and pathways, and weak predictors of outcome. Whether the new variables that we measure using novel -omics methods will primarily define the mechanisms by which diet acts or will identify new strategies for prevention or treatment remains unclear. Importantly, findings from such studies will be difficult to interpret without including detailed dietary assessments in the analyses. Almost surely the data to come from these studies will make us more knowledgeable, but whether that will make us substantially healthier is less clear.

Another direction in which our field is moving is to address the macro issues of diet and health, often described as public health nutrition. A major challenge is to reduce the huge gap between what we already know about diet and health and the widespread adoption of healthy diets. For example, in our cohorts, we found that a simple combination of good diet, not smoking, moderate physical activity, and avoidance of overweight could prevent about 70 to 80% of coronary heart disease and 90% of type 2 diabetes, yet only about 4% of participants had adopted this simple package. Closing this gap will require many strategies, beginning with education and awareness but also including economic and policy strategies, which need to be guided by research, ongoing surveillance, and evaluation.

The ongoing epidemics of obesity and diabetes continue unabated in most countries and require increased attention as efforts so far have been inadequate. The full impact of this epidemic on health will not be felt for many more decades when the generation of children first affected become older adults because the full sequence of obesity, diabetes, cardiovascular disease, and renal, neurologic and other system failures develops over a lifetime. In the U.S., rates of obesity-related cancers that had been declining are now increasing in adults under age 50, and this trend will likely extend to older years as these birth cohorts age. For the first time in many decades, life expectancy in the U.S. has declined, and unless more serious actions are taken, we will likely see the gains in public health over the last 50 years eroded. These trends for the U.S. are likely to be replicated elsewhere. Although much can be achieved by acting on existing knowledge about diets, beverages, and physical activity, powerful economic interests continue to obstruct progress. Even if a more effective "obesity pill" were to be developed, this would not adequately address the epidemics we are experiencing because obesity and diabetes are actually symptoms of societies off-track with respect to diet, physical activity, and equity. Further, poor diets, inactivity, social isolation, inequality, and depression have many adverse consequences independent of body weight, and dealing with these underlying conditions would yield far more benefits than any pill can provide.

An even broader and more fundamental issue in nutrition is the role of our diets and food systems in environmental sustainability. The challenge of feeding a global population that is 2–3 billion people larger than today a diet that is both healthy and sustainable is huge because even now most of

the world's population eats a poor quality diet that is supplied by food systems that are accelerating climate change and environmental degradation. Dealing with this will require adoption of healthy, largely plant-based diets, and our community needs to play a lead role in this transition. However, we will also need to work with colleagues in agriculture and other related areas if we hope to pass on to our children and grandchildren a healthy and stable world rather than a disintegrating planet that is racked with conflict and suffering.

In summary, my nutritional crystal ball appears hazier than it did 40 years ago, when we viewed our main challenges as testing a series of concrete hypotheses and filling in the nutritional gaps of children in poor countries. On one hand, we have unprecedented scientific opportunities but at the same time, we face existential challenges for human civilization as we know it. This a special field for anyone wanting to be at the cutting edge of biomedical science and also to work on the most challenging issues of our time.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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