Published in final edited form as:
J Nutr. 2005 July ; 135(7): 1613–1616.

The Nutritional Phenotype in the Age of Metabolomics

S. H. Zeisel[1], **H. C. Freake**, **D. E. Bauman**, **D. M. Bier**, **D. G. Burrin**, **J. B. German**, **S. Klein**, **G. S. Marquis**, **J. A. Milner**, **G. H. Pelto**, and **K. M. Rasmussen**
American Society for Nutritional Sciences Long Range Planning Committee, Bethesda, MD 20814-3990

Abstract

The concept of the nutritional phenotype is proposed as a defined and integrated set of genetic, proteomic, metabolomic, functional, and behavioral factors that, when measured, form the basis for assessment of human nutritional status. The nutritional phenotype integrates the effects of diet on disease/wellness and is the quantitative indication of the paths by which genes and environment exert their effects on health. Advances in technology and in fundamental biological knowledge make it possible to define and measure the nutritional phenotype accurately in a cross section of individuals with various states of health and disease. This growing base of data and knowledge could serve as a resource for all scientific disciplines involved in human health. Nutritional sciences should be a prime mover in making key decisions that include: what environmental inputs (in addition to diet) are needed; what genes/proteins/metabolites should be measured; what end-point phenotypes should be included; and what informatics tools are available to ask nutritionally relevant questions. Nutrition should be the major discipline establishing how the elements of the nutritional phenotype vary as a function of diet. Nutritional sciences should also be instrumental in linking the elements that are responsive to diet with the functional outcomes in organisms that derive from them. As the first step in this initiative, a prioritized list of genomic, proteomic, and metabolomic as well as functional and behavioral measures that defines a practically useful subset of the nutritional phenotype for use in clinical and epidemiological investigations must be developed. From this list, analytic platforms must then be identified that are capable of delivering highly quantitative data on these endpoints. This conceptualization of a nutritional phenotype provides a concrete form and substance to the recognized future of nutritional sciences as a field addressing diet, integrated metabolism, and health.

Concept of the nutritional phenotype

Our understanding of the relations among nutrition, integrated metabolism, and health will be revolutionized by the considerable advances in genomics (the study of gene expression), proteomics (the study of changes in proteins), and metabolomics [the study of small molecular weight molecules within the spectrum of biochemical pathways; see our earlier publication (1)] made possible by new scientific technologies. It is now possible to prioritize and consolidate the measures potentially relevant to nutrition and health in a defined and integrated set of genetic, proteomic, metabolomic, anthropometric, and behavioral measurements that would serve to estimate actual nutritional status: we call this the nutritional phenotype. Nutritional status modulates virtually all body functions, including various ongoing metabolic processes; taken together, these processes have a profound effect on the development of and potential for each individual's future health. Although scientists in other disciplines appreciate that metabolism and metabolic regulation are central to the understanding of how molecular events result in health or disease, their work should be coordinated with that of nutrition scientists to address the task of measuring the nutritional phenotype.

[1]To whom correspondence should be addressed. E-mail: steven_zeisel@unc.edu.

We are familiar with assessing nutritional status; why is it necessary to propose the concept of the nutritional phenotype? In the past, only a limited number of biomarkers, physical attributes, and eating behaviors were used for assessing nutritional status. Research was typically designed to address focused hypotheses about the links between existing nutrition deficiencies and diseases and was not designed to be either comprehensive or to predict future health. The measured markers allowed only limited insight into overall nutritional status and often were constrained by the narrow range of focus of the evaluator. In one study, methyl group status may be measured, in another, calcium status, but rarely was it possible to pursue an integrated assessment of many components. Nutrition science has been limited by the amount of tissue available, the cost of analyses, and the capabilities of the analytical technologies. It will soon become possible to measure thousands of metabolites in small (microliter) amounts of biological tissues and fluid at modest cost (2). Just as gene oligoarrays made it possible to study tens of thousands of genes simultaneously, new metabolomics methods make it possible to obtain thousands of analyses from a single biological specimen. Our experience suggests that adding carefully selected parameters to an existing risk analysis strengthens the predictive value of the measures for disease. For example, in the area of cholesterol and heart disease, the predictive value for biomarker measures increased as additional layers of technical analyses were added: total cholesterol measures were enhanced when LDL assessment was added; this was improved when HDL measures were added and further improved with the addition of homocysteine, fibrinogen, lipoprotein(a), LDL particle size, and C-reactive protein (3). This expanded analytical capability suddenly creates an opportunity for a marked expansion of our understanding of diet-related processes; to do so, however, we have to reach consensus about the smallest set of measures that provides an adequate estimate of actual nutritional status, i.e., the nutritional phenotype. This set of measures could then be included in research protocols, permitting comparison across many different experimental studies. By defining the nutritional phenotype now, nutrition will focus the development of analytic and informatic capacity on methodology that is most likely to enhance our understanding of nutrition and its effects on health.

The well-being of an individual can be described along a continuum that ranges from disease and dysfunction, to health and optimal function. Although well-being is influenced by a diverse set of inputs (genes, environment, behaviors), nutritional phenotype influences the response to these inputs and the precise location of the individual on the well-being continuum. Genes are important for determining function, but nutrition modifies the extent to which different genes are expressed and thereby modulates whether individuals achieve the potential determined by their genetic background. Nutrition modifies both physical and cognitive aspects of performance. It also has an important effect on the risk of disease. Estimates in the literature indicate that nutrition may account for 50% or more of risk for disease and, depending on the individual, may be as important as or more important than environmental factors such as cigarette smoking (4). Although many diseases and other threats to health are independent of nutrition, the outcome of those diseases and the extent to which they affect health can be influenced by nutritional phenotype. For these reasons, it is important that the concept of the nutrition phenotype become a scientific reality.

The process for developing the nutrition phenotype

To define the nutritional phenotype, we must measure the diet-responsive subset of metabolites [metabolome (2)], gene expression (transcriptome), protein expression (proteome), anthropometrics, and functional and behavioral changes (Fig. 1). The functional measures relevant to nutrition include body composition, BMI, cognitive function, physical performance, and behaviors that are influenced by nutrient intake. Behavior is both a part of the nutritional phenotype (e.g., fatigue resulting from iron deficiency anemia) and an influence upon it (e.g., food choices).

The technologies required to measure discrete biological and functional elements of organisms continue to advance, but those developing these methods have not often been focused on nutritional phenotype as a primary objective for these methods. For example, the developing field of metabolomics is being driven by the capabilities of available analytical platforms and by the pharmaceutical industry's pursuit of metabolically active drugs. Nutrition science should lead the field of metabolomics to develop analytical platforms capable of measuring the metabolites that are most important for nutrition. To obtain such a focus, nutritional scientists should be active participants in establishing the priorities of what to measure and what informatics are needed to ask questions that are relevant to nutrition. Nutrition should be the major discipline establishing the variation in these compositional elements as a function of diet, and then linking these variations to the functional attributes in organisms that derive from them. A similar process is ongoing in proteomics and in genomics. Characterization of the nutritional phenotype will require the participation of scientists with a very broad range of skills (Fig. 2), and nutritional scientists should lead efforts to involve these potential collaborators.

Establishing the nutritional phenotype will be an evolving process. Current limitations in both technology and resources will constrain the capacity to measure all of the elements of potential interest. Of necessity, research will have to first address a narrower scope of the components of the nutritional phenotype, focusing on those measures that are assigned priority because they are most likely to be useful in predicting health-disease outcomes. To this end, it will be important to develop a consensus prioritized list of the measures in the nutritional phenotype that form the minimal set usable to estimate nutritional status and can now be made accurately in accessible tissues. This minimal list might expand as technology and knowledge base improve. Such prioritization would require a determination of which pathways can be reliably evaluated and are understood well enough to interpret relative to establishing a link between nutrient intake and health and disease. Active collaboration among nutrition scientists and analytical chemistry and biotechnology scientists is required to decide the size and scope of the list of genes, proteins, and metabolites to measure. Similar collaborations with biotechnology and behavioral scientists will help refine methods for making the functional and behavioral measures proposed. Reaching a consensus about which measures are appropriate and practical as part of human and animal studies is a logical and appropriate task for the membership of our society. Nutritional science contains some of the interdisciplinary expertise to begin to define such a listing, but scientists from many other disciplines will be necessary. It will require an organized attempt by nutrition science to reach consensus about the components of the nutritional phenotype and then to communicate this consensus to scientists external to nutrition, who are currently making the choices as to which intellectual and financial investments to make in analytic instrumentation.

Now is the time for nutrition scientists to partner in the development of the technologies of metabolomics. Although genomic and proteomic methodology is relatively mature, analysis of the metabolome is only beginning. NMR spectroscopy (5), MS (6), nanoprobe technology (7,8), and classical chemistry approaches all address portions of the metabolites to be measured at the accuracy necessary. Identifying the components of the metabolome that are most important for measuring the nutritional phenotype and most closely linked to metabolic health will accelerate the development and application of one or more of these technologies. At the same time, increased understanding about the capabilities of new analytical platforms could stimulate new approaches in nutrition research. Nutritional priorities should guide the research and development of analytical chemistry and vice versa to accelerate the capacity to measure nutritional phenotype. A closer relation between the major academic societies and their companion industries, such as could be obtained by holding joint national meetings, would create new opportunities for both. In addition, technology-driving initiatives from the major funding institutions, including the National Institutes of Health (NIH), United States

Department of Agriculture (USDA), and the National Science Foundation (NSF), should include nutritional sciences priorities within the stated goals for the new analytical platforms being developed. As a visible consensus concept, the nutritional phenotype would facilitate this goal.

Although there have been significant advances in our capacity to measure the genome, proteome, and perhaps soon the metabolome, we have advanced slowly with developing methodology for measuring functional and behavioral components of the nutritional phenotype. As discussed above for metabolomics, nutrition scientists should partner with other disciplines and with biotechnology scientists in a focused attempt to develop methods for a prioritized list of measures to be included in the nutritional phenotype.

Bioinformatics tools will be essential for management of data and its transition to actionable knowledge because the nutritional phenotype will consist of thousands of measurements, even in its first stages. Currently, bioinformatics is often used to manage genomic data. The nutritional phenotype will certainly contain extensive genomic data per sample but must also include more disparate biological, physiological, and behavioral data to describe more fully the nutritional inputs and responses in an overall phenotype. A first-generation prioritized listing defining the components of the nutritional phenotype and an appreciation of the questions that nutritional science will be asking would guide informatics specialists to develop the tools needed to create an integrated synthesis of the nutritional phenotype. In addition, nutrition science must train future bioinformatics scientists who can address the complexity of combining metabolic pathways with an individual health phenotype.

Actions and questions

The conceptualization of a nutritional phenotype provides a concrete basis for recognizing nutrition science as a field that is developing and applying appropriate tools of modern life sciences to address integrated metabolism (1,2). Nonetheless, the nutritional phenotype raises a large number of important, unanswered questions with implications for the future of the American Society for Nutritional Sciences (ASNS), Society for International Nutrition Research (SINR), and the American Society for Clinical Nutrition (ASCN). By providing a concrete substance to the basic ideas of integrative metabolism of humans, the nutritional phenotype can be used to identify specific actions that these societies can take to address important nutrition issues and to move nutrition phenotyping forward. Working with the NIH and the USDA, ASNS, SINR, and ASCN will have to identify consensus panels to characterize the different components of nutritional phenotype more precisely. Workshops (FASEB conferences, symposia at Experimental Biology, NIH-ASNS-SINR-ASCN partnered conferences) will serve to expand, refine, and communicate this model, explore new questions, and develop collaborations with the disciplines of biotechnology, bioinformatics, functional assessment, analytical chemistry, and other sciences. Finally, our societies will be responsible for defining the structures and contents of the training programs for the next generation of students who must become the nutrition scientists of the future (e.g., cross-disciplinary training/broader exposure to diverse technologies). With such training and direction, we hope that young scientists will develop a better understanding of the nutritional phenotype in the relation between nutrition and health.

LITERATURE CITED

1. Zeisel SH, Allen LH, Coburn SP, Erdman JW, Failla ML, Freake HC, King JC, Storch J. Nutrition: a reservoir for integrative science. J. Nutr 2001;131:1319–1321. [PubMed: 11285344]
2. German JB, Bauman DE, Burrin DG, Failla ML, Freake HC, King JC, Klein S, Milner JA, Pelto GH, et al. Metabolomics in the opening decade of the 21st century: building the roads to individualized health. J. Nutr 2004;134:2729–2732. [PubMed: 15465774]

3. Kullo IJ, Ballantyne CM. Conditional risk factors for atherosclerosis. Mayo Clin. Proc 2005;80:219–230. [PubMed: 15704777]

4. McGinnis J, Foege W. Actual causes of death in the United States. J. Am. Med. Assoc 1993;270:2207–2212.

5. Wang Y, Holmes E, Nicholson JK, Cloarec O, Chollet J, Tanner M, Singer BH, Utzinger J. Metabonomic investigations in mice infected with *Schistosoma mansoni*: an approach for biomarker identification. Proc. Natl. Acad. Sci. U.S.A 2004;101:12676–12681. [PubMed: 15314235]

6. Watkins SM, Zhu X, Zeisel SH. Phosphatidylethanolamine-*N*-methyltransferase activity and dietary choline regulate liver-plasma lipid flux and essential fatty acid metabolism in mice. J. Nutr 2003;133:3386–3391. [PubMed: 14608048]

7. Vo-Dinh T. Nanobiosensors: probing the sanctuary of individual living cells. J. Cell Biochem. (suppl.) 2002;39:154–161. [PubMed: 12552615]

8. Looger LL, Dwyer MA, Smith JJ, Hellinga HW. Computational design of receptor and sensor proteins with novel functions. Nature (Lond.) 2003;423:185–190. [PubMed: 12736688]

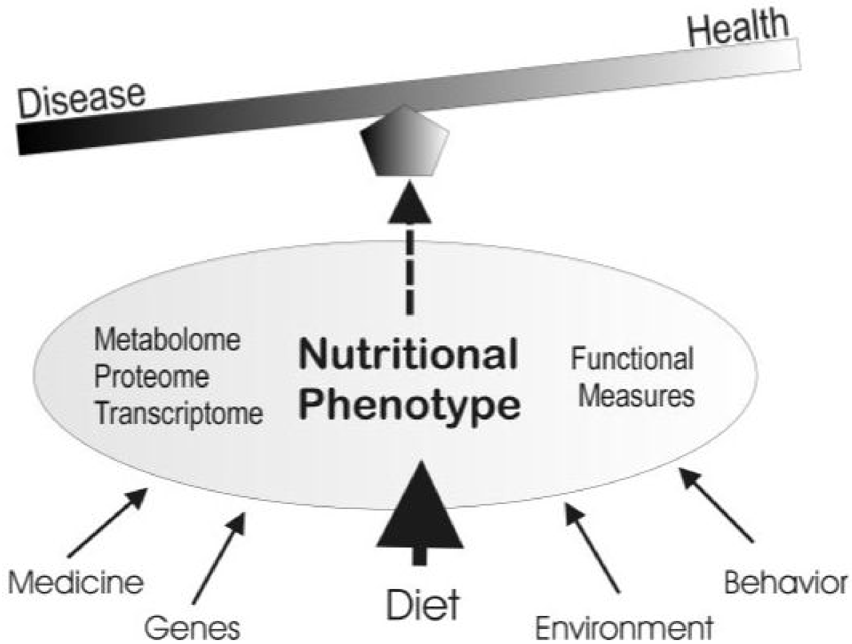

FIGURE 1.
Components of the nutritional phenotype. The nutritional phenotype consists of biochemical measures of metabolites (metabolome), proteins (proteome), and of RNA (transcriptome) as well as of functional measures (such as body weight or behaviors). This nutritional phenotype can be related directly to health.

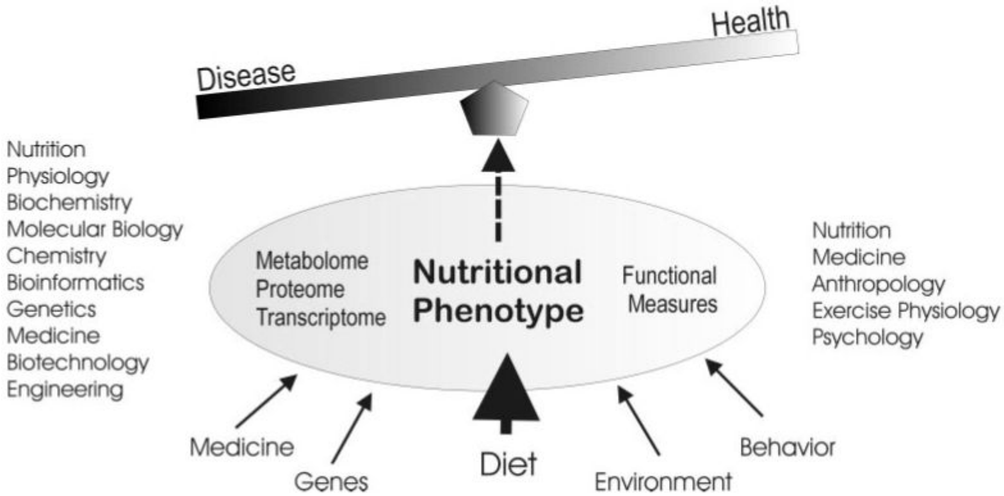

FIGURE 2.
Many disciplines must be involved in the development of the nutritional phenotype. Nutrition must interact with a diverse set of biological sciences to develop the metabolomic, proteomic, and genetic components of the nutritional phenotype. At the same time, clinical, behavioral, and other social sciences will have to collaborate on the identification and assessment of the functional measure components of the nutritional phenotype.