Nutritional Ecology and Human Health

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Abstract

In contrast to the spectacular advances in the first half of the twentieth century with micronutrient-related diseases, human nutrition science has failed to stem the more recent rise of obesity and associated cardiometabolic disease (OACD). This failure has triggered debate on the problems and limitations of the field and what change is needed to address these. We briefly review the two broad historical phases of human nutrition science and then provide an overview of the main problems that have been implicated in the poor progress of the field with solving OACD. We next introduce the field of nutritional ecology and show how its ecological-evolutionary foundations can enrich human nutrition science by providing the theory to help address its limitations. We end by introducing a modeling approach from nutritional ecology, termed nutritional geometry, and demonstrate how it can help to implement ecological and evolutionary theory in human nutrition to provide new direction and to better understand and manage OACD.

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INTRODUCTION

> *Nutrition has often been the subject of conjectures and ingenious hypotheses—but our actual knowledge is so insufficient that their only use is to try to satisfy our imagination. If we could arrive at some more exact facts they could well have applications in medicine.*
>
> —François Magendie (1783–1855)

Written in the early nineteenth century by French physiologist François Magendie, these words heralded the beginning of a new era in nutrition science (14). Over the following century, advances in chemistry and physiology were integrated to substantially increase knowledge of food components and their relationship to health. Initial research, inspired by the pioneering work of German chemist Justus von Liebig, distinguished the macronutrients protein, fats, and carbohydrates and discerned their broad functions. In the early twentieth century, rapid advances were made in the discovery of vitamins and minerals and identifying their roles in preventing noncommunicable diseases such as scurvy, beriberi, and rickets (16). These discoveries played an important role in elevating nutrition to a quantitative science (78) and were transformational in public health (17).

Nutrition science has not fared as well with the rise over the second half the twentieth century of obesity and associated cardiometabolic disease (OACD), a syndrome in which excess body fat is associated with a state of chronic inflammation and increased cardiometabolic disease risk

(61). Despite several decades of intensive research, empowered by substantial scientific and technological advances in the research tools available, including the rise of molecular biology (95), a recent comprehensive global survey concluded, "[O]besity has become a major global health challenge. Not only is obesity increasing, but no national success stories have been reported in the past 33 years. Urgent global action and leadership is needed to help countries to more effectively intervene" (60, p. 766). Similar conclusions have been reached about type 2 diabetes (55, 63), cardiovascular disease (77), and some cancers (28).

Why have the successes of nutrition science in dealing with diseases of micronutrient deficiency not been repeated for the new generation of nutrition-related diseases? Here we examine this question, and identify key differences between micronutrient deficiencies and OACD that account for the contrasting successes of nutrition science in relation to these classes of diseases. We suggest that an important problem is that human nutrition science has uncritically retained the framework that guided its successes in combating diseases of micronutrient deficiency, which is in fundamental respects incompatible with the new suite of nutrition-related diseases.

In particular, the role of the biology-environment interface is more complex and challenging in relation to OACD than to micronutrient-deficiency diseases, and progress in this area will benefit from an ecologically inspired theoretical framework. We show that the field of nutritional ecology, the study of animal nutrition that is based on ecology and evolution, can provide a step in the right direction, and we introduce an approach termed nutritional geometry for modeling the organism-nutrition interface in a more sophisticated way than is currently practiced in the science of human nutrition.

Nutritional geometry is a framework for examining how mixtures of nutrients (and other dietary components) influence biological outcomes such as health and disease rather than considering any particular nutrient in isolation. The focus on mixtures provides an approach for modeling the ways that nutrients interact to determine the nutritional properties of foods and how foods in turn combine into meals, diets, and dietary patterns to influence health. This multilevel framework provides contact points across the many domains that affect human nutrition, from biology (e.g., evolved appetites and taste responses) to economics and other influential facets of modern food environments, enabling multiple influences to be integrated in a single model. We end by presenting a body of work to illustrate the application of nutritional geometry to humans, showing how this approach can produce fresh insight into the problem of OACD.

NUTRITION SCIENCE: PAST AND PRESENT

The Golden Years

François Magendie, quoted above, is credited with pioneering experimental physiology (81). In Magendie's time it was known that animals were composed partly of nitrogen and that nitrogen was also present in the air, but it was not clear whether the nitrogen needed to be eaten in the diet or could be obtained through breathing. In 1816, Magendie reported experiments in which dogs died when they were fed only foods known to be in other respects nutritious but that contained little or no nitrogen, such as sugar, gums, olive oil, butter, and bread; these results suggested to him that nitrogen was an essential dietary component. Magendie's subsequent experiments, however, showed that dogs also died when fed bone-derived gelatin alone, even though this did contain nitrogen, from which he concluded that there must be essential dietary components other than nitrogen: "It could perhaps be iron or other salts, fatty material or lactic acid . . ." (quoted in Reference 81).

By the late nineteenth century, such experiments had been combined with other observations to produce a picture in which there were four essential nutrient groups, proteins, carbohydrates, fats, and minerals, with most of the research having been carried out on the energy-yielding components, now known as macronutrients (50, 81). As with Magendie's work, the broad goal of this research was not to investigate specific diseases associated with malnutrition but rather to identify the components of a complete diet (76), with the social subtext of developing ways to feed a productive working class on minimal wages (52).

It was, however, vaguely recognized that some diseases might be associated with dietary deficiencies (76). This recognition was based partly on known associations between particular foods and the amelioration of specific diseases (16); for example, the ancient Greeks and Egyptians had recommended liver, which is rich in vitamin A, as a cure for night blindness, which results from vitamin A deficiency (50). However, the prevailing principle was that diseases were caused not by shortages of physiologically essential substances but instead by entry into the body of infectious organisms or toxins (the germ theory). This view had a firm empirical grounding, having been scientifically established for several diseases, including malaria, anthrax, tuberculosis, and cholera. Other diseases, such as scurvy, beriberi, rickets, and pellagra, remained unexplained and were believed by some to likewise be caused by unknown pathogens or toxins (81).

As evidence accumulated that animals could not live on a mix of proteins, carbohydrates, fats, minerals, and water alone, it became clear that there was some additional and unidentified essential dietary component. Researchers N. Lunin (in 1881), C.A. Pekelharing (in 1905), and F.G. Hopkins (in 1906) communicated experiments in which laboratory animals died when they were fed purified mixtures of proteins, carbohydrates, fats, and minerals, whereas they survived if the diet was supplemented with whole foods such as dairy products, cod liver oil, and egg yolk. In his 1906 address, Hopkins specifically associated these findings with unexplained human diseases: "Scurvy and rickets are conditions so severe that they force themselves upon our attention; but many other nutritive errors affect the health of individuals to a degree most important to themselves, and some of them depend upon unsuspected dietetic factors" (quoted in Reference 81). Hopkins continued his work in nutrition over many years, for which he was awarded, jointly with Christiaan Eijkman, the Nobel Prize in Physiology or Medicine in 1929.

These early findings established a tradition of nutrition experiments in which, at first, foods or food components and, with advances in biochemistry, purified nutrients were selectively removed and reintroduced into the diets of experimental animals to assess their role in health and disease. Advances were substantial, leading over a 30-year period to the discovery of many of the vitamins as well as their structural characterization, synthesis, and use in combatting a range of diseases including scurvy, rickets, beriberi, pellagra, night blindness, and xerophthalmia (15). The successes of the experimental model extended beyond vitamins to include the discovery of associations between specific diseases and mineral deficiencies, for example anemia (iron) and goiter (iodine), and of essential fatty acids and amino acids.

By 1936, Magendie's prediction that "some more exact facts . . . could well have applications in medicine" had been realized, with Hutchison and Mottram proclaiming in their text *Food and the Principles of Dietetics* that dietetics "can claim to be regarded as an exact science" (quoted in Reference 78). Nutrition science was converging on the "hard" sciences of physics, chemistry, and mathematics with its discovery of tight causal relationships between specific nutrients and specific physiological symptoms and diseases.

The successful model was based on three main premises (46).

1. A simple cause-effect relationship exists between a specific disease and a particular nutrient.
2. Each nutrient deficiency disease can be explained physiologically in terms of the role played by the respective nutrient.
3. Providing the nutrient in the diet can prevent, and in many cases reverse, the disease.

We refer to this paradigm as the single-nutrient model to highlight its emphasis on individual nutrients.

A New Generation of Diseases

Based on its historical successes, the single-nutrient model took a lead role in the response of nutrition scientists to the global rise in the incidence of OACD in the second half of the twentieth century. When it became evident in the 1950s and 1960s that this syndrome was emerging as a significant public health problem in the United States and Britain, attention was focused on the question of what is the responsible nutrient. One suspect, most vocally vilified by American epidemiologist Ancel Keys, was fat (41, 80). British physiologist and nutritionist John Yudkin disagreed, arguing that the culprit was carbohydrate. To this day the debate continues as to whether fats or carbohydrates are to blame for the rise in OACD, albeit with more nuanced undertones that distinguish subcategories of these nutrients (e.g., see References 31, 88, 90 and the ensuing correspondence).

Meanwhile, the rise in OACD has continued unchecked (28, 55, 60, 63), causing a growing number of researchers to question the traditional nutritional approach. This traditional approach has even been implicated in exacerbating the problem by projecting discord among experts, which devalues healthy guidelines for eating and, as further discussed below, creates opportunity for exploitation by the processed-food industry (59, 80).

WHAT'S WRONG WITH NUTRITION SCIENCE?

The limited success in combatting the epidemic of OACD has generated discussion of the need to reformulate the approach to understanding and managing the links between nutrition and health. In this section, we provide a brief overview of prominent challenges for nutrition science that have been discussed in the literature.

The Boundaries Problem

The boundaries problem concerns the extent to which nutrition science is constrained by boundaries that limit the exchange of perspectives, theory, and techniques with other research fields and sectors, and between nutrition research and its translation into public health benefits (13, 94, 95). This is, by definition, not a problem that is unique to nutrition science, but part of broader discussions on the importance of interdisciplinary research (99) and "implementation science," a variant of interdisciplinarity that integrates research findings into health-care policy and practice (3). Arguably, however, nutrition is a field in which the need for interdisciplinarity is particularly pronounced, given the pervasive influence of nutrition on humans, from physiological to social, global, and planetary levels, and its extensive relationships with other domains including economics, politics, and environmental science (1).

The Levels-of-Focus Problem

The levels-of-focus problem, which is more particular to nutrition science than is the boundaries problem, concerns the question of what the relative emphasis should be in nutrition research and its translation to public health benefits on nutrients, foods, or dietary patterns (6, 80); it is, broadly, a particular case of the "reductionism-holism" concept. Several authors have argued that the limited progress of nutrition science in dealing with OACD stems from its reductionist underpinnings: In emphasizing specific nutrients, it fails to take into account the fact that food components interact in complex ways to give rise to emergent properties of diets that are not explicable at the level of individual chemical parts (27, 39, 45, 46, 80). As an alternative, it has been suggested that nutrients should be relegated to the background in nutrition science, with foods, diets, and dietary patterns forming the primary focus. The traditional approach has been termed nutritionism (80), emphasizing its reductionist underpinnings; the food and diet-centered alternative has been termed the food synergy paradigm (46).

The Need for Systems Science

A frequently cited priority is for nutrition science to adopt a systems approach, which is needed to deal with the complexity of interacting factors that are inevitably brought into focus in interdisciplinary science (1, 49, 54). This is all the more apparent considering the high degree of complexity even within the boundaries of conventional nutrition science, due in part to the large number of nutrients, foods, diets, and dietary patterns that constitute human nutrition (1). A systems approach can reduce this complexity through revealing key interactions that influence the outcomes of interest and then targeting these as priorities for research and management interventions. For example, a systems approach can help to identify common causal factors underlying the otherwise seemingly opposite problems of malnutrition and obesity (32).

Quality of Data

An issue that is increasingly attracting attention is the quality of data in nutrition research (1). In addition to the challenges of collecting representative population dietary data (4) and of establishing causality in long-term links between diet and health, concerns have been raised about deviations from good scientific practice. This is not an issue that is confined to nutrition science, but it may be accentuated in that field for a number of sociological reasons, including the strong links with economics (1) and politics (59).

These links and their impact on scientific impartiality are closely associated with the levels-of-focus problem. The alignment of researchers to specific nutrients, as in the debate between Ancel Keys and John Yudkin, opens the way for advocacy, while uncontrolled confounds (due to the context-specificity of nutrient effects) contribute to a proliferation of disparate and contradictory results that are difficult to unify within a cohesive explanatory framework. The resulting uncertainty and factionalism are exploited and abetted by commercial interests that are aligned with particular nutrients, foods, food groups, or diet programs, for example through the "health halo" effect in which labeling statements such as "low fat" spuriously associate unhealthy products with health benefits (18, 96). The successes of these sales strategies, in turn, provide incentive for biased interpretation and publicization of evidence, and for biasing science through selectively supporting researchers and research projects that are likely to provide expedient results (59, 80).

A NUTRITIONAL ECOLOGY PERSPECTIVE

The issues described above present important challenges, which if solved will contribute to helping nutrition science address its core responsibilities. We believe, however, that the most fundamental challenge is that nutrition science has lacked a general framework that allows for the integration of knowledge within its own field and across the range of other relevant disciplines (6, 22, 51). The field of nutritional ecology shares many of the challenges of human nutrition science, but it has developed within the fundamental theoretical framework of ecology and evolution (EE).

This framework provides a conceptual depth that can help to deal with many of the impediments currently being encountered in human nutrition science, and it can help to identify new approaches for solving problems in human nutrition.

What Is Nutritional Ecology?

Central to the EE framework is the premise that outcomes such as health and disease arise from the interaction between the animal and its environment. These interactions play out over a continuum of timescales, from short-term homeostatic responses to environmental variability, to the long-term process of natural selection driving adaptation through changes in population gene frequencies. Nutritional ecology, therefore, focuses not specifically on the organism or its environment, but rather on the dynamic interface between organism and environment (72, 73).

Importantly, biological adaptation is context specific: A response that is adaptive in one environment can be maladaptive in another (73). For cases in which significant and rapid environmental change has occurred, for example through climatic shifts or anthropogenic activities, it is therefore important to consider not just the animal's responses to the current environment but also the characteristics of the ancestral environment to which those responses are evolutionarily adapted.

In nutritional ecology, the integration of nutrition, animal, and environment is substantial. All three target domains are explicitly represented in the sense that the framework can enable research to be structured so as to directly address questions pertaining to each—it can resolve issues in nutrition science, ecological science, and organismal science (72). The field's boundaries are thus drawn broadly to encompass nutrition and ecology as well as organismal sciences, such as behavior and physiology. This contrasts with approaches that are centered primarily on ecology, nutrition, or the organism but draw on one or both of the other domains at lower resolution than the primary domain. For example, the EE framework of optimal foraging theory, which applies optimality models to understand the foraging and food choices of animals, commonly uses energy as a proxy for nutrition. Energy might in many cases correlate sufficiently well with nutritional gain to make the optimal foraging framework a useful modeling strategy, but this approach does not contribute much to understanding the roles of the different energetic macronutrients, or other food components, in the biology or ecology of the animal. In this respect optimal foraging theory is not nutritionally explicit (72). Steps have, however, been taken to explicitly integrate increased nutritional detail into optimality theory (e.g., 7, 34, 40, 87).

Related Applications of Ecology and Evolution in Nutrition Science

Elements of both ecological and evolutionary theory have already been assimilated in the broader context of human health and nutrition. For example, the family of models termed ecological models of health promotion is amended from ecology to provide a framework that emphasizes the interrelationship between people and their physical and social environments (74). There are also many evolutionary models of human obesity and other nutrition-related problems in modern human environments (e.g., 33, 53, 93, 101). Although not explicitly developed within a nutritional ecology context, these applications of ecological and evolutionary theory to human health are well aligned with the aims and methods of nutritional ecology in the sense described above.

A field in which nutritional ecology has explicitly been applied to human nutrition is anthropology. As a framework for structuring questions around the drivers of diet choices in foraging societies, some anthropologists have adopted optimal foraging models from behavioral ecology;

these models (as discussed above) often simplify nutrition into a single primary dietary component, usually "energy" (reviewed in 7, 47). A similar approach has been applied to humans in industrialized food environments (53). In a series of papers, Hockett and collaborators (36–38) have argued for a deeper integration of the facts of human nutrition science into anthropological models of human foraging choices. A positive step in this direction has been a modification of optimality models to distinguish the roles of specific macronutrients, rather than energy per se, in studies of the foraging choices of hunter-gatherer societies (34).

Such integration of greater nutritional detail into EE-inspired models of human foraging is strongly compatible with our goal of recommending nutritional ecology as a framework more generally for human nutrition science. However, in this review we approach the issue from a different, yet complementary, perspective. Our goal is to introduce into human nutrition science insights developed in comparative nutritional ecology, which we believe can help to organize the plethora of existing data and inspire future research to deal more effectively with the specific challenges of OACD.

KEY INSIGHTS IN NUTRITIONAL ECOLOGY

In this section, we discuss insights from comparative nutritional ecology that are relevant to the question of why the single-nutrient model has had contrasting success in relation to micronutrient-related diseases and OACD. We end the section by considering some implications of these insights for human nutrition.

Foraging Is Complex

Nutritional ecology has a long history of using EE theory to understand the foraging behavior of animals both in the laboratory and in the wild. A defining feature of the field is that it is broadly integrative, drawing on a range of related fields beyond nutrition, ecology, and evolution, including behavior and physiology (72). The combination of perspectives converges to produce a picture in which the seemingly simple processes of foraging to meet nutrient requirements are underlain by an immensely complex set of challenges for animals, especially dietary generalists like humans.

Many nutrients are needed to maintain health, and each nutrient is required at its own particular level. Requirements for nutrients change, for example with age, stress levels, infection, reproductive state, and physical activity. Foods, likewise, are complex mixtures of nutrients, many or most of which are different from the optimal mixture that would satisfy the animal's nutrient needs, and some of which also contain antinutritional factors, such as toxins. The challenge for an animal is to spread its feeding across different foods so as to compose a meta-mixture (a mixture of mixtures) that more closely resembles its requirements than do the individual food types, and to find alternatives when the availability of particular foods constrains this process.

This multidimensional problem poses complex challenges for animals, even under ideal circumstances in which a variety of suitable foods is freely available. In most ecological situations, however, an added level of complexity is that variability and uncertainty in food availability can force the animal into a state of dietary imbalance. Although unable to achieve an optimally balanced diet in such circumstances, the animal nonetheless can select among a range of options to minimize the negative consequences of dietary imbalance. The optimal solution in that predicament is a highly complex computational problem, especially if there can be costs not only to shortages but also to ingested excesses of the various nutrients.

Both Deficits and Excesses Can Be Costly

By definition, dietary imbalance is a predicament in which the animal cannot achieve its target intake for all nutrients simultaneously and therefore is forced to ingest too much of some nutrients and/or too little of others. That physiological costs can result not only from shortages but also from nutritional surpluses was generalized and mathematically formalized for micronutrients as early as 1912 in the context of agriculture (Bertrand's rule) (56). Ecological models of foraging, however, were slow to assimilate the possibility that nutrient excesses as well as deficits can be harmful. This is partly because foraging models were not developed in relation to micronutrients but rather energy (hence macronutrients), and the models were developed against a backdrop in which animal populations were considered to be primarily limited by shortages of energy (the undifferentiated mix of macronutrients) or protein. More recently, studies of nonhuman animals have demonstrated that dietary imbalance can lead to the ingestion of toxic surpluses both of macronutrients (66, 87) and micronutrients (9).

Complex Problems Can Have Simple(r) Solutions

Numerous examples from biology demonstrate that the complexity of biological adaptations need not be commensurate with the complexity of the problem they have evolved to solve. For example, birds do not need to solve the equations of aerodynamics to optimize flight performance; they need only behave as if they do, by adopting simple strategies that compress the problem to a small number of relevant variables. Indeed, evolutionary reasoning predicts that in many if not most cases, evolved solutions will be, to paraphrase Einstein, as simple as possible, but no simpler.

One reason is constraint. Regardless of whether it would benefit an animal to compute the nutrient composition of its perfect diet and the vast range of potential food combinations that could achieve that, animals might be unable to do so on account of fundamental constraints on the architecture of the brain (8). This explains why, in general, as the number of possible choices increases beyond some level, the ability to make good choices declines, and why animals, including humans, show an aversion to an excessive number of choices (42). Furthermore, brains cannot be dedicated to nutrition alone but need to spread their capabilities between nutritional and other priorities, such as avoiding predation and acquiring mates, and there are computational trade-offs between the various behavioral choices. These relationships explain the evidence from animal studies for a trade-off in the ability to perform many tasks and the ability to perform any one task well (44).

Even if a brain could, theoretically, perform the high-dimensional multivariate optimization computations to compose the perfect diet while also avoiding predators and securing unrestricted access to mating partners, the opportunities for benefiting from this would in most cases be ecologically limited by the availability of foods that enabled it to achieve its ambitious dietary target. Indeed, beyond a certain level of nutritional perfectionism it would be penalized because gains from foraging run into diminishing returns and time would be better spent on other activities, such as sheltering, mating, and caring for offspring. Thus a trade-off exists not only in allocating computational power to nutrition and other adaptive functions, but also in optimizing the allocation of time and effort across functions.

For these reasons, behavioral decisions are often based on simple heuristics, or rules of thumb, in which the problem is compressed to the functionally most relevant subset of variables while other variables are ignored (43, 82). In nutrition, two important, interacting criteria that will influence the nature of the compressed model are the availabilities of various nutrients in the relevant ecological context and the asymmetric cost-benefit relationships between ingested surpluses and deficiencies of different nutrients. For some nutrients, deficiencies are functionally more relevant, whereas for others, surpluses are, and the evolved behavior is expected to reflect this cost-benefit matrix. For example, an animal living in an environment in which sodium is deficient is likely to evolve sodium-seeking mechanisms but is unlikely to evolve the means for avoiding or dealing with sodium excesses if ecological scarcity ensures that sodium toxicity is not a likely occurrence. Conversely, where ecology presents a risk of overeating but not undereating a nutrient, mechanisms for avoiding or dealing with excesses but not deficits are expected. In many cases, correlations will be sufficiently strong between nutrients in the diets of animals that satisfying the requirements for some will automatically result in adequate intakes of others. In such cases, we would expect to see specific adaptations for acquiring or synthesizing only some nutrients. For example, through regulating the intake of macronutrients (67), frugivorous primates obtain their required intakes of ascorbic acid and have consequently lost the ability to synthesize this vitamin (25). Likewise, the reliable correlation between the intakes of the minerals calcium and phosphorus with macronutrients likely explains why primates apparently have no taste mechanisms for these micronutrients, despite their importance in the diet (23).

In general, therefore, foraging and dietary regulation by animals reflect an appropriately compressed representation of the potential complexity of nutritional challenges, with the degree of dimension reduction and the relevant subset of focal factors depending on the specific ecological and evolutionary circumstances of different animals. The broad challenge for nutritional ecologists is to identify the particular compression that animals adopt in relation to the problem at hand.

The Importance of Appetite

How can we identify the subset of factors that is most important in the nutritional decisions of animals? A powerful lesson from evolutionary theory is that there is a goal-directedness in biological systems that can provide a guide to the factors that are functionally most important for animals. To be clear, we are not implying conscious goals but rather organizational goals in the systems sense (62, 97), broadly equivalent to the operation of a thermostat or to power regulation under cruise control in a motor vehicle. An effective way to understand animal biology is to reverse engineer these goal-directed systems (19), inferring from their organization which subset of factors the animal has evolved to prioritize in its engagement with the environment. Related fields that have exploited the concept of goal directedness to good effect are physiology (homeostasis theory) and behavior (motivational theory) (73).

In the context of nutrition, some forms of foraging behavior (35), appetite (71), and postingestive homeostatic regulation (73) are examples of goal-directed processes. Of these, appetite has proved to be a particularly important focus in nutritional ecology models because it provides the proximate link between the animal's nutritional environment and its physiology (including physiological homeostasis), and thus between environment and performance (71). Appetite was first recognized as a form of behavioral homeostasis in the 1930s, when Curt Richter showed that rats could correct for surgically induced micronutrient deficiencies by specifically targeting the deficient micronutrient (58). In the 1970s and 1980s, Gil Waldbauer and colleagues showed that insects could self-select proportions of natural foods or nutrients from synthetic foods to compose a diet that was balanced to support optimal performance (reviewed in 100).

We subsequently developed a modeling approach, the geometric framework (70, 84) (a form of nutritional geometry), for measuring how the appetite systems for different nutrients interact to enable insects to balance their diet. The framework was subsequently elaborated and applied to a wide range of species, from slime molds to wild primates, domesticated animals, and humans. It is not our intention to expound in detail upon those studies here (for a recent review, see 86) except to say that they illustrate how, by placing appetite at the center of nutritional models, nutritional geometry can go a long way toward identifying the combinations of factors that animals integrate to optimize the process of foraging. In particular, the questions of how appetites for different nutrients interact and how these interactions engage with the food environment to generate different patterns of nutrient intake have emerged as especially powerful guides for understanding animal nutrition, both in the laboratory and the wild (67, 86).

Implications for Human Nutrition Science

What can these EE-inspired insights reveal about why the single-nutrient model succeeded with micronutrient-related diseases but in the context of OACD has led to the problems discussed in a previous section? At a general level, the single-nutrient approach represents a highly compressed, low-dimensional nutrition model that is effective for simple cause-effect relationships of the sort observed in gross manipulations of dietary micronutrient content. However, the complexities of OACD are in many respects far greater than for micronutrient deficiencies; for example, a recent synthesis listed 104 putative causes of human obesity (24). A model is needed that reduces this complexity while retaining the key causal components that link nutrition to health in modern food environments.

One basis for the greater complexity of OACD concerns the fact that both deficits and excesses of macronutrients can be detrimental. The emphasis on nutritional deficiency in the first half of the twentieth century ensured that nutritional surpluses did not feature prominently in the development of human nutrition science, as was true in the history of foraging theory (discussed above). Indeed, by the 1930s a "balanced" diet was generally considered to be one that contained sufficient amounts of essential micronutrients to avoid deficiencies rather than the correct proportions of nutrients (78). With the subsequent rise of OACD, nutrition science did turn its attention from nutritional deficits to surpluses, reengaging with the basic premise of germ theory that disease can be caused by the entry into the body of dangerous substances. However, this shift was too categorical, substituting "surplus" for "deficit" without consideration of the possibility that surpluses and deficits can interact in powerful ways to influence diet and health.

A likely reason that such interactions were not effectively integrated into nutritional approaches to OACD is that due consideration has not been given to the complexities of appetite in human nutrition. As discussed above, appetite systems for different nutrients interact to influence the patterns of food and nutrient intake, and measuring these interactions is critical for understanding why animals and people eat what they do. This is one respect in which diseases associated with micronutrient deficiency are simpler than those associated with nutrient surpluses, because simply providing a deficient nutrient is likely to result in its intake, either passively (as discussed above for calcium and phosphorus intake by primates) or in some cases actively through nutrient-specific appetites or associative learning (21, 79, 98). Instances wherein the organism actively ingests damaging surpluses of a nutrient, as is the case in OACD, are substantially more complex. The management challenge here is that the dietary problem is not driven exclusively by the distribution of nutrients in the environment but rather is actively abetted by regulatory behavior of the animal; the scientific challenge is to understand how and why.

To answer these questions and deal with the problem, an understanding is needed of how the human appetite prioritizes the intake of different nutrients, including the relative priorities that it assigns to avoiding surpluses and deficits of each. These are not simple problems. But as we demonstrate in the next section, addressing them can help interrelate the burgeoning and often disparate knowledge of nutrition-related disease and can increase efficiency by helping to direct future research.

FROM THEORY TO PRACTICE: THE NUTRITIONAL ECOLOGY OF HUMAN OBESITY

In the previous section, we have argued that insights from nutritional ecology can help to explain why the single-nutrient model, which has been so successful in dealing with micronutrient-deficiency diseases, has failed in relation to OACD. In this section, we show how the nutritional geometry framework, briefly introduced above, incorporates these insights from nutritional ecology, and we provide an example where the framework has been applied to generate new insight into the causes of obesity.

Levels of Focus: from Problem to Opportunity

The nutritional ecology perspective suggests that the important question is not whether nutrients or foods should be considered primary in nutrition science (45, 80) but rather how these can be combined in a model to understand the ways that food components interact to determine the properties of diets that affect behavior and health. **Figure 1** illustrates that nutritional geometry can help to answer this question by incorporating all levels of the nutritional combinatorial hierarchy (e.g., nutrients, foods, meals, and diets) and modeling the relationships among them, using a geometric method known as the right-angled mixture triangle (64). In this model, we focus specifically on the macronutrients because of their fundamental roles both in intake regulation and in OACD; other models might involve micronutrients, a combination of macro- and micronutrients, or dietary components that are not conventionally considered "nutrients," such as fiber, antioxidants, alcohol, or plant-produced toxins. In what follows, we therefore interchangeably refer to the model-specific macronutrients and the general case of food components.

Figure 1 shows how the three-dimensional macronutrient ratios of individual foods can be represented and how these combine into meta-mixtures, including meals and diets. Geometrically, the set of meta-mixtures that is achievable by combining two mixtures is defined by the line connecting the two parent mixtures. If three or more foods are combined, then the achievable meal composition is represented by the area enclosed by the polygon connecting those foods. Other levels in the hierarchy of meta-mixtures could be derived in the same way, for example dishes (composed of foods and other ingredients), daily diets, or dietary patterns (e.g., the Mediterranean, Okinawan, or Atkins dietary patterns, discussed further below).

The focus in nutritional research and dietary advice on nutrients has been criticized as reductionist (80). This charge is well founded within the context from which it derives, namely the dominance within human nutrition science of the single-nutrient model. Singling out individual food components, such as fat or simple carbohydrates, as the cause of OACD is too blunt an approach to provide a useful representation of the problem. It is a case of "greedy reductionism," where "in their eagerness for a bargain, in their zeal to explain too much too fast, scientists and philosophers . . . underestimate the complexities, trying to skip whole layers or levels of theory in their rush to fasten everything securely and neatly to the foundation" (20, p. 82).

We are wary, however, that an uncritical adoption in nutrition science of the premises "nutrients = reductionism" and "reductionism = bad" might do more harm than good, inter alia fueling factionalism between reductionists and holists at a time when unification within and beyond the field is more important than ever. A different perspective is that all nutrition research

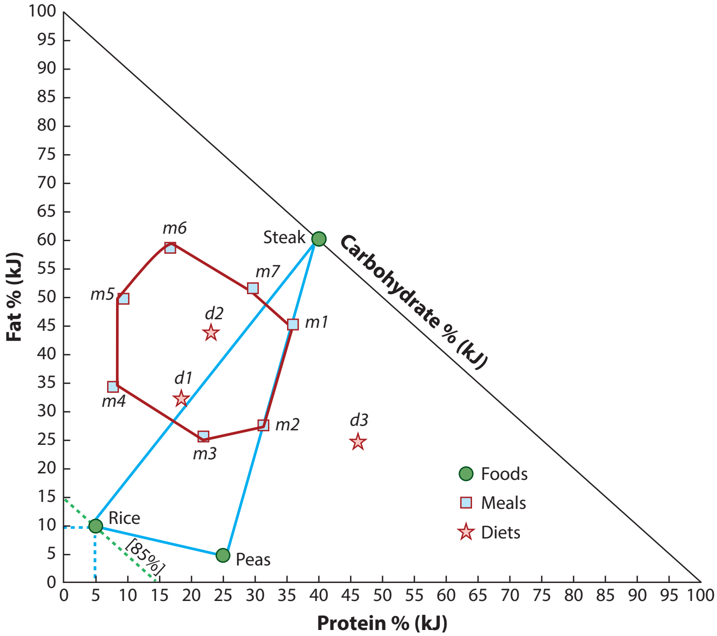


Figure 1

Right-angled mixture triangle (64) illustrating how components (in this case the macronutrients) combine into foods (rice, peas, and steak), meals (*m1–m7*), and diets (*d1–d3*). Points represent the percentage contributed by each component (protein, fat, and carbohydrate) to the sum of the three. Thus, the macronutrient composition of rice is 5% protein and 10% fat, and since protein, fat, and carbohydrate sum to 100%, carbohydrate = 100 − (5 + 10) = 85%. This value is represented by the negative dashed diagonal joining 15% on the *x* and *y* axes, such that any mixture of macronutrients containing 85% carbohydrate will fall on that line. A meal composed from two foods (e.g., peas and steak) is constrained to fall on the line connecting those foods (e.g., *m1* and *m2*), with the exact position along the line being determined by the proportion of the foods in the meal. Adding a third food (e.g., rice) expands the set of possibilities to a triangle (meals *m1*, *m2*, and *m3* can be composed from the three foods, but *m4–m7* cannot). By extension, diets *d1* and *d2* can be composed from meals *m1–m7*, but *d3* cannot.

should be open to both reductions and syntheses, and the challenge is to judge on a case-by-case basis the appropriate levels within the mixture hierarchy that are most relevant to the problem.

Figure 1 illustrates this perspective. The initial decision as to which subset of food components to model (in this case the macronutrients) represents a reduction of the very high-dimensional mixtures that are foods and diets. Identifying the subset of components on which to focus is a standard first step in constructing any model, which by definition represents a simplified depiction of the system under study. A second step is to explore how the components interact to produce the properties of the whole. In nutrition this is in itself a decision point, because there are a nested series of wholes that build from nutrients, including foods, meals, diets, and dietary patterns. No matter where we start in this hierarchy, however, as we move downward to lower-level components we are performing a reduction, and as we move upward, a synthesis. Representing peas as a mixture of macronutrients is thus reductionist, but no more so than representing a meal as a mixture of foods, a diet as a mixture of meals, or a dietary pattern as an aggregate of diets.

In general, the appropriate starting point and end point will depend on the question being asked. For example, if we are interested in the association between dietary patterns and disease, we could legitimately represent dietary patterns in terms of their nutrient composition. But to understand how food environments lead to unhealthy dietary patterns, we might also need to consider foods and meals because these are the levels in the hierarchy with which behavior most directly interacts; otherwise, we risk falling into the trap of "greedy reductionism." We would argue, however, that for many purposes, reduction to the level of nutrients is particularly important. Nutrients are the level that most intimately links diet and physiology to generate outcomes such as health and disease, and they are also the common strand that runs through all levels as we ascend the hierarchy from food components to dietary patterns, foods, meals, and diets.

The hierarchical nature of nutrition therefore presents challenges, but these are not insurmountable when using a flexible model that enables the different levels to be interrelated. Indeed, a powerful advantage of such models is that the multiple interrelated levels and components provide many links to a wide range of factors in the broader nutritional system, from human biology through various aspects of the socioecological environment, and thus provide a template for integrating across the different domains in interdisciplinary research (68).

Pulling the Pieces Together

An important challenge is to better understand the interrelationships among the myriad factors that influence and are influenced by human nutrition. The mixture space (**Figure 1**) provides a systematic and clearly defined reference point around which nutritional compositions (foods, meals, diets, etc.) can link data, concepts, and methods from across different areas of the nutrition sciences and also to other disciplines. We now provide an example to illustrate this in the context of macronutrient balance and human health.

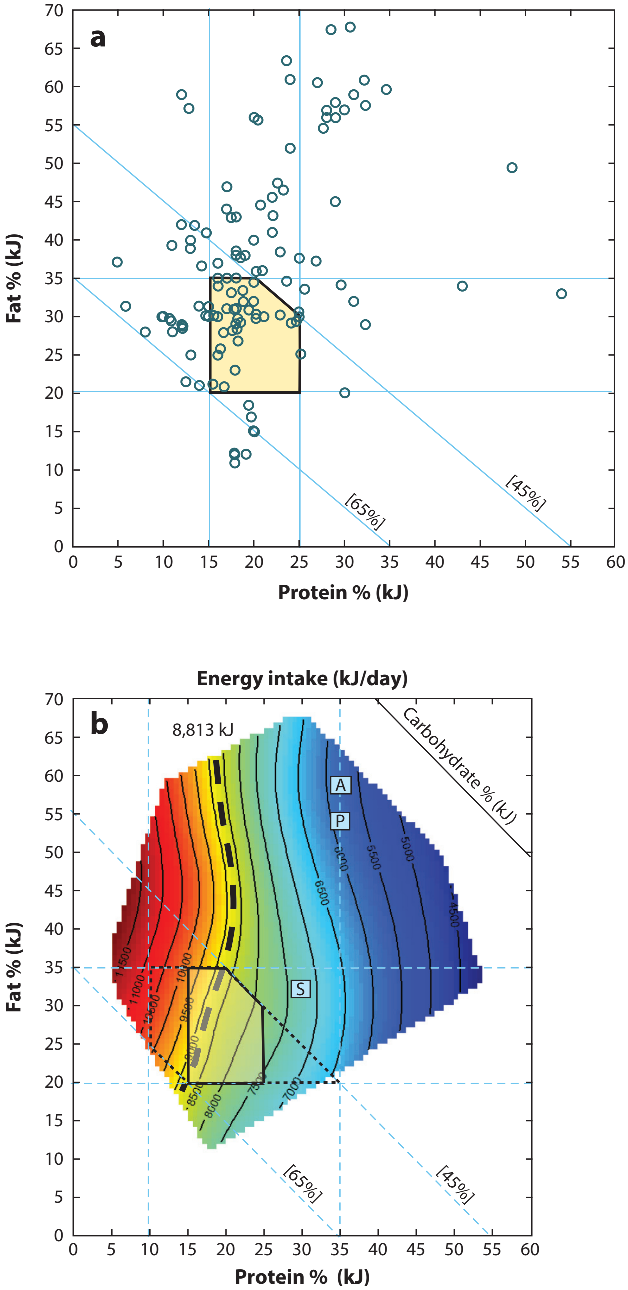
Dietary recommendations: Acceptable Macronutrient Distribution Ranges. **Figure 2*a*** presents plotted data for the proportional compositions of 116 experimentally fixed diets, compiled from published studies examining the relationship between dietary macronutrient ratios and energy intake in adult humans (30, 65) as they relate to the Acceptable Macronutrient Distribution Range (AMDR) (69) for Australians and New Zealanders.

Energy intakes. A question of considerable importance for understanding the drivers of OACD is how dietary macronutrient balance relates to energy intakes under free feeding conditions.

Figure 2

(*a*) Macronutrient compositions of 116 experimentally fixed diets [from a previously published meta-analysis (30) supplemented with 22 data points from more recent experiments (65)]. The yellow polygon is an integrated representation of the Australian/New Zealand Acceptable Macronutrient Distribution Range (AMDR; protein = 15–25%, fat = 20–35%, carbohydrate = 45–65%); diet points falling within this polygon are macronutrient balanced, and diets falling outside are macronutrient imbalanced with respect to the AMDR. (*b*) Contour plot showing ad libitum daily energy intakes associated with the experimental diet compositions plotted in (*a*). The dashed contour represents estimated equilibrium energy requirements (8,813 kJ) for sex and weight, assuming a physical activity level of 1.5, which is commensurate with levels in the experimental subjects. The data suggest that energy equilibrium was achieved on diets with 15–20% protein, with energy balance being negative and positive for diets with higher and lower % protein, respectively. The model is consistent with the association between weight loss and high-protein diets, such as the Atkins (A), Protein Power (P), and Sugar Busters (S) diets: Their macronutrient compositions fall within the blue region of low ad libitum energy intakes (compositions from Reference 2). The dotted polygon represents the AMDR for the United States, which has the same ranges for fat and carbohydrate as the Australian/New Zealand AMDR but a wider protein range (spanning 10–35%). **Figure 2*b*** adapted with permission from Reference 68.

To examine this, we superimposed onto the dietary macronutrient compositions data presented in **Figure 2*a*** a response surface representing the ad libitum energy intakes associated with the experimental diets (**Figure 2*b***). The predominant pattern of vertical contours shows that energy intakes increased as the dietary protein concentration decreased (i.e., horizontally) but changed little with the ratio of dietary fat to carbohydrate (i.e., vertically, for a fixed value of dietary % protein).



The plot therefore shows that across the data overall, energy intakes ranged from approximately 4,000 to 11,500 kJ/day, with the Australian/New Zealand AMDR region encompassing a range of 10,000 kJ/day (top left of the AMDR polygon) to 7,500 kJ/day (bottom right). The energy intakes encompassed by the larger permissible range of dietary protein concentrations under the US AMDR are considerably greater than those associated with the Australian/New Zealand AMDR, spanning approximately 11,000 kJ/day to 6,500 kJ/day.

Energy balance. To investigate how the range of energy intakes relates to energy balance, the equilibrium energy intake (EEI) for sex and body size was calculated for each subject, assuming a physical activity level of 1.5 (which is commensurate with the conditions of such dietary trials) (65). The average of these values, which was 8,813 kJ/day, is plotted in **Figure 2*b*** onto the response surface as the vertical dashed contour. This line delineates the region of positive energy balance (to the left of the EEI contour) and negative energy balance (to the right). Consistent with this is the association of high-protein diets (e.g., Atkins, Protein Power, and Sugar Busters diets)—which fall well within the region of negative energy balance—with weight loss (5).

It is interesting and encouraging that the EEI contour fell within the AMDR range of dietary protein concentrations for both Australia/New Zealand and the United States, suggesting that for this study population, under a physical activity level of 1.5, EEI would be achieved within the AMDR protein range but not outside of it. However, although the range of protein densities under which EEI would be expected (approximately 15–20%) corresponded well with the lower end of the range recommended by Australia/New Zealand, the US AMDR encompassed dietary macronutrient compositions that were associated with considerably higher energy intakes; for example, energy intakes at 10% protein ranged between 10,000 and 10,900 kJ/day.

The role of appetite. What drives the relationship between dietary macronutrient ratios (**Figure 2*a***) and total energy intake (**Figure 2*b***)? Since these data represent experiments in which macronutrient ratios were fixed for different treatment groups, but subjects could eat as much as they wished, this relationship represents the interaction of human appetite systems with the macronutrient composition of foods. To explore this interaction, we plotted the relationship between absolute protein intake (kJ/day) and the combined intake of fat and carbohydrate (kJ/day) (**Figure 3**). The figure shows that in humans, protein intake remains relatively constant, and consequently the intake of fat, carbohydrate, and therefore total energy varies passively with dietary protein concentration. That this effect is not due to foods with a higher concentration of fats and carbohydrates (i.e., lower-protein foods) being more palatable than high-protein foods has been demonstrated in two independent experiments that obtained the same result (i.e., negative relationship between dietary protein concentration and energy intake) when low-protein (10%), intermediate-protein (15%), and high-protein (25%) experimental diets were matched for palatability (11, 29). This phenomenon has been named protein leverage to emphasize the fact that the strong human appetite for protein leverages the intake of fats, carbohydrates, and total energy (85).

The interaction of appetite with the food environment. Protein leverage in humans suggests that the relatively strong appetite for protein might interact with variance in protein density in human food environments to generate energy overconsumption (the protein leverage hypothesis) (85). The protein leverage hypothesis provides clarity and focus for research examining the ecological causes of OACD by identifying as a priority the need to examine the ecological and biological factors that cause humans to eat diets that fall to the left on the % protein axis in **Figure 2** and hence overeat energy.

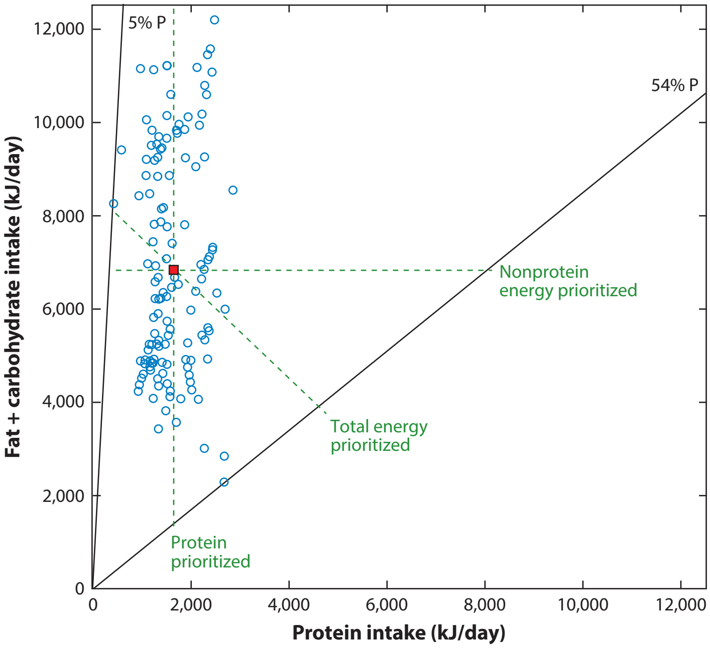


Figure 3

Interaction of human appetite systems with dietary macronutrient ratios. Data are absolute protein (x axis) and nonprotein energy (fat + carbohydrate; y axis) ad libitum intakes by subjects restricted to one of the experimental diets plotted in **Figure 2*a***. The black solid radials represent the protein:nonprotein energy ratios for the diets with the highest (54%) and lowest (5%) proportional protein (P) content. The area between the radials is the region of the nutrient space within which points for nutrient intakes are constrained to lie, with the exact pattern of actual intakes being determined by the ways that appetites for protein, fat, and carbohydrate interact. If the appetite system prioritized total energy intake, regardless of its macronutrient source, the data would align along a negative-sloped diagonal representing constant energy intake ($x + y =$ constant); if nonprotein energy was prioritized, the data would align along a horizontal line ($y =$ constant); and if protein was prioritized, the data would align along a vertical line ($x =$ constant). The exact position of the three lines would depend on the target values for total energy, nonprotein energy, or protein energy intakes under the respective models (i.e., of the constant in the above equations). For the example models illustrated by the green dotted lines in the figure, these are arbitrarily assumed to be equivalent to the mean of the observed x values and y values (*red square*). The analysis shows that the human appetite maintains absolute protein intake relatively tightly, with nonprotein energy intake varying more passively with dietary macronutrient ratios.

For example, an ecological factor that is widely associated with obesity is socioeconomic status (48). This gives rise to the question of whether the differential cost of the three macronutrients might cause individuals from lower socioeconomic status groups to eat protein-dilute diets that lead to energy overconsumption. **Figure 4** shows, as predicted by the protein leverage hypothesis, that the cost of supermarket foods is positively related to their protein content (but not fat or carbohydrate content) (10), suggesting that protein leverage might be a causal factor in the relationship between OACD and socioeconomic status. A recent review has identified several other candidate environmental causes (68), including the influx of low-protein processed foods into the human food chain (12, 57) and the reduction in plant protein associated with rising atmospheric carbon dioxide concentrations (75).

In addition to such influences on the composition of foods in the diet, environmental factors might interact directly with human biology to influence the parameters of protein leverage

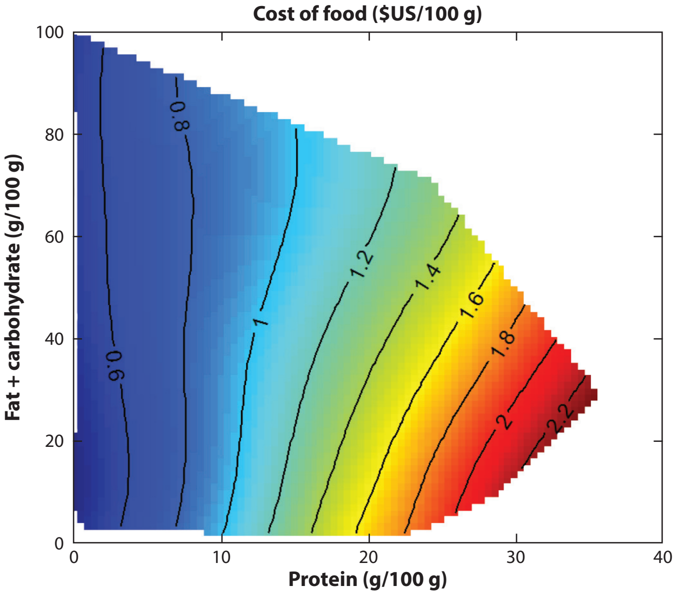


Figure 4

The relationship between the concentration (g/100 g) of macronutrients (protein, fat, and nonstructural carbohydrates) and the cost (in US dollars/100 g) of 106 supermarket foods. Cost increases from dark blue to red. The graph suggests that the cost of food increases with protein density but is unaffected by fat and carbohydrate content. Figure adapted with permission from Reference 68.

and hence health. For example, any factor that reduces protein utilization efficiency will exacerbate protein leverage (68, 85), and this might explain a number of known but poorly understood correlations between obesity and environmental factors. These correlations include the association of obesity with cultural transitions from traditional high-protein to Westernized diets (85), with an early developmental history of high-protein diets [e.g., human infants fed milk formulas with protein content higher than that of breast milk (68)], and with circadian disruption associated with shift work (68). Whether or not research demonstrates that protein leverage provides a connection linking such ecological factors with the observed patterns of OACD, we mention them to illustrate how an appetite-focused model that spans the hierarchy of foods, meals, diets, and dietary patterns can be used as a guide for unifying disparate observations and using theory to identify priority research areas.

Beyond energy: dietary balance also influences protein intake. Our model shows that the greatest influence of dietary macronutrient balance was that strong regulation of protein influenced the intake of fat and carbohydrate; nonetheless, some variance exists in protein intakes (see the scatter around the protein prioritization line in **Figure 3**). The question arises as to whether protein intake varied systematically with dietary composition or whether it was random. To examine this question, in **Figure 5** we show a response surface relating absolute protein intakes (kJ/day) to dietary macronutrient balance, with an estimate of approximate average protein requirements for the study population represented by the dashed contour (65). The positive relationship between the concentration of protein in the experimental diets and protein intakes suggests that the strong regulation of protein is not absolute; rather, high concentrations of fats and carbohydrates restricted protein intake to some extent, whereas low concentrations resulted in compensatory

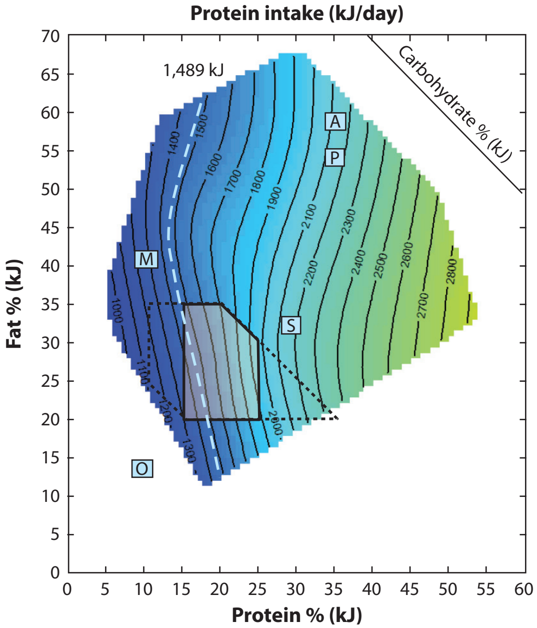


Figure 5

Contour plot showing ad libitum protein intakes associated with the experimental diet compositions plotted in **Figure 2*a***. The dashed contour represents approximate average protein requirements for the study population (1,489 kJ/day), calculated as the mean of Estimated Average Requirement and Recommended Daily Allowance using the method in Reference 26. The figure shows that protein intakes considerably higher than estimated requirements are associated with diets having macronutrient compositions equivalent to high-protein weight-loss diets [i.e., Atkins (A), Protein Power (P), and Sugar Busters (S)] (compositions from Reference 2). Conversely, low protein intakes are associated with the macronutrient composition of the traditional Okinawan (O) and Mediterranean (M) diets, which are linked to exceptionally long-lived human populations (compositions from Reference 102). Figure adapted with permission from Reference 65.

responses leading to excess protein intake, but to a lesser extent than protein influenced carbohydrate and fat (**Figure 3**) and total energy intake (**Figure 2*b***).

Given recent evidence relating high protein intakes to accelerated rates of aging and poor late-life cardiometabolic health, especially when coupled with low carbohydrate intakes (83, 91, 92), this analysis suggests that the interaction of appetite systems for protein, fats, and carbohydrates might provide a fundamental mechanism underlying the reason that AMDRs have both an upper and lower protein limit. The analysis also shows why high-protein diets (**Figure 5**), although effective for weight loss through limiting energy intake (**Figure 2*b***) as a result of protein feedbacks (**Figure 3**), have been associated with unhealthy metabolic profiles and premature death (83, 89). It is also consistent with the exceptional longevity and late-life health associated with the traditional Okinawan and Mediterranean dietary patterns (**Figure 5**).

CONCLUSIONS

Nutrition science has in some respects come full circle since Magendie's assessment quoted in the Introduction. The escalation of research into OACD over recent decades, coupled with technological advances, has yielded a proliferation of data and knowledge, but what is limiting is the theory to generate Magendie's "conjectures and ingenious hypotheses" that can help to unify the observations, identify priorities for future research, and better guide application of research findings in OACD prevention and management. Significant steps in the right direction have already been taken, with a growing body of critical literature having identified key problems and challenges. Foremost among these issues is the need for greater interdisciplinarity (the boundaries problem); a more nuanced view of the role of nutrients, foods, and diets in health and disease (the levels-of-focus problem); better application of systems thinking to help guide research through the complexities of nutrition and its many connections across disciplinary boundaries; and improved attention to the quality of evidence. Underlying all of these challenges, we suggest, is a need for nutrition science to engage with the deep theories of biology developed within the ecological and evolutionary sciences. The integration of these theories into nutrition has already begun in the field of nutritional ecology. Nutritional geometry provides a way of implementing these theories by modeling how nutrients interact with each other to produce the properties of foods and diets and how behavioral and physiological mechanisms engage with these interactions to influence health. Although more complex than the single-nutrient model, in the long run this framework can simplify the study of human nutrition by helping to identify those subsets of factors and their interactions that are driving negative health outcomes in our rapidly changing environments. The application of nutritional ecology to humans can also benefit that field through extending its comparative scope to a highly distinctive species whose biology and environment are researched more intensively than any other.

DISCLOSURE STATEMENT

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LITERATURE CITED

1. Allison DB, Bassaganya-Riera J, Burlingame B, Brown AW, le Coutre J, et al. 2015. Goals in nutrition science 2015–2020. *Front. Nutr.* 2:26
2. Anderson JW, Konz EC, Jenkins DJA. 2000. Health advantages and disadvantages of weight reducing diets: a computer analysis and critical review. *J. Am. Coll. Nutr.* 19(5):578–90
3. Anthes E. 2015. The trouble with checklists. *Nature* 523:516–18
4. Archer E, Pavela G, Lavie CJ. 2015. A discussion of the refutation of memory-based dietary assessment methods (M-MBs): the rhetorical defense of pseudoscientific and inadmissible evidence. *Mayo Clinic Proc.* 90(12):1734–40
5. Astrup A, Raben A, Geiker N. 2015. The role of higher protein diets in weight control and obesity-related comorbidities. *Int. J. Obes.* 39(5):721–26
6. Beauman C, Cannon G, Elmadfa I, Glasauer P, Hoffmann I, et al. 2005. The principles, definition and dimensions of the new nutrition science. *Public Health Nutr.* 8(6A):695–98
7. Belovsky GE. 1987. Hunter-gatherer foraging: a linear programming approach. *J. Anthropol. Archaeol.* 6:29–76
8. Bernays EA. 2001. Neural limitations in phytophagous insects: implications for diet breadth and evolution of host affiliation. *Annu. Rev. Entomol.* 46:703–27

9. Boersma M, Elser JJ. 2006. Too much of a good thing: on stoichiometrically balanced diets and maximal growth. *Ecology* 87(5):1325–30
10. Brooks RC, Simpson SJ, Raubenheimer D. 2010. The price of protein: combining evolutionary and economic analysis to understand excessive energy consumption. *Obes. Rev.* 11(12):887–94
11. Campbell CP, Raubenheimer D, Badaloo AV, Gluckman PD, Martinez C, et al. 2016. Developmental contributions to macronutrient selection: a randomized controlled trial in adult survivors of malnutrition. *Evol. Med. Public Health* 2016:158–69
12. Canella DS, Levy RB, Bortoletto Martins AP, Claro RM, Moubarac J-C, et al. 2014. Ultra-processed food products and obesity in Brazilian households (2008–2009). *PLOS ONE* 9:e92752
13. Cannon G. 2002. Nutrition: the new world map. *Asia Pac. J. Clin. Nutr.* 11(Suppl. 3):S480–97
14. Carpenter KJ. 2003a. A short history of nutritional science: part 1 (1785–1885). *J. Nutr.* 133(3):638–45
15. Carpenter KJ. 2003b. A short history of nutritional science: part 2 (1885–1912). *J. Nutr.* 133(4):975–84
16. Carpenter KJ. 2003c. A short history of nutritional science: part 3 (1912–1944). *J. Nutr.* 133(10):3023–32
17. Carpenter KJ. 2003d. A short history of nutritional science: part 4 (1945–1985). *J. Nutr.* 133(10):3331–42
18. Chandon P, Wansink B. 2012. Does food marketing need to make us fat? A review and solutions. *Nutr. Rev.* 70(10):571–93
19. Csete ME, Doyle JC. 2002. Reverse engineering of biological complexity. *Science* 295(5560):1664–69
20. Dennett DC. 1995. *Darwin's Dangerous Idea: Evolution and the Meanings of Life*. New York: Simon & Schuster
21. Denton D. 1984. *The Hunger for Salt. An Anthropological, Physiological and Medical Analysis*. Berlin: Springer-Verlag
22. Doering F, Stroehle A. 2015. Nutritional biology: a neglected basic discipline of nutritional science. *Genes Nutr.* 10(6):55
23. Dominy NJ, Lucas PW, Osorio D, Yamashita N. 2001. The sensory ecology of primates. *Evol. Anthropol.* 10(5):171–86
24. Downey M. 2015. The putative 104 causes of obesity update. *Downey Obes. Rep.* **http://downeyobesityreport.com/2015/10/the-putative-104-causes-of-obesity-update**
25. Drouin G, Godin J-R, Page B. 2011. The genetics of vitamin C loss in vertebrates. *Curr. Genom.* 12(5):371–78
26. Elango R, Humayun MA, Ball RO, Pencharz PB. 2010. Evidence that protein requirements have been significantly underestimated. *Curr. Opin. Clin. Nutr. Metab. Care* 13(1):52–57
27. Fardet A, Rock E. 2014. Toward a new philosophy of preventive nutrition: from a reductionist to a holistic paradigm to improve nutritional recommendations. *Adv. Nutr.* 5:430–46
28. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, et al. 2015. The global burden of cancer 2013. *JAMA Oncol.* 1(4):505–27
29. Gosby AK, Conigrave AD, Lau NS, Iglesias MA, Hall RM, et al. 2011. Testing protein leverage in lean humans: a randomised controlled experimental study. *PLOS ONE* 6(10):e25929
30. Gosby AK, Conigrave AD, Raubenheimer D, Simpson SJ. 2014. Protein leverage and energy intake. *Obes. Rev.* 15(3):183–91
31. Hall KD, Bemis T, Brychta R, Chen KY, Courville A, et al. 2015. Calorie for calorie, dietary fat restriction results in more body fat loss than carbohydrate restriction in people with obesity. *Cell Metab.* 22:427–36
32. Hammond RA, Dube L. 2012. A systems science perspective and transdisciplinary models for food and nutrition security. *PNAS* 109(31):12356–63
33. Hardy K, Brand-Miller J, Brown KD, Thomas MG, Copeland L. 2015. The importance of dietary carbohydrate in human evolution. *Q. Rev. Biol.* 90(3):251–68
34. Hill K. 1988. Macronutrient modifications of optimal foraging theory—an approach using indifference curves applied to some modern foragers. *Hum. Ecol.* 16(2):157–97
35. Hills TT. 2006. Animal foraging and the evolution of goal-directed cognition. *Cogn. Sci.* 30(1):3–41
36. Hockett B. 2016. Why celebrate the death of primitive economic man? Human nutritional ecology in the 21st century. *J. Archaeol. Sci. Rep.* 5:617–21
37. Hockett B, Haws J. 2003. Nutritional ecology and diachronic trends in Paleolithic diet and health. *Evol. Anthropol.* 12(5):211–16

38. Hockett B, Haws JA. 2005. Nutritional ecology and the human demography of Neandertal extinction. *Quat. Int.* 137(1):21–34
39. Hoffmann I. 2003. Transcending reductionism in nutrition research. *Am. J. Clin. Nutr.* 78(3 Suppl.):514–16S
40. Houston AI, Higginson AD, McNamara JM. 2011. Optimal foraging for multiple nutrients in an unpredictable environment. *Ecol. Lett.* 14(11):1101–7
41. Hujoel P. 2009. Dietary carbohydrates and dental-systemic diseases. *J. Dent. Res.* 88(6):490–502
42. Hutchinson JMC. 2005. Is more choice always desirable? Evidence and arguments from leks, food selection, and environmental enrichment. *Biol. Rev.* 80(1):73–92
43. Hutchinson JMC, Gigerenzer G. 2005. Simple heuristics and rules of thumb: where psychologists and behavioural biologists might meet. *Behav. Process.* 69(2):97–124
44. Irschick D, Dyer L, Sherry TW. 2005. Phylogenetic methodologies for studying specialization. *Oikos* 110(2):404–8
45. Jacobs DR Jr, Tapsell LC. 2007. Food, not nutrients, is the fundamental unit in nutrition. *Nutr. Rev.* 65(10):439–50
46. Jacobs DR Jr, Temple NJ. 2012. Food synergy: a paradigm shift in nutrition science. In *Nutritional Health—Strategies for Disease Prevention*, ed. NJ Temple, T Wilson, DR Jacobs Jr, pp. 311–22. New York: Springer
47. Kelly R. 2013. *The Lifeways of Hunter-Gatherers: The Foraging Spectrum*. Cambridge, UK: Cambridge Univ. Press
48. Krueger PM, Reither EN. 2015. Mind the gap: race/ethnic and socioeconomic disparities in obesity. *Curr. Diabetes Rep.* 15(11):95
49. Kussmann M, Morine MJ, Hager J, Sonderegger B, Kaput J. 2013. Perspective: a systems approach to diabetes research. *Front. Genet.* 4:205
50. Lanska DJ. 2010. Historical aspects of the major neurological vitamin deficiency disorders: overview and fat-soluble vitamin A. *Handbook Clin. Neurol.* 95:435–44
51. Leitzmann C, Cannon G. 2005. Dimensions, domains and principles of the new nutrition science. *Public Health Nutr.* 8(6A):787–94
52. Levenstein H. 2003. *Revolution at the Table: The Transformation of the American Diet*. Berkeley: Univ. Calif. Press
53. Lieberman LS. 2006. Evolutionary and anthropological perspectives on optimal foraging in obesogenic environments. *Appetite* 47:3–9
54. Lounsbury DW, Hirsch GB, Vega C, Schwartz CE. 2014. Understanding social forces involved in diabetes outcomes: a systems science approach to quality-of-life research. *Qual. Life Res.* 23(3):959–69
55. Mattei J, Malik V, Wedick NM, Hu FB, Spiegelman D, et al. 2015. Reducing the global burden of type 2 diabetes by improving the quality of staple foods: the Global Nutrition and Epidemiologic Transition Initiative. *Glob. Health* 11:23
56. Mertz W. 1981. The essential trace elements. *Science* 213(4514):1332–38
57. Monteiro CA, Levy RB, Claro R, Martins APB, Louzada MLC, et al. 2013. Ultra-processed food and drink products and obesity: a new hypothesis, and evidence. *Ann. Nutr. Metab.* 63(Suppl. 1):1007
58. Moran TH, Schulkin J. 2000. Curt Richter and regulatory physiology. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 279(2):R357–63
59. Nestle M. 2002. *Food Politics: How the Food Industry Influences Nutrition and Health*. Berkeley: Univ. Calif. Press
60. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, et al. 2014. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 384(9945):766–81
61. Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. 2014. The concept of normal weight obesity. *Prog. Cardiovasc. Dis.* 56(4):426–33
62. Pittendrigh CS. 1958. Adaptation, natural selection and behavior. In *Behaviour and Evolution*, ed. A Roe, GG Simpson, pp. 390–416. New Haven, CT: Yale Univ. Press
63. Popkin BM. 2015. Nutrition transition and the global diabetes epidemic. *Curr. Diabetes Rep.* 15(9):64

64. Raubenheimer D. 2011. Toward a quantitative nutritional ecology: the right-angled mixture triangle. *Ecol. Monogr.* 81(3):407–27
65. Raubenheimer D, Gosby AK, Simpson SJ. 2015a. Integrating nutrients, foods, diets, and appetites with obesity and cardiometabolic health. *Obesity* 23(9):1741–42
66. Raubenheimer D, Lee K-P, Simpson SJ. 2005. Does Bertrand's rule apply to macronutrients? *Proc. R. Soc. B* 272(1579):2429–34
67. Raubenheimer D, Machovsky-Capuska GE, Chapman CA, Rothman JM. 2015b. Geometry of nutrition in field studies: an illustration using wild primates. *Oecologia* 177(1):223–34
68. Raubenheimer D, Machovsky-Capuska GE, Gosby AK, Simpson S. 2014a. Nutritional ecology of obesity: from humans to companion animals. *Br. J. Nutr.* 113(Suppl.):S26–39
69. Raubenheimer D, Rothman JM, Pontzer H, Simpson SJ. 2014b. Macronutrient contributions of insects to the diets of hunter-gatherers: a geometric analysis. *J. Hum. Evol.* 71:70–76
70. Raubenheimer D, Simpson SJ. 1993. The geometry of compensatory feeding in the locust. *Anim. Behav.* 45(5):953–64
71. Raubenheimer D, Simpson SJ. 2010. Hunger and satiety. In *Encyclopedia of Animal Behaviour*, ed. M Breed, J Moore, pp. 117–26. Amsterdam: Elsevier
72. Raubenheimer D, Simpson SJ, Mayntz D. 2009. Nutrition, ecology and nutritional ecology: toward an integrated framework. *Funct. Ecol.* 23(1):4–16
73. Raubenheimer D, Simpson SJ, Tait AH. 2012. Match and mismatch: conservation physiology, nutritional ecology and the timescales of biological adaptation. *Philos. Trans. R. Soc. B* 367(1596):1628–46
74. Richard L, Gauvin L, Raine K. 2011. Ecological models revisited: their uses and evolution in health promotion over two decades. *Annu. Rev. Public Health* 32:307–26
75. Robinson EA, Ryan GD, Newman JA. 2012. A meta-analytical review of the effects of elevated CO2 on plant-arthropod interactions highlights the importance of interacting environmental and biological variables. *New Phytol.* 194(2):321–36
76. Rosenfeld L. 1997. Vitamine—vitamin. The early years of discovery. *Clin. Chem.* 43(4):680–85
77. Roth GA, Nguyen G, Forouzanfar MH, Mokdad AH, Naghavi M, Murray CJL. 2015. Estimates of global and regional premature cardiovascular mortality in 2025. *Circulation* 132(13):1270–82
78. Santich B. 2005. Paradigm shifts in the history of dietary advice in Australia. *Nutr. Diet.* 62(4):152–57
79. Schulkin J. 2001. *Sodium Hunger: The Search for a Salty Taste*. Cambridge, UK: Cambridge Univ. Press
80. Scrinis G. 2013. *Nutritionism: The Science and Politics of Dietary Advice*. New York: Columbia Univ. Press
81. Semba RD. 2012. The discovery of the vitamins. *Int. J. Vitam. Nutr. Res.* 82:310–15
82. Simon HA. 1997. *Models of Bounded Rationality*, Vol. 3. Cambridge, MA: MIT Press
83. Simpson SJ, Le Couteur DG, Raubenheimer D. 2015. Putting the balance back in diet. *Cell* 161(1):18–23
84. Simpson SJ, Raubenheimer D. 1993. A multi-level analysis of feeding behaviour: the geometry of nutritional decisions. *Philos. Trans. R. Soc. B* 342(1302):381–402
85. Simpson SJ, Raubenheimer D. 2005. Obesity: the protein leverage hypothesis. *Obes. Rev.* 6(2):133–42
86. Simpson SJ, Raubenheimer D. 2012. *The Nature of Nutrition*. Princeton, NJ: Princeton Univ. Press
87. Simpson SJ, Sibly RM, Lee KP, Behmer ST, Raubenheimer D. 2004. Optimal foraging when regulating intake of multiple nutrients. *Anim. Behav.* 68(6):1299–311
88. Siri-Tarino PW, Chiu S, Bergeron N, Krauss RM. 2015. Saturated fats versus polyunsaturated fats versus carbohydrates for cardiovascular disease prevention and treatment. *Annu. Rev. Nutr.* 35:517–43
89. Sjogren P, Becker W, Warensjo E, Olsson E, Byberg L, et al. 2010. Mediterranean and carbohydrate-restricted diets and mortality among elderly men: a cohort study in Sweden. *Am. J. Clin. Nutr.* 92(4):967–74
90. Smith R. 2014. Are some diets "mass murder"? *BMJ* 349:g7654
91. Solon-Biet SM, McMahon AC, Ballard JWO, Ruohonen K, Wu LE, et al. 2014. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab.* 19(3):418–30
92. Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. 2015. Macronutrients and caloric intake in health and longevity. *J. Endocrinol.* 226(1):R17–28
93. Speakman JR. 2013. Evolutionary perspectives on the obesity epidemic: adaptive, maladaptive, and neutral viewpoints. *Annu. Rev. Nutr.* 33:289–317

94. Stefani MC, Humphries DL. 2014. Boundary development in the field of international nutrition science. *Adv. Nutr.* 5:193–98
95. Stroehle A, Doering F. 2010. Molecularization in nutritional science: a view from philosophy of science. *Mol. Nutr. Food Res.* 54(10):1385–404
96. Sundar A, Kardes FR. 2015. The role of perceived variability and the health halo effect in nutritional inference and consumption. *Psychol. Mark.* 32(5):512–21
97. Thompson NS. 1987. The misappropriation of teleonomy. In *Perspectives in Ethology*, ed. PPG Bateson, PH Klopfer, pp. 259–74. New York: Plenum
98. Tordoff MG. 2001. Calcium: taste, intake, and appetite. *Physiol. Rev.* 81(4):1567–97
99. Van Noorden R. 2015. Interdisciplinary research by the numbers. *Nature* 525(7569):306–7
100. Waldbauer GP, Friedman S. 1991. Self-selection of optimal diets by insects. *Annu. Rev. Entomol.* 36:43–63
101. Wells JCK. 2006. The evolution of human fatness and susceptibility to obesity: an ethological approach. *Biol. Rev.* 81(2):183–205
102. Wilcox DC, Wilcox BJ, Todoriki H, Suzuki M. 2009. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J. Am. Coll. Nutr.* 28(Suppl.):500–16S