Metabolomics in the Opening Decade of the 21st Century: Building the Roads to Individualized Health


American Society for Nutritional Sciences Long Range Planning Committee

ABSTRACT It is rapidly becoming possible to measure hundreds or thousands of metabolites in small samples of biological fluids or tissues. This makes it possible to assess the metabolic component of nutritional phenotypes and will allow individualized dietary recommendations. ASNS has to take action to ensure that appropriate technologies are developed and that metabolic databases are constructed with the right inputs and organization. The relations between diet and metabolomic profiles and between those profiles and health and disease must be established. ASNS also should consider the social implications of these advances and plan for their appropriate utilization. J. Nutr. 134: 2729–2732, 2004.

Individualizing diet and metabolism

Foods are, ideally, a source of nourishment as well as delight, comfort, fuel, and protection. However, in many people inappropriate choices in diets lead to metabolic imbalances, thereby enhancing the risk of diseases such as atherosclerosis, obesity, type 2 diabetes, hypertension, food allergies and intolerances, gastrointestinal disorders, and inflammatory diseases. The solution would appear to be simply to choose a better diet. However, what is a better diet? The same diet is not ideal for everyone. The genetic and phenotypic variation among humans is so wide that a diet that might be optimal for one individual could predispose another to disease. Although this fact has become increasingly evident as public health agencies attempt to address diseases stemming from metabolic dysregulation, the scientific knowledge necessary to personalize diets in not yet in place. The nutrition scientific community must now build the basic knowledge required to link personal metabolism to optimal diets, one of the prerequisites for empowering individuals to make better food choices to support their quality of life.

Nutrition is, at its heart, a multidisciplinary field, focusing on the integrative metabolism of animals and humans (1). Nutritionists have strived for the last century to deduce the mechanistic basis of the relation between diet and health by understanding the interaction of nutrients with metabolic pathways. The tools to extend this approach to understanding integrative metabolism in each human will include genomics, proteomics, metabolomics, and the modern tools of bioinformatics. Genomics (the study of entire genomes of organisms) provides the blueprint and proteomics (the study of all expressed proteins in a cell, tissue or organism) provides the structures and catalytic activities. However, the actual performance of an organism in its environment is most vividly reflected by its dynamic metabolism, which will have to be measured by quantitative metabolic phenotyping (i.e., metabolomics, the study of all small-molecular-weight molecules within the entire spectrum of biochemical pathways in a cell, tissue, or organism). In some cases, the simple measurement of metabolite concentrations may not suffice because they fail to capture metabolic flux. Kinetic measurements of metabolite concentrations under defined circumstances may be required.

The following 4 key steps are necessary to generate the framework of basic knowledge required to support personalized metabolic health: 1) Technologies will have to be developed and implemented to measure metabolites in humans (and experimental animals) quantitatively and comprehensively. 2) Databases will have to be assembled that contain data from a representative subset of the population in which individual metabolic (metabolomic) data are arrayed against a wide range of phenotypic endpoints. 3) Causal relations will have to be drawn between metabolism and phenotype. 4) The biochemical relations between diet and metabolism will have to be established with sufficient mechanistic understanding to make quantitative predictions of how to employ diet to guide metabolism. Steps 1 and 2 are essential to establish the foundation for this work, and Steps 3 and 4 are concerned with the discovery process itself.

Once the basic framework is established, other issues emerge. These include the creation of systems for collecting, storing, and accessing databases, as well as mechanisms for delivering the new technology for clinical and public health use. This statement focuses on activities that are essential for the development of the basic science framework and the role that ASNS can play in its development.

Phase 1: the foundation

The technologies of metabolomics. The strength of genomics and proteomics as analytical targets is that they can
both be addressed, at least conceptually, by single analytical platforms. That is, all genes expressed in a sample can be determined by a single DNA array (2) and all proteins by a single polyacrylamide gel (3). This is not the situation for metabolites. These small molecules exist in cells, tissues, and biofluids as complex mixtures varying in concentration by orders of magnitude. No single analytical platform is capable of measuring all metabolites simultaneously. Separate quantitative techniques will have to be linked in technology chains to complete the analysis of single samples. Once in place, however, these chained technologies can be scaled to high-throughput, low-cost and high-speed data production systems as readily as those of genomics and proteomics. Perhaps more importantly for individual assessment of health, analytical strategies for measuring metabolites are more amenable to miniaturization and remote sensing than genomics and proteomics. In principle, there are no fundamental hurdles to establishing a system of high-throughput, quantitative metabolomics, comparable to the human genome project. A nutritional dimension is essential to the metabolic profiling initiatives by the NIH and the National Institute of Environmental Health Sciences; nutritional scientists and ASNS can initiate by the NIH and the National Institute of Environmental Health Sciences; nutritional scientists and ASNS can play a vital role in emphasizing this (4). The scientific membership of ASNS must then guide the development of technologies to ensure that methods are quantitative, comprehensive, and amenable to creating the legacy databases that are required to define the role of diet in metabolism. Legacy databases are those datasets considered to be sufficiently quantitatively accurate and well described to allow subsequent investigators to compare data absolutely and to mine the data electronically. Compromises will invariably be required, but it will be essential that nutrition researchers, not technologists, make decisions regarding the specific metabolites and samples for analysis.

Issues to resolve. These include the following: 1) What are the key (i.e., minimum necessary) metabolites that should be measured quantitatively? 2) Which nonessential nutrients should be included in the analysis? 3) What metabolites will require kinetic measurements of flux? 4) Which fluids, cells and/or tissues should be sampled?

Actions to be taken. These include the following: 1) Establish formal collaborations with analytical chemistry as a companion to Nutrition Symposia at Experimental Biology, and presentations by the American Chemical Society, the American Oil Chemists’ Society, and the Pittsburgh Conference (PITTCON). 2) Establish interactions with the biotechnology industry that develops and commercializes high throughput analytical platforms to establish priorities and accelerate the process of developing the key analytical devices. 3) Incorporate modern analytics as a course/workshop in nutrition graduate education.

The databases of individual metabolic health

Because the technologies that permit the generation of large databases of human metabolites are largely available, it is possible to begin measuring human metabolites in specific populations in connection with public health programs such as National Health and Nutrition Examination Survey. However, it is important for the ASNS to participate in the phrasing and context of these databases. This participation is necessary to ensure that the databases include not only metabolites, but also the nutritional variables and phenotypic endpoints necessary to understand the associations among metabolites, diet and health, not simply the difference between health and disease. For example, it is critical that the metabolomic databases include both the fasted and the postprandial state in the same individuals in response to clearly defined diets. It is equally important to include data from individuals at varying ages and individuals who have grown and aged under different dietary and metabolic backgrounds. Once in place, these phenotypically annotated databases will constitute the core resource for the next decades of nutrition research and application.

Some issues to resolve. These include the following: 1) When during the diurnal and life cycles should metabolic profiles be measured? 2) What type of meal should constitute the fed condition, including consideration of which basic nutrients, food matrices, and nonessential components (e.g., nondigestible polysaccharides, flavonoids, carotenoids)? 3) Which endpoints of health in addition to disease should be measured? 4) What are the variables or markers that reflect health maintenance and disease prevention? 5) How can endpoint variables, such as behavior, sensation, and performance, be quantified absolutely rather than relatively?

Actions to be taken. These include the following: 1) Establish collaborations with behavioral and sensory scientists to develop quantitative endpoints for including behavior data of importance to nutrition; and 2) organize symposia and workshops on the quantitative assessment of multiple aspects of acute and chronic health.

Phase 2: discovery

The association between metabolism and health. The value of defining a single, electronically accessible, well-annotated database containing extensive human metabolic data, annotated for phenotype, is undeniable, and represents a key resource for the future of human health. However, bioinformatics and its ability to mine large datasets will be compromised if the metabolite and endpoint data are not quantitative. This point is most vividly made using the example of serum cholesterol. The misperception that cholesterol is a biomarker of disease (i.e., cardiovascular disease) has slowed progress in a great many fields of nutrition, physiology, and health. Cholesterol is not a biomarker of disease; it is a metabolite whose abundance in blood is a direct quantitative reflection of various processes related to lipoprotein metabolism and that can in some individuals indicate an accelerated rate of development of disease. The decision to measure cholesterol absolutely instead of relative to, for example, serum triglyceride, was critical to its emergence as a predictor of future health problems. It is equally important that the lessons learned from cholesterol be translated into the next generation of quantitative metabolic profiling, i.e., metabolomics. Data must be quantitative, not relational. Data must be individual and not the averages of populations. Metabolic data must be defined in context, temporally, physiologically, and nutritionally. Finally, data must be obtained from humans spanning a range of genotypes, phenotypes, diets, and ages. With this dataset in place, ASNS can exploit its assets in research and application, and education. Graduate programs will use the databases as a core environment in which to teach and illustrate the relations between diet and health, diet and development, diet and behavior, genetics and dietary responsiveness, genetics and dietary choices, and the application of epidemiologic tools. Just as the various genomes have become datasets that are guiding and inspiring the next generation of geneticists and biochemists around a single consensus knowledge base, the metabolomics database will guide and unite nutritionists in their pursuit of the associations between diet, metabolism and health.
Actions to be taken. These include the following: 1) Broaden curricula to include bioinformatics at the nutrition graduate level as a companion to statistics. 2) Collaborate with biostatisticians to include the data management requirements of personalized nutritional assessment. 3) Recruit epidemiologists and bioinformaticians seeking new applications of their science to conduct research relevant to nutrition.

Pathway modeling, target identification and mechanism definition

The basic rationale for creating quantitative databases of metabolites drawn from humans is that these data reflect the metabolic systems in action. They are the entry into understanding how metabolism is functioning in each individual. It is likely that a substantial branch of nutritional science will emerge as the modeling of metabolic pathways becomes increasingly detailed and better able to use metabolic profiling data. ASNS can guide this emergence by encouraging nutritionists and collaborating scientists to develop the bioinformatic tools necessary to map metabolic data onto human biochemistry, metabolism, and physiology. Because many of these tools are already being developed, nutritionists will not have to build these independently. However, nutritionists should help to guide their development. It will not be sufficient to simply illuminate the associations between phenotypes and metabolic profiles to predict how diet should be changed in individuals. For a metabolomics systems approach to be valuable, it must accelerate the progress of scientific research toward the goals of understanding metabolism in molecular detail and systemic organization. Identification of metabolic profiles that are consistent with specific health outcomes will invariably lead scientists to propose competing hypotheses as the causal mechanisms behind these relations. These hypotheses will be tested independently. The major value of a central database structure will become evident when the scientific tests of these hypotheses constitute another informatic layer of annotation within the same electronically accessible resource.

Actions to be taken. These include the following: 1) Reenergize the metabolic modeling subject within ASNS with symposia and workshops. 2) Develop formal liaisons with the fields of metabolic modeling to include the biodiversity of human metabolism and encourage these fields to develop methods that predict diet-responsive targets from metabolite patterns

Phase 3: implementation

The role for nutritional scientists and ASNS in bringing metabolomics into the public domain. Over the next 10 years, nutrition scientists will guide the major health organizations to establish the reference databases relating to human metabolism as public knowledge. These databases will consist of quantitative metabolomes annotated by phenotypic endpoints. Precise mapping of these databases according to the associated metabolic pathways and the genetic, nutritional, and pharmacologic means to alter them will provide a knowledge system for guiding individual health promotion in a variety of ways. A critical question that arises with the creation of new knowledge and new technologies is how to utilize them to benefit the health and welfare of individuals and populations. The expanding body of research in policy sciences and public health shows that this is always a complex social process. Thus, it is reasonable to expect that the implementation of metabolomics in clinical and public health will face major challenges. Nutrition scientists will have the opportunity to influence health policy and health organizations to realize the potential of measuring metabolic phenotypes and building the reference databases of human metabolism over the next 10 years, but they must be prepared to recognize these challenges and play constructive roles in addressing them. ASNS, as an organization, can support and facilitate the preparation of nutritional scientists to meet these challenges through educational activities, organization of research forums, activities of Research Interest Section groups, and through the actions of special committees. Indeed, nutritional scientists can be actively and effectively involved in the application of metabolomics to improve health through collaboration with policy scientists, particularly those whose areas of expertise relate to health interventions, as well as other inter-disciplinary activities aimed at mapping-out, monitoring, and evaluating implementation processes.

It is possible to develop models describing how people will interact with this knowledge resource. ASNS scientists will take an active role in producing this resource and should also be involved in determining how it will be applied. Perhaps such a knowledge base will become the “stock in trade” of the next generation of dieticians and practicing nutritionists being trained by ASNS members. That is, having been trained at the university level in the science of integrative metabolism and how it is directed by diet, graduates would become the practicing clinicians that interface between individual consumers and the scientific knowledge. One could imagine, for example, that people would obtain quantitative data on their personal metabolic status through existing clinical outlets. Experience suggests that even with single-measure indicators, such as a blood cholesterol test, translating that knowledge into daily lifestyle changes is typically a complex process for individuals. One can anticipate that to utilize information on their full metabolic profile, people will require substantial professional guidance on interpreting, planning, and implementing choices that are commensurate with their desired outcomes.

Actions to be taken. These include the following: 1) Organize workshops/Experimental Biology symposia on the utilization and social implications of metabolomics data. 2) Begin planning for educational needs for dieticians/clinical nutritionists who will be able to utilize both personalized metabolic and nutritional assessment data, as well as the technologies of e-based diagnostics and intervention.

Going to scale: methods for personalized assessment.

Once databases of metabolism and the tools to interact with them are established, the next challenge is to develop systems that will make them accessible and useful. To become feasible on a public health scale, the assessment technologies will have to be miniaturized relative to the research phases, an essential step to facilitate cost reduction and speed. Although whole-scale metabolic analysis is unlikely to be cost effective, a modified spectrum of analytes will be capable of being acquired more immediately and noninvasively (breath, urine, saliva, skin, and/or micro-blood samples). In a practical real-world implementation of routine human health assessment, it is imperative that the knowledge database provide directions for identification of the key metabolites to measure, and when and under what circumstances samples should be collected.

Actions to be taken. These include the following: 1) Organize symposium planning for miniaturized assessment technologies. 2) Coordinate ASNS representatives with a spectrum of health and policy scientists and representatives of industry to develop mechanisms for building and implementing noninvasive and affordable technologies.
LITERATURE CITED


FURTHER READING