Nutrition as a Biological Variable (NABV)

Integrating Nutrition into Basic and Clinical Research and Care
A Conceptual Framework

Daniel J. Raiten, Ph.D.
Program Director - Nutrition

Eunice Kennedy Shriver National Institute of Child Health and Human Development
Historical Perspective

**Chemical-Analytical Era:**
- Known for the discovery and characterization of dietary essential nutrients and their roles in metabolism/health
- Followed by investigations of clinical events associated with nutrient deficiencies
- Once nutritionists had discovered the cause and treatment of the classic deficiency syndromes (e.g., scurvy, pellagra, beriberi), they turned to:

**Dietary Prescription Era:** creation of dietary recommendations (RDA/DRI, DGA), and nutrition education.

These latter efforts, along with a diversified and accessible food supply, have largely eliminated the classic deficiencies in most of the industrialized world.
So, where are we today?

While periodic review of dietary recommendations remains necessary, contemporary nutrition questions concern health effects of marginal nutrient status more than those of acute deficiency.

We can measure and prescribe, but do we really know what it means particularly in an increasingly complex health context?

Do we appreciate how nutrients interact within biological systems?

Can our current approach help us to avoid unintended health consequences or confused/confusing messages?

*IT’S TIME FOR A NEW ERA!*
Considering Nutrition as a Biological Variable: NABV
What is NABV?

• An effort to improve the credibility of nutrition as a scientific discipline
• A more effective integration of nutrition (not just food/diet) in all aspects of biomedical research and by extension to efforts to promote health, prevent and treat disease
• An effort to provide new tools and approaches to support the constituencies involved in nutrition related research
• An acknowledgement of the importance of interdisciplinary research at all levels (basic, clinical, translational)
What’s the Problem?

• Applications often do not reflect an appreciation of nutrition science and design.

• “Matchmaking” nutrient(s) to disease: based on presumptive/tenuous connections, siloed views of nutrients, or “one-size-fits-all” generalizations.

• RCTs often treat nutrients as drugs and lack essential features of nutrition science.

• A disconnect often exists between basic nutrition science and its translation to clinical research. This results, in part, from use or lack of relevant animal/experimental models and diets.
NABV May Require

• Investigators to consider the nutritional status of their subjects

• A harmonized approach to selection, use and interpretation of:
  ▪ High quality nutrient intake or dietary pattern assessments in research studies
  ▪ Current and new nutritional biomarkers
  ▪ Combining complementary bio-indicators of function/effect to give meaning to nutrient status measures

• A candid consideration of appropriate experimental models, diets and interventions to enable better translation to human conditions
Context and Conceptual Framework
Nutrition research should not be limited to what we consume.

Nutrition is inextricably involved in all biological systems.

Knowing an individual’s nutrient status reveals little about function or effect.

Nutritional status is both an input and an outcome.
Complex Health Context: not just about *too much* or *too little*!

Under-nutrition → *Nutrition Transition* → Malnutrition (over/under)

Infectious Diseases ← *Microbiome Inflammation* ← Non-communicable Disease

*DOHaD*
**Food** = accessible and available sources of essential nutrients and bioactive components

**Diet** = food and other sources of nutrients consumed; diet quality and nutritional security

**Nutrition** = biological outcome resulting from a series of processes beginning w/ consuming food (optimally, in a well-balanced diet)
Nutrition: Working Definition

The sum of all processes involved in the taking in and utilizing food substances by which growth, repair and maintenance of normal functions of the body as a whole or in any of its parts.

Because nutritional status can affect or be affected by any/all of these processes, each must be considered in determining nutritional needs, standards of care, or the roles of diet/nutrition in health and/or disease.
Tools and Approaches to Integrate Nutrition
Objectives of Nutritional Assessment

Determine the best types and amounts of evidence that fully integrate and address the roles of diet and nutrition in all aspects of health promotion, disease prevention and treatment in order to:

1. Support the safe and effective application of existing standards of clinical care, or to establish new standards;

2. Develop and evaluate programs, policies and guidance; and

3. Ensure the validity and reliability of research data and its appropriate translation.
Components of Nutritional Assessment

- Measurement of dietary intake/consumption patterns
- Inferences from anthropometry
- Measurement of biochemical indices / biomarkers of nutrient status
- Consideration of health context and factors that might impact on ingestion, digestion, absorption, metabolism, transport or utilization of nutrients
- Measure of responses to nutritional intervention

Because health context matters and because nutrition involves more than what goes in the mouth, it’s difficult to rely on single measures to draw conclusions about functional roles of diet/nutrition. *Think diabetes!*
Objectives of Nutritional Assessment

The ability to answer core questions about the role of nutrition in health or disease is contingent on the tools needed to address:

**Exposure**: what has been consumed, including bioavailability

**Status**: where an individual/population stands relative to accepted cut-offs, e.g., adequate, marginal, deficient;

**Function**: reflecting the role of a nutrient within a relevant biological system; and

**Effect**: impact of a given status or intervention on relevant functional outcome(s).

**Users**: bench/clinical researchers, care providers, program developers and implementers, M&E, policymakers
Phase 1: Lessons learned

Need for more complete view of the biology of nutrition via better understanding of:
• Nutrient interactions within biological systems:
  ➢ Fundamental understanding of nutrient biology/physiology
  ➢ Understanding bi-directional relationships: e.g., nutrition ↔ inflammation
• Ability to detect differences between nutritional need/response and physiology (e.g. iron)

Each will improve discovery, development and implementation (including interpretation) of biomarkers.
Nutrition and Inflammation: Why Does it Matter?

• Inflammation shares a bi-directional relationship with nutrition - each affects the other in ways that we are just beginning to appreciate.

• Without accounting for inflammation, interpretation of many of the most common biomarkers of nutrient status is compromised:
  ➢ Both acute and chronic inflammation can directly affect the selection, use and interpretation of biomarkers of nutrient status, function or effect.
  ➢ Inflammation can directly affect nutrient intake, absorption or homeostasis.

Reponses: INSPIRE and BRINDA
Nutrients are not drugs.

Drugs/toxins and nutrients mutually affect each other.

Potential mechanisms
- ingestion
- absorption
- transport/distribution
- metabolism
- elimination
## Potential Impact of Nutrients on Drug Metabolism

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>EFFECT ON MFO METABOLISM</th>
<th>POTENTIAL MECHANISM(S)</th>
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</table>
| proteins       | **Deficiency:** ↓ rate of metabolism  

Excess: can ↑ rate of metabolism.  

↓ protein synthesis; ↓ in synthesis of other elements, such as hormones, involved in enzyme induction. |
| lipids         | deficiency (or diet high in saturated fatty acids): ↓ excess (or diet high in polyunsaturated fatty acids): ↑ activity and inducibility of MFO enzymes.  

↓ activity of MFO possibly connected to the requirement for polyunsaturated fatty acid in the β-position of phosphatidylcholine (lecithin) which is an essential component of the MFO system. |
| carbohydrates  | excess: ↓  

secondary effect due to ↓ protein or possibly inhibition of P$_{450}$ via ↓ in supporting enzyme components. |
| vitamin C      | deficiency: ↓  

excess: ↓ MFO activity  

alterations in activities of P$_{450}$ and P$_{450}$ reductase. |
| vitamin B-6    | deficiency: ↓  

↓ synthesis of heme; possible impairment of protein synthesis. |
| thiamin (vitamin B$_{1}$) | deficiency: ↓ activity of cytochrome P$_{450}$  

excess: ↓ (both reductase and P450)  

↓ activity of specific P$_{450}$ isozymes and perhaps other enzymes in deficiency by an unknown mechanism.  

Effect of excess may be due to ↑ substrate binding. |
| riboflavin (vitamin B$_{2}$) | deficiency: ↑ or ↓ depending on the severity.  

↓ reductase activity but ↑ P$_{450}$ activity such that metabolism of some drugs will be ↑ while others may be ↓. |
| vitamin E      | deficiency: ↓↑  

because activities of P$_{450}$ and reductase are unaffected it may be due to maintenance of the lecithin component. |
| iron           | deficiency: ↑ and ↓  

excess: ↑ in microsomal lipid peroxidation  

differential effects on various components of the MFO system. ↑ lipid peroxidation could lead to damage to the integrity of the system. |
Take Home Messages

- Nutrients are intimately involved in systems regulating drug metabolism.
- The table presents a “siloed” single nutrient perspective.
- We need to learn more about:
  - Interrelationships of multiple nutrients in systems regulating drug metabolism
  - Implications of anomalies in multiple nutrients
  - How to discern differences due to:
    - Nutrient exposure scenarios
    - Physiological response to disease
    - Normal development (impact on both nutrient requirements and developmental pharmacology)
    - Drug nutrient interactions on these scenarios

For the sake of both scientific rigor/reproducibility and to advance the science, nutrition must be integrated into studies of current and new therapeutics
How Do We Understand Effect?

Effect of interventions and/or status can be measured by assessing:

- Direct Impact on specific nutrient dependent system: e.g. transketolase (vit B₁); EGPT (vit B₆)
- Indirectly *via* assessment of non-specific changes in function: e.g., changes in growth, immune function, neurodevelopment

What are the roles of:

- Outcomes that reflect some aspect of function or effect, but independently are not sensitive/specific measures of particular nutrient relationships (e.g., neurodevelopment)?
- Measures traditionally used for program development and evaluation, but may not be sensitive/specific to nutrition in other contexts (e.g., growth, anemia, DALYs)?
Definitions and Expectations

Biomarkers
- Sensitive and specific measures of nutrient exposure, status and function
- With the exception of exposure (where valid), measure of function must be of use clinically or programmatically

Bio-indicators
- Sentinel measures of functional change due to nutritional status, disease or intervention
- Lacks sensitivity and specificity as sole measures of nutrition, but have value when used with biomarkers of particular nutrients

Public Health Indicators
- Non-specific and non-sensitive with regard to nutrition and health
- Reflection of “system” responses and/or shifts in response to population manipulation
A New Era:

How Can We Get There?
Objectives:

• Raise consciousness about the intimate and inextricable role of nutrition in all aspects of human biology.

• Fill gaps in the continuum from basic biology to translation by changing the emphasis from prescription to a more effective integration of nutrition as a biological variable, i.e., both an input and an output affecting and affected by all aspects of human/animal biology.

• Improve messages about the importance of diet and nutrition in health promotion and disease prevention.

• Enable translation of evidence generated to support standards of care, programs and health policy guidance.
The Lexicon

The neologism “-omics” refers to biological fields of study involving the drawing of inferences from multiple, interacting variables. Omics technologies measure some characteristic of a large family of cellular molecules, such as genes, proteins or metabolites.

Oomics technologies **provide the tools** needed to identify differences in DNA, RNA, proteins, and other cellular molecules between species and among individuals.
New Paradigm: *the Nutriome*

**Definition:**

The pattern of nutrients and their interrelationships in biological systems, i.e., *nutriomics*.
Nutriomics: nutrient interactions in maintaining homeostasis in metabolism and inflammation
Nutriomics: Implementation:

• Characterize the **functional roles and interrelationships** of nutrients;

• Improve the **validity of findings** by integrating sound principles of nutrition assessment;

• **Provide a platform** for complementary bio-indicators for nutritional evaluation (COMBINE);

• **Incorporate nutriomics approaches** into ongoing efforts to characterize and understand:
  o metabolome
  o microbiome
  o exposome
  o etc.
Components:
As part of the NIH Rigor and Reproducibility Efforts, integrate:

• Approaches to the selection of appropriate experimental/animal models;

• Approaches to design of studies exploring specific aspects of nutrition in humans; and

To advance the science:

• Nutriomics: characterization and mapping of nutrients and their interacting functions in biological systems.
NABV:

Action Plan
Core Components of a Strategic Plan

- Biology
  - Basic/clinical
  - "Nutriomics"

- Health Translation

- Assessment (Clinical/population)
- Intervention
Components of NABV I:

- **Improved Rigor and Reproducibility** through integration of "best practices" including:
  - In human studies assessment of
    - exposure
    - status (biomarkers): BOND
    - effect (complementary bio-indicators of nutritional evaluation: COMBINE)
    - health context pre-existing/endemic disease (infectious/NCD) in individuals and populations
  - Basic research
    - Selection of most appropriate/relevant model systems
    - Use of relevant diets
Components of NABV II:

Advancement in understanding the “biology of nutrition: Nutriomics initiatives to:

• Define/map the pattern of nutrients within biological systems, e.g.,
  o Pharmacology
  o Inflammation/immunology
  o Neurobiology: BRAIN

• Characterize the nature and extent of their interrelationships in biological systems

• Test findings within specific “disease states” e.g., diabetes, cancer, HIV etc.
Thank you!