2001 W.O. Atwater Memorial Lecture and the 2001 ASNS President's Lecture: Human Nutrient Requirements: The Challenge of the Post-Genome Era[1]

Vernon R. Young[2]

Laboratory of Human Nutrition, School of Science, Massachusetts Institute of Technology, Cambridge, MA 02139

It is a privilege to be the 2001 Wilbur O. Atwater lecturer for many reasons. Important among these is the fact that I join an impressive list of distinguished previous lecturers, many of whom are my colleagues and friends. It is also a particular honor to have been asked by our President, Lindsay Allen, to give a parallel presentation as the ASNS President's Lecture. I am, of course, deeply grateful to the U.S. Department of Agriculture, Agricultural Research Service for its sponsorship of this award lecture as well as to ASNS for its support and confidence in me.

When I was informed about this Award in late January, 2001, we had just entered a new year and new millennium; in a recent issue of *Science* (December 2000) (1) we had read that the breakthrough of the year 2000 was the torrent of genomic data that had emerged during the course of the previous 12 mo. The runners-up included the determination, in fine detail, of the structure of the subunits of the ribosome and the 1.7 million-year-old skulls of humans discovered at Dmanisi, Georgia, CIS. At the time too, we were anticipating the appearance of separate issues of *Nature* (2) and *Science* (3) revealing the first drafts of the publicly and privately funded human genome sequences, respectively. Finally, I was also preparing to attend another meeting of the Institute of Medicine (IOM)/Food and Nutrition Board's Standing Committee on the Scientific Evaluation of Dietary Reference Intakes that was to be held at the National Academy of Sciences in Washington, DC. [see, for example, (4,5)]. For these reasons, I thought it would be a timely opportunity to bring genomics, among other aspects of contemporary biological advances, into a consideration of the challenges that face an improved quantitative determination of human nutrient requirements, which serve as the central body of knowledge in nutrition. Even more to the point was the fact that the actual sequencing of the human genome revealed far fewer genes (~30–40,000) rather than the ~100,000^{+} that had been expected for some time. This finding suggested that not only the regions of the genome that are not genes may be fundamental to the complexity seen in humans vs. that of simpler organisms such as yeast (~5800 genes), round worm (~20,000 genes), the fruitfly (~14,000 genes) and mustard plant (~26,000) (6), but also that there must be a significant role of regulation and of the environment in shaping our variability and individuality. As Craig Venter said in his press announcement of Celera's draft of the human genome (3), "We are not hard wired . . . and that the environment acting on these biological steps may be key in making us what we are" (http://www.eurekalert.org/E-lert/current/public-releases/scipak/venter.html, accessed February 17, 2001).

Surely, among the most important of the environmental influences must be our nutritional environment. This raises the following question and statement that I have paraphrased from an editorial (7) that appeared just before the publication of the first draft of the human genome: "What does the human genome sequence mean for me, my research and my institution?" As was also pointed out, "this is a question all biologists (including, I might add, nutritional scientists) should be asking themselves." Hence, this question serves as the engine behind this presentation because I believe its answer will affect the way in which we accomplish the following: 1) explore the role(s) and mechanism(s) of action of nutrients; 2) establish quantitative nutrient requirement values and understand the molecular and cellular basis for individual variation in requirements; 3) predict, with an increased precision, the nature of genotype-environmental interactions, especially in relation to chronic disease and its nutritional antecedents; and 4) optimize food production and the nutritional value of foods for specific populations in given ecological/cultural/social settings.

My "contact" with Atwater

Before turning to the specifics, I should add that Wilbur O. Atwater has long been a scientific hero of mine, due in part to the fact that our respective research interests in nutrient requirements and the nutrient content of foods have clearly overlapped (8). On a more personal note, I have been intrigued by a number of articles on small world networks in the sciences (9) and on their dynamics and connectivity (10,11). Thus, in the world of mathematicians, it is a common activity for mathematicians to work out of what their "Erdos" number is. The Erdos number measures a mathematician's proximity, in bibliographic terms, to Paul Erdos, who was a Hungarian itinerant and who lived out of a suitcase and walked around hungry looking for shelter (9). For any of his friends willing to give him food and shelter, he would include that person as a coauthor on the next paper he wrote. Hence, for an individual

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[2] To whom correspondence should be addressed. E-mail: vryoung@mit.edu.

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who appears as a coauthor on a paper with Erdos, his/her Erdos number is number one. If, however, an individual coauthored a paper with an author who was, in turn, a coauthor of an Erdos paper, then that individual's Erdos number is number two, and so on. Hence, I asked initially what my "Atwater number" might be, but because he is better known for his Atwater factors I wondered what my Atwater factor might be! To answer this, I consulted Munro's family tree in protein metabolism (12) to help me establish a link with Atwater as follows: my MIT and ultimate mentor, Nevin Scrimshaw, and I both collaborated with Hamish Munro when he was at MIT; he, in turn, worked with Cathcart who spent time in Carl Voit's laboratory in Germany where Atwater had also worked. Therefore, in terms of mentorship, rather than publication, my Atwater factor appears to be ~4, or that for protein! More seriously, however, and in the context of the scientific lineage illustrated by Munro, it was his comment after an analysis of the history of research in protein metabolism that is worth reiterating, i.e., "In the course of constructing this historical review it also became apparent that single-minded devotion to a subject is more profitable than dilettante exploration over a wide field in hope of some chance discovery of importance. Lavoisier, Leibig and Voit were all systematic and industrious" (12). For the younger generation of nutritional scientists I believe this is a message worth thinking about; stick with it and try to challenge a dogma! It can be exhilarating and rewarding.

Nutritional science and nutrient requirements in the postgenome era

In their millennium essay, Genomics: Journey to the Center of Biology, Lander and Weinberg (13) wrote: "The 21st century discipline will focus increasingly on the study of entire biological systems, by attempting to understand how component parts collaborate to create a whole. For the first time in a century, reductionists have yielded ground, to those trying to gain a holistic view of cells and tissues." I would add to this, as a nutritional biochemist: "organs, whole bodies and, ultimately, populations" because it is at these more complex levels of biological organization that nutritional science and knowledge find a particular relevance and application. Hence, I thought it would be a challenge to offer a vision of what might be ahead. This is not a prediction, because a vision is a picture of how the world could be or perhaps serves as a pointer in a particular direction. In a foreword to a *Nature Insight* issue on Paths to Unforeseeable Science and Technology, the editor, Phillip Campbell (14), wrote "It surely is one of scientists' roles to look unflinchingly at feasible extrapolations of current knowledge, however unpopular that may make them." Nevertheless, it is a difficult task to bring my intended message, regarding nutrient requirements and the postgenome era, to complete clarity. One reason is that we are concerned with multiple nutrients and other food constituents that interact at various stages in their utilization and that have multiple roles and consequences for cell and organ function (**Table 1**); nutrients catalyze reactions and serve as cofactors; they are substrates for macromolecules; they may act like a network of computers, participating in signaling systems (15) and they interact at the most basic level (16–18); they can alter macromolecular structure and they can, of course, be harmful. Although we are just beginning to identify the important roles that amino acids, for example, play in the control of gene expression (19) and the specific signaling systems involved (20–23), how they interact and the molecular mechanisms involved remains unclear. We are still defining new roles and actions for various nutrients and how nutrient homeostasis is achieved at the cellular level. Thus, recently it was proposed that vitamin C might induce lipid hydroperoxide decomposition (24), but the pathophysiologic significance of this effect is as yet unclear (25); although much is known, for example, about the biology of zinc (26) we have only a rudimentary understanding as to how zinc uptake or efflux is sensed and regulated (27) or how cells capture and maintain copper, which is relatively scarce in the environment (28,29). Some also have considered oxygen to be a nutrient (30), and in this context also, research has revealed a hypoxia response pathway in which a specific transcription factor, hypoxia-inducible factor, serves as a key regulator (31). Such detailed, mechanistic knowledge about how cells respond to changes in nutrient availability is essential if approaches to nutritional requirement estimations and nutritional assessment are to be substantially improved.

TABLE 1

Nutrients, including other food constituents: their actions and functions[1,2]

- Catalyze reactions and play co-factor roles.
- Substrates for macromolecules with an extraordinary array of functions—proteins, complex lipids, nucleic acids.
- May act like computer—executing a sequence of instructions (e.g., PUFA and the transcription factors PPAR and SREBP-1; neurotransmitters).
- Can alter molecular/macromolecular structure.
- Functions and cellular consequences are still incompletely understood.
- Can promote assembly of mechanistic structures.
- Can be harmful.

[1] Such as phytochemicals and nondigestible polysaccharides.
[2] Abbreviations: PUFA, polyunsaturated fatty acids; PPAR, peroxisome proliferator-activated receptor; SREBP-1, sterol regulatory element binding protein-1.

The goal of achieving a clear vision is made all the more difficult because it is not easy to secure a universally acceptable definition of a *nutrient*. As stated in the Executive Summary of a Ceres Forum (32), "a couple of decades ago, answering the question 'What is a nutrient?' was much easier than it is today."

In an editorial in ASNS Nutrition Notes entitled Your Chance to Help Define a Nutrient, Gordon (33) suggested that the U.S. Food and Nutrition Board (FNB) in establishing a definition for dietary fiber will effectively define a nutrient. He asked "Is dietary fiber a nutrient?" and then presented his suggestion as to a definition of dietary fiber. More specifically, in my view, this editorial is an opportunity to identify a new group or class nutrients, namely, "dietary fibers." Nevertheless, it is important to define what a nutrient is because it should then be easier to appreciate the proximate boundaries of the discipline we call Nutritional Science. Hence, I define a nutrient as follows: *"It is a fully characterized (physical, chemical, physiological) constituent of a diet, natural or designed, that serves as a significant energy yielding substrate, or a precursor for the synthesis of macromolecules or of other components needed for normal cell differentiation, growth, renewal, repair, defense and/or maintenance or a required signaling molecule, cofactor or determinant of normal molecular structure/function and/or a promoter of cell and organ integrity."* I admit, as I learned by attending the ASNS/ASCN Public Information Symposium at this annual meeting, one is advised that for a message to be effective, it is best stated in ~12 words or less.

Therefore, my proposed definition of a nutrient may not resonate but, in my view, it is the diversity of nutrient function that defies a compact definition. It should be pointed out that there is no reference in this definition to level of intake; at intakes that correspond to "usual" intakes, the emphasis is on physiology. At intakes that would be difficult to achieve via a usual diet, the implications may be of a pharmacologic/therapeutic significance. However, the latter intakes encompass the discipline of nutritional science and are directly relevant to issues of human nutrient requirements. Indeed, to meet recent FNB recommendations for intakes of iron by pregnant women (34), the usual diet would have to be accompanied by an iron supplement. Furthermore, the definition does not allude to the concept of nutrient essentiality, which requires revision (35) and probably elimination.

With an increased knowledge about the functions of nutrients and of the host response to changes in nutrient intake, there has been an evolution of nutrient requirement research/recommendations (36). Among the earliest of dietary recommendations were those concerned with protein and energy; these recommendations were generated from dietary intake data (37,38). Atwater (39) recommended an intake of 125 g protein "for a man at moderate muscular work." However, it is well appreciated that intake-based recommendations do not define physiologic requirements. Hence, there have been further developments with the use of a number of different approaches, including metabolic, tracer and biochemical techniques, in human studies to establish minimum physiologic intake levels for specific nutrients. Data generated via application of such approaches/methodology have provided the basis for the ongoing IOM review and new recommendations for nutrient intakes (4,34,40,41). Furthermore, in addition to specific requirement estimates as presented recently by IOM, some recommendations have been based on observed or experimentally defined approximations of intakes. These include nutrients such as calcium, fluoride, vitamins D and K, and panthothenic acid. This scarcely represents a significant advance over the approach used by Atwater in the mid- to late 1800s. In this context, the science of nutrient requirements would not seem to have progressed as much as desirable over the past ~50 years. One of the limitations to progress continues to be the lack of good biomarkers of specific nutrient adequacy in apparently healthy individuals (42). Benzie (43) considered the requirements for a reliable functional marker, with a particular concern for assessment of micronutrient status, and proposed that they include the following characteristics: *1*) the marker should respond sensitively, specifically, and predictably to changes in the concentration and/or supply of the micronutrient; *2*) there should be a measurable dose-response relationship; *3*) the marker should be accessible for measurement in a form and quantity that can be measured objectively and with good reproducibility; and *4*) the marker should reflect a change in the target tissue that has a direct effect on health. In other words, the level or change in the marker must relate to a physiologic or pathologic end point.

-Omes and -omics

The postgenome era offers a major opportunity to explore such desirable characteristics as those noted above for biomarkers of nutrient adequacy. Therefore, it might be worth reflecting on how we might respond to this challenge. Thus, there are various levels of research focus that might be considered in studying the links between the genome and the nutritional phenotype. These are indicated in **Table 2**, which I have modified from Oliver (44). At the most fundamental level of biological organization, with least complexity, is the genome that is defined by the sequence of nucleotides in the DNA. This sequence provides knowledge about the basic genetic map or the amino acid sequence of gene transcripts. However, gene function is regulated at many steps beyond the level of the imprint represented by the nucleotide sequence; these steps may include cytosine methylation (45,46) [the methylome; (47)]; acetylation, methylation and phosphorylation of histone (48), mRNA editing and stability (the transcriptome) (49). Further, the products of most genes are proteins, and their function is dependent on the cellular context as well as on post-translational modifications and environmental factors, including the presence or absence of specific nutrients. Nevertheless, DNA sequence data can be used to provide dynamic pictures of living genomes (50,51) and in doing so facilitate the systematic study of gene expression patterns that can inform us about the possible fundamental aspects of specific nutrient function (52) and its relationship to human diseases. This is nutritional science undertaken at a distinctively reductionist level. Although characterizing changes in gene expression and their relationships with nutrient function and requirements will be a complex task (53) this technical and conceptual opportunity promises to yield exciting and important nutritional information. Of course, it will be necessary to probe at a higher level of biological complexity if

TABLE 2

Levels of gene-nutrient analysis for assessment of nutrient requirements[1,2,3]

Level	Definition	Example of analysis
1 Genome	Genomic imprint	Nucleotide sequencing
2 Methylome	DNA methylation modifications	Microarray analyses
3 Transcriptome	mRNA expression	Hybridization assays; temporal
4 Proteome	Set(s) of cellular proteins	Mass spectrometry; two hybrid; 2D gel; post-translational modifications
5 Metabolome	Low molecular weight metabolites in cells/organs	μTAS: IR, NMR
6 Physiome/phenome	Quantitative integration of cell and organ processes	Viable cell, organ and whole-body systems, with focus on flux and mass balance models
7 Populome	Complete nutritional characterization of a population group, from data sets 1–6	The above, as relevant, plus dietary and socio/cultural data

[1] Levels 1 and 2 are gene-centric in foci and are largely context independent. Other levels include a supra-genome strategy and are context dependent.
[2] Abbreviations: 2D, two-dimensional; μTAS, micro-total analytic systems; IR, infrared; NMR, nuclear magnetic resonance.
[3] Modified from (44).

we are to understand fully how we respond to our nutritional environment at various stages in the life cycle.

Parenthetically, it might be noted here that both the value and limitations of the reductionist approach are articulated in a paper entitled The Theory of Everything (54) in which it is concluded that the correct theory of everything has revealed nothing about many things of importance of the understanding of the natural world; we might well include here nutrition! Therefore, we move up the ladder of biological complexity to the level of proteomics (Table 2) (a global analysis of cellular proteins), which is of particular significance because proteins are the workhorses of cells and are far more diverse than nucleic acids. They are more versatile due to such factors as conformational changes resulting from binding of small or large molecules, the effects of select cofactors such as zinc and B-12 on protein function and the multiple forms of post-translational modification brought about by phosphorylation, formation of disulfide bridges, polysaccharide chains and lipid additions, for example. As more and more and larger and larger genomes are sequenced, research will be increasingly focused on structural or functional genomics (55–58), which involves identifying the structure, function and interactions of all of the cellular proteins. This will be a large task but as has been pointed out (59), protein engineering and its application in medicine and perhaps in nutrition will benefit from this new area emphasis. What particularly matter in advancing nutrition knowledge are the snapshots of proteins produced at a particular time in particular cells under defined conditions of nutritional status and nutrient intake. Thus, looked at from this perspective, the proteome is accordingly infinitely dynamic and one can only largely wonder at this time how changes in nutrient intake and balance affect the structure and function of the $>500{,}000^{+}$ human proteins! Due to a lack of protein stability, mutants of proteins account for a wide range of diseases, and it seems reasonable to ask to what extent do specific nutrients participate in the stabilization or destabilization of proteins and/or affect protein-protein interactions. Because "function follows form," this aspect of modern biology and technology surely promises to be an exciting area for modern nutrition research.

As might be expected, there is also a limitation to a proteomic emphasis alone in nutritional research. This point can be underscored by reference to the phenomenon that has been called "moonlighting proteins" (60). For example, the enzyme phosphoglucose isomerase catalyzes the second step in glycolysis, the interconversion of glucose 6-phosphate and fructose 6-phosphate. However, if the protein is secreted by the cell it can serve at least four additional roles, including that of a nerve growth factor (61). Similarly, enolase performs several functions in addition to its role in glycolysis (62). Hence, as I have already suggested, protein function depends on cell location, the concentration of the ligands that are associated with it, cell type, substrate, oligomeric states and so forth. Basically, the point I am making is that this context-dependent situation adds difficulty to the interpretation genomic sequences and understanding the functions of and interactions among proteins and, therefore, of how nutrients affect cells. Thus, proteomics, although clearly an important and exciting level of enquiry, must be integrated with studies of metabolism and with the metabolome (Table 2). This is an even more complex and integrative level of study, but one that is key to improving approaches for assessment of nutrient requirements. As Watkins et al. (63) cogently emphasized, metabolomics is a logical next step in understanding the role of nutrition (or nutrients) in modifying metabolism and ultimately in promoting health. A metabolomic approach augments and complements the information provided by measuring genetic and proteomic responses to nutritional factors. Although the science of nutritional metabolomics is in its infancy, major growth in this area can be anticipated. Thus, the development and evolution of metabolic profiling technologies, including mass spectrometry (64) and nuclear magnetic resonance spectroscopy (65), coupled with advances in high throughput analytical and computing technologies, will revolutionize our ability to discover how nutrients determine the level and activity of specific gene products (66) and the function of genes (67). Further, metabolomics will inform us how nutrient-gene activity is integrated into the jigsaw of global gene activity which is, in turn, responsible for molding the functional and nutritional status of the complex, whole organism. In reasonable contrast to the genome, and like the proteome, the metabolome is not stable over time. Thus, the complete study of metabolomics requires that the quantitative dynamic features of the metabolome be defined and examined under various conditions. This can be achieved in part by the application of micro-total analytic systems (68) and by material balancing and tracer technology (69). Further, we have proposed and begun to apply a "metaprobe" approach, exploiting the phenomena of *underground metabolism* and *metabolic hijacking*, which is aimed at quantifying in vivo rates of specific biochemical steps or of metabolic pathways in specific organs or sites of the body (70,71,72) (**Fig. 1**). Our ability to adequately predict the consequences of nutrient intake and balance for health and well-being will depend upon genetic/cellular representations that also include kinetic, mass balance, information on enzymatic steps and pathways. Fundamentally, this amounts to a complete and quantitative nutritional phenotyping, which includes all elements, genetic, post-transcriptional and post-translational, that determine the need for and affect the utilization of a nutrient. Finally, we should also note the development of ultraminiaturized biosensors (73,74) for continuous in vivo monitoring of multiple metabolites that would provide further information about the activity of metabolic networks and pathways via informatic techniques including pattern recognition and cluster analysis.

It is clear that nutrients regulate metabolism and that they exert their effect at various levels of biological complexity; they influence gene transcription, RNA processing, mRNA stability, post-transactional modifications, and the activities of various steps in and of entire biochemical pathways (**Fig. 2**). The point I wish to make is that contemporary nutritional science requires that our studies move back and forth among these various levels of gene-nutrient analyses mentioned above (Table 2), but with the focus of research being, in this instance, on the quantitative determination of human nutrient requirements.

To further consider and perhaps highlight some of the opportunities for postgenome era research into the nutritional needs of humans I have selected a few areas as follows, for illustrative purposes.

Some selected areas of emphasis in relation to nutrient requirements

Nutrition, aging, the elderly. In a recent *Nature Insight* series on aging, there were a number of highly instructive presentations, including one describing the sources and cellular responses to reactivate oxygen species (75). Just a few years ago a mechanism by which energy restriction increases the life span of rodents and other animal models (76) was thought to be associated with an effect on endogenous oxidants that operated in a random, indiscriminate and cumulative manner

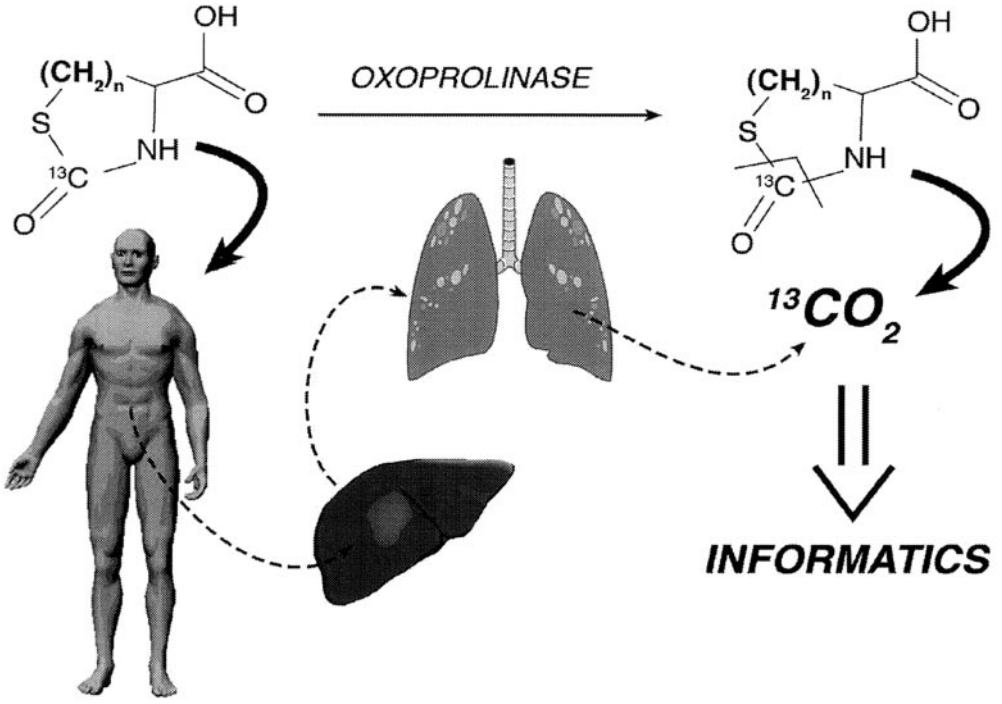

FIGURE 1 An illustration of the concept of the "metaprobe" tracer approach for quantifying in vivo the dynamic aspects of specific biochemical steps, at specific sites. Here an analog of 5-oxoproline (L-2-[^{13}C]oxothiazolidine-4-carboxylic acid; $n = 1$) is used to assess the activity of the γ-glutamyl cycle of glutathione synthesis via the rate of appearance of ^{13}C in expired air.

(75). However, we now know that oxidants, and particularly reactive oxygen and nitrogen species, work through redox-sensitive signaling pathways that are under genetic control (77). For example, in the roundworm, fruitfly and mouse, mutations in specific genes change the responses of these organisms to stress by chemicals, with a consequent change in life span (75). Further, Lin et al. (78) using *Saccharomyces cerevisiae* as a model organism, described results that may help link energy restriction to the control of gene expression and to the suppression of DNA damage caused by mitotic recombination. Nutrition, aging and genetics now should become an integrated area of study as further attempts are made to better understand the basis for and possible changes in the nutritional requirements in the older sector of the population (79–81).

Nutritional programming. The foregoing comment on aging and nutrient requirements might also alert us to the fact that nutrient genome interactions may differ profoundly depending upon the life stage of the organism. Hence, any visionary thinking about nutrient requirements in the postgenome era should view nutrient-gene interactions in the context of the life cycle (**Fig. 3**) (82). At specific stages during the life cycle, these interactions might be expected to have more profound influences than during others, and this raises the issue of nutritional programming. The classical studies of McCance (83) and his co-workers showed, for example, that if rats were food restricted during the suckling period and then subsequently consumed food ad libitum, there was a permanent effect on growth (**Fig. 4**). However, if the restriction was delayed until the postweaning period, there was a prompt and essentially complete capacity to catch up when food was again available. This offers a dramatic illustration, therefore, of the

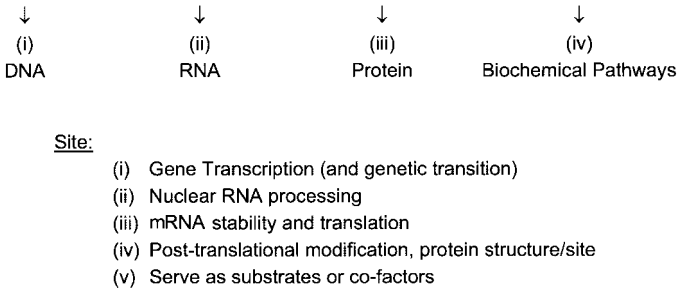

FIGURE 2 Sites at which nutrients interact with the functional genome.

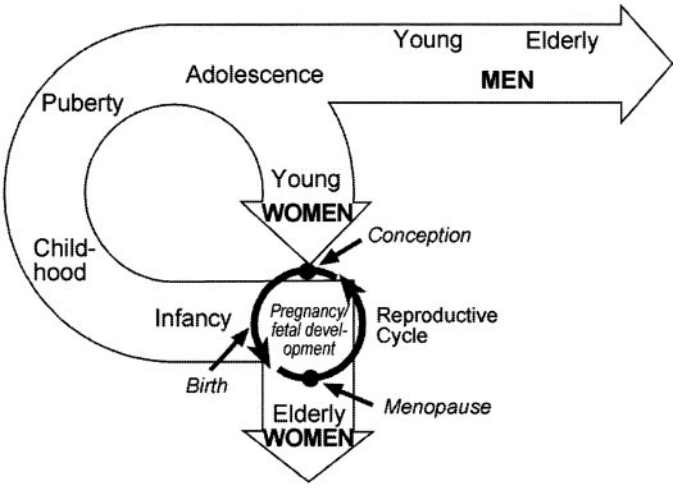

FIGURE 3 Stages in the life cycle at which nutrient-gene interactions might be expected to have a particular importance for health and well-being. Slightly modified from (82).

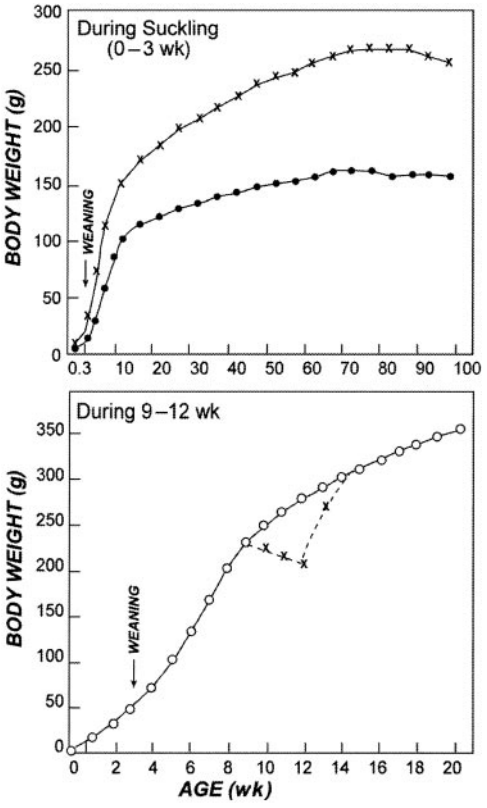

FIGURE 4 Effects of food restriction on growth in rats during the sucking period (*upper panel*) and postweaning periods (*lower panel*) on subsequent growth and development. Combined from McCance (83).

fact that nutrient-genome interactions are affected by the life stage of the organism.

This also raises the question whether stem cells are key nutritional targets. Stem cells are undifferentiated, unspecialized cells that can renew themselves and also give rise to one or more specialized cells (84). There are embryonic and adult stem cells, and mammals appears to contain ~20 different types of somatic stem cells. What is particularly intriguing to me is that various external signals and nature of the microenvironment can control stem cell fate; depending upon which growth factor might be present in the medium, muscle stem cells can give rise to blood cells and bone marrow cells can give rise to liver cells (85). Thus, there are not only moonlighting proteins that have "day" and "night" jobs, metaphorically speaking and as noted earlier, there are also cells that are willing to switch entire careers! This is another challenging area for nutritional scientists to explore, particularly in terms of defining nutrient requirements for maximizing specific function, whether it be resistance to disease, longevity or optimum physical performance.

Variations in nutrient requirements. Nutrient requirements vary between different physiologic groups, including age and gender, and also among apparently similar individuals. It seems likely that this latter variation would be due to individual variability in functional systems that have an important genetic basis. Thus, for example, allelic variations in the vitamin D receptor gene correlate with differences in intestinal calcium absorption, and response of bone density to long-term intake of dietary calcium (86) and polymorphisms of methylenetetrahydrofolate reductase may have implications for optimal folate intakes (87,88); the variation in iron absorption, which may account for a significant proportion of the difference in iron requirements among men and among nonmenstruating women, might have a genetic origin. Possibly this may be due to the responsiveness of a gene that encodes for a protein, duodenal cytochrome B, which plays a role in reducing iron for transport across the gut wall (89). Although this is frank speculation because human studies have not yet been conducted, these genetic/cellular findings emphasize the desirability of characterizing the range of polymorphisms at specific sites in the genome and establishing their nutritional implications. Perhaps it might be suggested that single nucleotide polymorphisms may not generally be sufficiently strong to affect the requirement/function/cell response because of the presence of multiple signaling or effector pathways. This results in a built-in redundancy to the control of nutrient homeostasis and raises the desirability of performing genome-wide searches, using high throughput screening methods, as a powerful means for elucidating the polygenomic basis for variations in nutrient requirements among individuals. Such an approach should become an integral part of the nutritional phenotyping paradigm, thus helping to optimize nutrient requirement assessment and recommendations for specific subsets of genotypes in a population.

Food composition and food/nutrient intake. As illustrated in **Figure 5**, there are other research components to a more complete understanding of how individuals and populations respond to nutrient intakes. Thus, in addition to developing better markers of nutrient function and status and an integration of studies focused on the multiple levels of nutrient-gene interaction discussed above, there is a great need to more completely characterize the composition of foods. Further, there has to be an improvement in methods used to obtain quantitative estimates of nutrient intakes by groups and individuals. These are equally important areas of activity for nutritional science to advance, although they are not usually considered to be as intellectually challenging as those involving molecular genetics and cell biology. However, it seems to me that there may be exciting technologies that might be adapted to help resolve the problems we face in estimating simply how much food somebody consumes over a given timeframe. For instance, do wearable computers and remote sensing techniques offer promise in this area? This brings up the question of technology.

Integrative science and technology. Thomas Kuhn, in *The Structure of Scientific Revolutions* (90), said that technology has often played a vital role in the emergence of a new science. It is in this regard that we, as nutritional scientists, must be prepared to vigorously exploit the new and also advanced

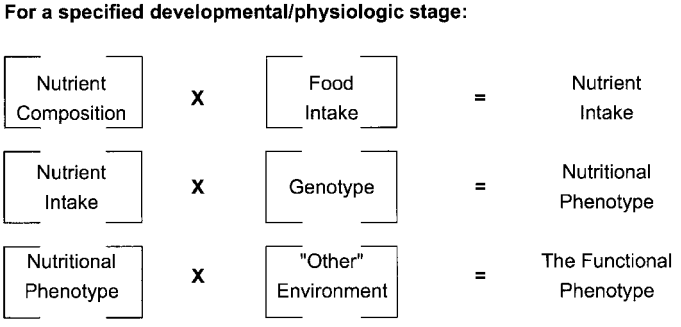

FIGURE 5 A diagram to emphasize the importance of knowledge and research on food composition and food intake and on characterizing the whole environment, as a basis for understanding the determinants of the nutritional-functional phenotype.

technology now available for enhancing our research. Thus, in the context of defining human nutritional requirements in functional terms, I can foresee an eventual integration of various technological approaches, ranging from surveys of whole genomes [whose potential value in nutrition research was discussed by Hirschi et al. (91)], continuing on through metabolic dynamic, quantitative isotopic studies, which may even include use of positron emission tomography (92) and functional magnetic resonance imaging (93) to provide an anatomic and behavioral (94) dimension to the metabolomic assessment of nutritional responses and requirements. It is time that we begin thinking "Big Science" and develop strong collaborations with those who have the skills in these advanced and expensive technologies if we are to significantly expand the frontiers of nutrition research. This reminds me of a quote (author unknown): "A man with one clock knows what time it is, a man with two clocks is never quite sure." We should not hesitate to use more than one clock in our nutrient requirement research. To be fully successful, this will require an elaboration and the strong support of a major interdisciplinary enterprise, which is really what nutrition science is all about.

A more global measure of the nutrient requirement

New lines of investigation for nutritional requirements must be established. There should be a move away from the present paradigm in which simple/single indicators of nutrient adequacy dominate the approach and major basis for assessment in so many studies. There is need to explore and develop more comprehensive indices of functional significance; this demands a global approach, which may include simultaneous assessment of processes such as apoptosis, activity of signaling pathways, the metabolic and functional activity of membranes and the fluxes of relevant biochemical pathways, depending upon the nutrient and its anticipated mechanism(s) of action. This should be done in real time with quantitative metabolic kinetics included and all examined during the different states of fasting and prandial metabolism in clinical investigations with humans. An outcome would be an ability to define, diagnose and study more effectively deficiencies/inadequacies and requirements of so-called Type II nutrients (such as protein, lysine, magnesium, zinc), which, according to Golden (95) contrast with Type I nutrients (such as thiamin, vitamin D, copper, folate) whose inadequacy is relatively simple to diagnose. Of course, this latter view may also be questioned. However, this new postgenome approach should remove the need for this distinction among nutrient classes, which I have found intriguing since it was first proposed. Having spent a great deal of time recently with my colleague Will Rand, evaluating nitrogen balance data and adult protein requirements (96), it would be a significant advance if this "gene-to metabolic phenotype" approach could be successfully established for estimating protein or specific amino acid requirements. The sooner that it is possible to dispense with the technically and intellectually inadequate short-term N balance studies and data, the better off our science will be. Furthermore, despite the challenge, I do believe that this new paradigm is realistic. Again this demands that we truly integrate our discipline and it is, in my view, the multidisciplinary approach that is the key to the future and vigorous evolution of nutritional science. It must be fostered, and this will require infrastructural changes in research institutions and universities, as others have pointed out (97), so that we might more easily cross disciplines, become involved in teamwork and do different and new kinds of science. Nutrition will not survive as a rigorous science without our meeting this challenge head-on.

In conclusion, a few summarizing thoughts with respect to human nutrient requirements and the postgenome era: *1*) human and animal nutrition may be seen, as articulated also by the ASNS Long Range Planning Committee (98), as a catalyst that serves to promote the study and understanding of the integrative biology required to harvest fully the fruits of genome research; *2*) the functions played by and mechanisms that underlie traditional and new or novel nutrients will become more clear, and possibly bring reasonable closure to debates such as the role of dietary fat in atherosclerosis and obesity (99) or of salt and calcium in hypertension (100,101); *3*) the approach to predicting the consequences of a nutrient balance on physiologic and pathologic processes will be refined and improved; and *4*) plant food production will continue to undergo a genome-based research evolution, although space constraints have limited discussion here of this component of the human nutrient requirement dimension. Plants, after all, are the primary harvesters of the energy that we depend upon from the Sun, and they serve to concentrate minerals from the environment and produce many of the vitamins that we require for survival.

I believe that it is probably going to be a long time (perhaps 30 years or more?), due in part to the complex nature of the interaction between specific genotypes and nutrient intakes, before it is possible to personalize nutrient recommendations for most individuals (other than for those with well-defined monogenic differences) that are based on knowledge about nutrient-food-genetic pathways. However, we will much sooner and with greater precision be able to define the "right diet for the right population," if we are all prepared to move our science squarely into and become an active player in the advancing biology of the early 21st century.

What a wonderful time it is to be in nutritional science. However, let us not be swept away by the lack of vision or an insufficient recognition of the revolution in the life sciences that is rapidly unfolding. To recap, the question raised at the beginning of this article was "What does the genome mean for me, my research and my institution?" (7). Although I may not have answered the question fully or adequately, it was Eugene Ionesco who said "It's not the answer that enlightens but the question." Finally, we must be not only committed but also passionate in our quest to advance nutritional science along with the march of modern biology. According to Snyder (102), Arthur M. Sackler, who established the Medical Tribune newspaper, said, "Art is a passion pursued with discipline and science is a discipline pursued with passion. Passion is the engine that drives creativity." This says it all.

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