What do -omics mean for the science and policy of the nutritional sciences?¹–³

Gerald T Keusch

ABSTRACT

The development of systems biology is revolutionizing the way we are studying and learning about human health. It is a way of thinking and a systematic attempt to integrate information from several fields of study (physical, biological, chemical, engineering, etc) to develop a more kinetic and real-time understanding of complex biological processes. It uses mathematical modeling tools to chart dynamic interactions between the components of a biological system, eg, genes, transcripts, proteins, metabolites, and cells, to simulate and analyze networks and pathways and the spatial and temporal relations that exist in biological systems. The term -omics represents the rigorous study of various collections of molecules, biological processes, or physiologic functions and structures as systems, represented most prominently by genomics. In the field of nutrition, there is a systems approach been applied to evaluating the effect of vitamin A status on mortality rates in young children in developing countries, it might not have taken 20 years to go from the initial epidemiologic observations to global and real-time understanding of complex biological systems. Better understanding of the functional biology of retinoids on different tissues that mediate host resistance to infection, and their synergistic interactions in biological, metabolic, and functional terms, could have provided a plausible mechanism for the observed effect on mortality. There are 3 policy take-home messages: 1) When controversies exist, invest in the science needed to sort them out. 2) Increase the amounts of money available for health research and interventions relevant to developing countries. 3) Ensure that policymakers understand the issues and why they are important and understand the science and its relevance. Am J Clin Nutr 2006;83(suppl):520S–2S.

KEY WORDS Systems biology, vitamin A, retinoids, policy

INTRODUCTION

Science predictably moves ahead in leaps but is inherently dependent on all that has gone before, including the many small steps that an innumerable leap forward. As in politics, those who do not know the past are forced to repeat it. It has been this way in the mid-20th century. Soon thereafter, the term genomics was coined by McKusick and Ruddle as the catchword for a new journal they were editing, intended to reflect an emphasis on linear gene mapping and DNA sequencing as the critical elements of a modern genetics science.

FROM -OME TO -OMICS

Expansion of the -ome concept was probably inevitable and has created a host of new terms, eg, antigenome, bacteriome, cardione, epigenome, erythrome, immunome, microbiome, neurope, osteome, physiome, proteinome, psychome, transcriptome, and many others. Most of these terms are buried somewhere in the literature, without biological impact, and are neither in common use now nor likely to become so in the future. Nonetheless, there has been a steady shift to the scientific study of these various collections of molecules, biological processes, or physiologic functions and structures as systems, that is, a shift from -ome to -omics, as represented most prominently by genomics. Genomics science has, interestingly, garnered great public attention through the human genome project and the recent completion of the complete sequencing of the human genome. To take this information to the next step, a number of other -omics have evolved. The most well known is the separation of genomics itself into 2 related but distinct approaches, structural and functional genomics, which are closely linked to transcriptomics and proteomics, which focus attention on the expression of genes and their specific protein products. The approach is so powerful that it has escalated of late into a host of other -omics (Table 1) as scientists scramble to take a systems approach, while some, tongue-in-cheek, refer to the field of “unknowmics,” or the study of genes of unknown function.

SYSTEMS BIOLOGY: A REVOLUTION

What this has led to amounts to another revolution in biology, in this case, one taking place at the intersection of the new -omics. In essence, it amounts to a lumping, not splitting, of thinking and

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major intervention to reduce childhood mortality (3). However, the conclusion was to promote vitamin A supplementation as a major intervention to reduce childhood mortality (3). Additional studies conducted clinical trials were reported supporting the effects of vitamin A that supplementation was broadly accepted as a major public health intervention (8).

It took 2 decades, then, to go from observation to intervention (9). Why? First, there was a question as to whether the effect was biologically plausible (10). Second, there was a concern that the field data were not rigorous enough to go forward. After all, public health interventions seem to operate within a zero-sum game, wherein investments in one program come at the expense of investments in another. Third, the mechanisms underlying the observations were unclear. This was reinforced by a fourth concern, that only limited evidence existed that vitamin A deficiency had an effect on disease morbidity and therefore that no explanation existed for its apparent effects on mortality.

What might have shortened the interval from observation to intervention? A systems approach to vitamin A. Had there been a more comprehensive and organized approach, linking biochemistry, physiology, molecular and cellular biology, genetics, immunology, epidemiology, and clinical medicine—an integration of separate disciplinary approaches into a systems context—it is likely that the long delay could have been reduced. There have been 3 intervention approaches (Table 2). The major focus has been on just one, however: the provision of supplements, which requires external support and extensive logistics. It is often favored by external donors, because they can measure the delivery of the intervention, sometimes assess its impact, and take credit for both. The second approach requires

### VITAMIN A: A NUTRITION CASE STUDY

Although vitamin A was originally thought to be a vitamin with “anti-infective” properties, subsequent research focused on the role of vitamin A in vision, including rod function and the physiology of night vision, and then turned toward the biochemistry of the retinoids. A separate stream of public health research developed when the analysis of a population-based vitamin A supplementation intervention to prevent malnutrition-related keratomalacia revealed an unexpected large reduction in all-cause mortality in the experimental group (2). Additional studies by the same group supported the observation that vitamin A interventions reduced all-cause mortality by 25–30%. The logical conclusion was to promote vitamin A supplementation as a major intervention to reduce childhood mortality (3). However, the proposal generated considerable controversy, primarily because the effects observed seemed to be too good to be true, contradictory data were reported (4), and there was no clearly demonstrable impact on the major causes of morbidity (5, 6) and no plausible mechanism to explain a reduction in mortality (7). In addition, just one group of investigators had generated the supporting data from large field studies, which raised the possibility of unintended bias. It was not until other groups began to report similar results from the field in different settings and carefully conducted clinical trials were reported supporting the effects of vitamin A that supplementation was broadly accepted as a major public health intervention (8).

### TABLE 1

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Chemogenomics</td>
<td>The screening of chemical compounds against genes or gene products, such as proteins or other targets, as a method of drug discovery, to elicit gene responses, find potential drug candidates, and identify and validate therapeutic targets.</td>
</tr>
<tr>
<td>Epigenomics</td>
<td>A whole-genome approach to the study of environmental or developmental epigenetic effects on gene function, focusing on genes whose function is determined by external factors.</td>
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<td>Toxicogenomics</td>
<td>The combination of toxicology, genetics, molecular biology, and environmental health to determine the response of living organisms to environmental stress or toxic agents so that new drug candidates can be screened through a combination of gene expression profiling and toxicology to better understand responses at the gene level and predict the safety of potential therapeutic compounds.</td>
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<td>The integration of metabolic pathway engineering and fermentation production technologies to multiply product production per cell for the successful commercial synthesis or production of chemicals, including drugs.</td>
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<td>The study of gene products and their interactions.</td>
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<td>Kinomics</td>
<td>A subcategory of functional genomics and proteomics that concentrates on the kinetics of biomolecule interactions with their binding partners to better understand the consequences of these interactions.</td>
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<td>Metalomics</td>
<td>The study of the entire content of inorganic species within a cell or tissue type: where they are, what biomolecules they associate with, what their concentrations are as a function of time, and their functional implications.</td>
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<td>Regulomics</td>
<td>The study of gene expression at the level of genetic network regulatory mechanisms.</td>
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<td>Protein purification methods to provide a simple solution for each purification problem and scale-up for drug production.</td>
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This manner constitutes a reversal of scientific reductionism, which was the hallmark of and determinant of the success of the life sciences in the 20th century. The approach is called systems biology and represents a systematic attempt to combine information from several fields of study to develop an integrated and more kinetic and real-time understanding of biology. It proceeds through the development and use of mathematical modeling of the complex dynamic interactions between the components of a biological system, eg, genes, transcripts, proteins, metabolites, and cells, to simulate and analyze networks and pathways and the spatial and temporal relations that exist in biological systems. Systems biology is an approach to understand cause and effect in living systems, and it is proving invaluable in the modern attempts to unravel disease mechanisms, to validate drug targets, and to discover new drugs. It is an approach heavily dependent on biomathematics, and it has been the development of analytic algorithms and pattern recognition methods that has permitted systems biology to flourish. The unanswered question is whether systems biology can significantly contribute to the efforts to apply biomedical research to the improvement of human health.

### WHAT DO –OMICS MEAN FOR NUTRITIONAL SCIENCE

Term Definition

- **Chemogenomics**: The screening of chemical compounds against genes or gene products, such as proteins or other targets, as a method of drug discovery, to elicit gene responses, find potential drug candidates, and identify and validate therapeutic targets.
- **Epigenomics**: A whole-genome approach to the study of environmental or developmental epigenetic effects on gene function, focusing on genes whose function is determined by external factors.
- **Toxicogenomics**: The combination of toxicology, genetics, molecular biology, and environmental health to determine the response of living organisms to environmental stress or toxic agents so that new drug candidates can be screened through a combination of gene expression profiling and toxicology to better understand responses at the gene level and predict the safety of potential therapeutic compounds.
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- **Separomics**: Protein purification methods to provide a simple solution for each purification problem and scale-up for drug production.
the diversification of the diet to increase the intake of natural vitamin A and its precursors while ensuring its availability and the behavioral change necessary to ensure that people make the right dietary choices. The third, a genomics approach to increase the content and bioavailability of vitamin A in culturally acceptable foods, represents a delivery system that requires little behavioral adjustment (assuming that people will accept the genetically modified product as the equal of the natural product). Although science was able to deliver a genetically modified rice containing higher amounts of vitamin A precursors, the problem of stacked patents on individual processes or genes used in its development has hampered the ability to actually produce and introduce yellow rice at the global level. This is a legal problem independent of the ability of genomics to provide a viable solution, and because there is public opposition to genetically modified organisms on the basis of mis- and disinformation.

Still, we must ask whether genomics, applied early, would have made a difference? There are several reasons to think the answer is yes. A systems biology approach to understanding the functional biology of retinoids on different tissues that mediate host resistance to infection through their role in the regulation of cell maturation, synthesis of immune mediator molecules, and their synergistic interactions could have provided a plausible mechanism for the large observed effect on mortality. This might have led to targeted interventions, in which specific retinoids with immune system effects were taken to clinical studies to increase the favorable vitamin A effect. And finally, beyond the genomics involved in developing genetically modified rice, a systems approach to genetically modified plants might have addressed and resolved the lingering question on the environmental impacts of genetically modified organisms, their spread, interbreeding with indigenous plants, and their impact on biodiversity. Had this been done in a systematic manner, and in the case of vitamin A, before the legal patent issues arose, the yearly reduction in childhood mortality by some 3 million children per year, would have over the past 20 y, allowed ≈60 million children to survive early childhood.

THE SCIENCE POLICY ENVIRONMENT AND CONCLUSIONS

Over the past 20 y, there have been more squabbles over the science underlying vitamin A programs than over almost any other public health intervention. The controversies would have been better addressed by simply doing the science. This should not be so difficult, because it is primarily a matter of setting appropriate scientific priorities. However, a particular problem for this area of research is the difficulty of conducting large field studies or maintaining demographic surveillance sites so that effects of population-based interventions can be detected and separated from population trends and acquisition bias. Compounding the problem of late has been the unwillingness of traditional funders of large prospective studies to commit the long-term support required in favor of hypothesis-testing research. A second policy issue is how to end the current zero-sum game by increasing the amounts of money available for health research, and of course health interventions relevant to developing countries. Third, and related to the prior 2 issues, addressing global health disparities requires people who understand the issues and why they are important. In their absence, science policy typically serves narrow national rather than broader global concerns.

Vernon Young exemplified the best in science and policy, demonstrating the power of science and the need to apply it to real problems. He understood how genomics applied through sound policies could contribute to improving human nutrition (12). He was, in short, a leader, and leaders are in short supply. He would have loved this symposium.

REFERENCES