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Nature, Purpose and Implications of Research in Nutrition

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A fundamental feature of life: The needs for survival

> The subject of nutrition concerns the nature of foods and food nutrients and the needs of humans and animals for these substances.
> Metabolism is the name given to the sum of the chemical and physical processes continuously going on in the living organism.
> *(Lloyd, McDonald and Crampton 1959)*

1.1 Introduction: The defining characteristic

The enabling science for nutritional investigation embraces many disciplines, including mathematics, physics, chemistry, biochemistry, physiology, physical and mental development, disease prevention, clinical care, food production, food processing, food marketing, consumer behaviour and choice, social relations, micro- and macroeconomics, policy and planning. This invites the important question of whether nutrition is a discrete discipline in its own right. If these threads are to be brought together to make a whole, then it is important to be clear about the particular or defining characteristic of that whole that represents nutrition research. This requires an agreed conceptual framework based on fundamental principles. These principles underlie every aspect of nutrition and should be explicitly acknowledged and taken into account at all times.

By the end of this chapter you should be able to recognise that:

- Nutrition is a demand-led process, the study of which draws on many disciplines to understand how energy and nutrients are made available to the cells of the body to enable function.
- By its nature nutrition is integrative and complex, because it relates to how cells, tissues and the body are organised, as well as how people organise themselves in society, to ensure ongoing availability of a sufficient and appropriate mix of energy and nutrients.
- This complexity comes about because of the nature of two major systems and their interaction: the (internal) metabolic system of the body, and the (external) system through which food is acquired from the environment.
- Each system in its own right is inherently complex and their interaction adds an additional level of complexity, thus each system requires explicit investigation of how the component parts act in concert to satisfy the demand.
- Diet plays a pivotal role in these processes, but is only part of the story. The dietary intake is the ultimate source of energy and nutrients for the body, but in addition cells and tissues satisfy their needs for nutrients through integrated processes involving endogenous formation of nutrients, mobilisation of nutrients from structural and functional pools and the availability of nutrients as products of the gut microbiome.
- Research in nutrition requires a focus on a particular aspect of these complex interactions, but that focus needs to be interpreted as an integral part of the wider whole.

Therefore, research in nutrition can be seen at one level as quite simple, but at another as increasingly complex. The diet contains many components, some of which are necessary for metabolism (nutrients), others which have biological activity but are not metabolically essential or

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may be toxic, and still others which cannot be utilised. Consumption of too little, or of too much, of the nutrients themselves can have adverse effects in terms of deficiency or toxicity, respectively. Thus, there is a preferred range of consumption for each nutrient. Extreme changes in any one aspect of nutritional exposure can induce dramatic and readily measurable change. More modest variability within the usual or preferred range of consumption also has effects, but these may be more subtle and less immediately obvious, as the integrated system operates to maintain an assured and balanced supply of nutrients to the cells of the body.

This chapter outlines some of the fundamental principles of nutrition, how they contribute to building and maintaining the complex systems that represent the function of the body, and how the systems through which food is extracted from the environment can and do exert influence on this. The principles outlined here act as a foundation on which it is possible to consider different aspects of nutrition research methodology. At the same time, we highlight specific limitations of our conceptual understanding that need to be addressed.

1.2 Simplicity to complexity

The nature of nutritional science

We live, survive and thrive in a world of almost infinite variety and complexity. Like other living organisms, we are able to do this by maintaining a constant internal environment. Maintaining this constancy requires the behaviour of all cells, tissues and organs, which maintain structure and function and protect against challenge from the external environment, to be integrated and regulated. The integrity of the body depends on the complex interaction of physical and chemical processes that together characterise metabolism. This is supported by energy derived from the oxidation of macronutrients contained in food. These chemical reactions take place within an aqueous environment, so water is the major constituent of individual cells and the body as a whole. Hence, a fundamental feature of life is that we have to draw continually from the environment around us the oxygen, water and food that we require to stay alive. These are dynamic processes operating within a dynamic system and they are fundamental to the maintenance of health at all ages.

From the time of conception, normal growth and development through childhood to adulthood create a demand for energy and nutrients and depend on their availability, as well as on the body's ability to perform the processes of normal metabolism that allow it to utilise them. Healthy infancy, childhood, adolescence and pregnancy are characterised by a positive energy and nutrient balance, with ordered net tissue deposition leading to increased capability in both structure and function. Health in adulthood is generally represented by an energy and nutrient balance, with constant height and weight and similar body composition over extended periods of time, consistent with physical, mental, intellectual and social function.

By its nature, nutrition is an integrative discipline. A core feature of nutritional science is the exploration of how chemicals, most of which comprise the substance of other living organisms, are drawn from the environment to provide the energy, substrates and co-factors needed to support and enable life. Nutrition occupies the space between the food we eat and the health we enjoy. Its core is the endogenous environment, including the colonic microbiome, where a varied and inconstant intake is transformed into a constant and appropriate supply for normal function. Nutrition is by nature multifaceted, embracing a wide spectrum of biological and other human experience.

Any individual's needs vary with age, gender, physiological state, lifestyle and behaviour, as well as in comparison to other individuals. At the same time, the foods we consume are also very varied. This contrasts with the relative constancy of the internal environment within and among individuals. Such constancy is enabled through regulatory processes and assured through adaptive mechanisms. There is a need to organise our understanding, and our approach to scientific investigation, more effectively to determine more clearly the nature of our nutritional demands and how they might be adequately met across all contexts.

Maintaining integrity – the science of nutrition

The cell is the basic unit of all life. The maintenance of cellular integrity ensures integrated organ and tissue function, keeping intact the body's defences with appropriate inflammatory and immune responses. An intrinsic feature of health is the ability to cope with a changing environment associated with the usual challenges of everyday life, and unusual stresses from time to time, as well as the ability to recover. The stresses may be biological, such as infections with bacteria or viruses, or physical trauma; behavioural or psychological, as with smoking, alcohol, inactivity or poor mental health; or social, as associated with poverty, deprivation or lack of personal control. The ability to maintain the internal environment is called homeostasis; the ability to cope with external stresses, allostasis. The summary of all the internal and external stresses that tax the ability of the organism to maintain constancy represents the allostatic load. The ability of the organism to adapt – to accommodate changes in the internal and external environment – is fundamental to survival and is central to the achievement of homeostasis and allostasis. For this to be achieved in the face of the uncertain nature, extent, severity and duration of changes in the internal or external environment requires a reserve capability that can be drawn on as required, and that is known as resilience. Thus, the nutritional integrity of the organism requires the ability to maintain the usual function, but is intimately linked to the adaptive responses. An insufficient intake of food or a poor-quality diet constrain the adaptive responses, leading to loss of resilience and vulnerability to both internal and external perturbations and hence susceptibility to ill-health.

The balance and amount of energy and nutrients needed depend on this range of experiences with which the healthy body copes as a matter of course. The underlying objective of nutrition research is to understand the needs of individuals, groups and populations for energy and nutrients, and how these might best be met from dietary intake and through other processes.

Structured organisation

How can we manage this complexity, which extends from the molecular, through the cellular, to tissues and whole organisms interacting to maintain the body's function in different environmental contexts? One helpful way of conceptualising the complexity is to consider it as the interaction of two systems, with the whole body as the point of interaction. One system is within the body: its regulated biochemical, physiological and metabolic processes, which maintain the integrity of the system as a whole. However, the body itself is part of a wider social system with even higher levels of organisation within family and community, which incorporate complex social systems and interactions operating at national and global levels. Nutritional science in its broadest sense embraces the way in which each of the systems is organised and functions, but also the way in which they interact. Nutritional science seeks to understand how to ensure the ongoing availability of an adequate diet, in terms of quantity and quality of the pattern of foods consumed, to meet the needs of every individual in the population.

As with all systems, these relationships are dynamic and have multiple regulatory feedback loops. Think of riding a bicycle. It is easy to maintain control so long as the bicycle is in a dynamic state, moving forwards, but it becomes particularly challenging if the bicycle is stationary. The challenges for research in nutrition are to understand how the many relationships are held in dynamic tension, within and between levels of organisation; to be able to comprehend, measure and manage these relationships; and to be aware of the preferred point of equipoise to achieve a dynamic equilibrium for the component parts and the system(s) as a whole.

Simplified models have been developed to describe, measure and help understand this process. One of the best known is the UNICEF framework, which characterises the different levels of organisation that have to be considered in relation to the factors leading to ill-health and their interplay: proximal, intermediate and distal. This type of model is of value in helping to conceptualise the relationships. The bigger challenge is to quantify the dynamics within and across different levels of organisation. Central to this task is the ability to make valid measurements of the critical factors, and their interactions, and in particular the demand for energy and nutrients in relation to what is available, the supply.

1.3 Structure and function: Appreciating complexity

The individual as an organised system

Understanding the synthetic or integrative nature of nutrition presupposes knowledge and understanding of the component parts. While life starts with a single fertilised egg, ultimately each individual exists as an organised dynamic system, as a body that has boundaries in relation to the outside world. The dynamism within the system creates demands for energy and nutrients on an ongoing basis, which have to be satisfied and are 'topped up' intermittently, most obviously from the dietary intake. Foods represent the vehicle through which energy and nutrients are drawn from the environment. The heart of nutritional science is determining the energy and nutrients that are required to maintain the integrity of the organism, which are formally articulated as the Dietary Reference Values (DRVs), Recommended Daily Allowances (RDAs) or Population Reference Intakes (PRIs).

A major challenge within nutritional science is the inherent variability of many of the factors involved. Ultimately, molecular interactions enable cellular structure, function, replication, terminal differentiation and apoptosis. There are higher levels of complexity for organs and tissues and their interactions. From conception, through fetal life, infancy and childhood to adulthood, growth is based on the acquisition of energy and nutrients as tissues (structure), accompanied by the refinement of function with maturation. Increases in organ size lead to greater functional competence. Enhanced intellectual capability enables progressively increasing efficiency in the processes through which food is made available, thereby creating the space and time for individuals and groups to engage in wider creativity, exploration and discovery.

The demand

The dynamic state at every level of organisation is a reflection of continuing turnover and exchange. The cellular and physiological environment is maintained within relatively narrow limits by integrated metabolic regulation. Any individual's dietary intake is inherently variable from day to day, as is their physical activity. DRVs are captured as references: amounts that need to be taken in the diet to maintain health in otherwise healthy people. Their determination recognises the obvious physiological variability associated with age, sex, growth, maturation, pregnancy, lactation and different levels of physical activity. While it allows for environmental protection, it does not consider the effects imposed by infection, trauma or other exceptional stresses, the demands of recovering from such a challenge, or the need to repair the system subsequently. Nor can the values for individual nutrients take account of potentially simultaneous variations in other essential nutrients. Ongoing cellular replication is a critical feature of the usual environmental protection, for the maintenance of external boundaries (skin) and internal mucosal boundaries (gut, respiratory tract, bladder), as well as immune surveillance and continuing protection. All of these create demands.

In terms of energy, the body's ongoing demand under standardised resting conditions represents the basal metabolic rate. The demand comprises three major functions: membrane transport (especially brain and nervous tissue), macromolecular turnover (especially liver and muscle) and internal mechanical work (cardiac, respiratory, gastrointestinal and so on). These are continuous processes and the energetic need is met through the oxidation of macromolecules (protein, lipid and carbohydrate) drawn from the availability within the body itself. This resource is intermittently replenished through dietary intake, which for active individuals is exquisitely well regulated so that energy expenditure is matched by energy intake. The availability of macromolecules for oxidation is a regulated process ensuring that the pattern of macronutrients oxidised exactly matches that taken in the diet, which achieves balance and constancy of weight and body composition.

Meeting the demand (supply)

Food (in)security is the term that has been adopted to characterise a country's food supply status. Its use has evolved and it is now applied to the situation of individual countries, communities or even households; conceptually it can also be applied to individuals. A related but separate term is nutrition security, which similarly has been applied at different levels of organisation. The purpose of both is to capture as a simple, single statement the extent to which food and/or nutritional needs are adequately provided for in terms of dietary supply. Availability is considered, but this in itself is not enough, because the food also has to be acceptable and accessible for consumption. Although the degree of food security is important for different groupings, it is ultimately a summary of the adequacy of provision, availability and consumption at the level of the individual.

Food security consists of two elements, one quantitative and the other qualitative. The quantitative element is a statement of the extent to which food supply adequately meets nutritional needs. The qualitative element embraces the extent to which the pattern of nutrients available from the diet meets an individual's pattern of demands.

For all practical purposes, the quantitative aspect of the diet is determined by the amount of food that has to be consumed to satisfy an individual's energy needs. The maintenance energy needs are determined by that individual's basal energy needs (the basal metabolic rate or BMR) and the level of physical activity. The energy expenditure from most forms of physical activity is proportionate to the BMR, which varies with height, weight, sex, age, maturity and physiological state (pregnancy and lactation). The energy needs are met from the oxidation of amino acids, lipids and carbohydrates, in the same proportions as they are present in the diet. The quality of the diet is determined by the mix of foods and their nutrient composition; that is, the proportions of amino acids, lipids, carbohydrates, minerals, vitamins, trace elements and water.

In general terms, those who are less physically active expend less energy and need less food to meet their requirements. However, if less food is consumed, then the intake of all nutrients is likely to be less. Therefore, if a diet is marginal in any nutrient, that potential limitation is likely to become obvious sooner or more readily in those who are less active (unless they are eating more food than they need). This is one problem for subsistence societies where the quality of the diet might be poor. At the higher levels of physical activity associated with rural life, food consumption is likely to be higher to meet the higher energy requirements, so whatever diet is usually consumed is more likely to meet the needs for nutrients. With urbanisation, decreased energy expenditure and a reduction in the need for food consumption to meet the requirements for energy, any nutrient limitation in the diet is more likely to become exposed.

Similar considerations are likely to prevail in the sick, where illness is associated with reduced activity and energy expenditure, lower energy requirements and decreased food consumption. Illness or stresses such as infection or inflammation have an important effect on the relationship between energy requirements and food intake. The ability to cope with an allostatic load is associated with a stress response, manifest as increased activity of the hypothalamo-pituitary-adrenal and sympathetic nervous systems, and associated glucocorticoid and catecholamine responses. With more severe degrees of stress, there are increasingly obvious metabolic effects: loss of appetite, altered metabolic demands by the tissues, an acute phase response associated with altered delivery of nutrients to tissues, and an unbalanced increase in losses of nutrients from the body (breakdown of tissues and specific nutrient losses in their own right). The magnitude of these responses is related to the magnitude of the allostatic load, and the ability to cope through adaptive responses. One important consequence is that for those on a diet of marginal quality before the imposition of the stress, the ability of the same diet to match the pattern of nutrient needs during and beyond the stress is likely to be impaired. Full and adequate recovery will require a better-quality diet. The period of convalescence may also need to be extended to allow for full recovery from illness or stress.

What this discussion makes clear is that assessment of the adequacy of diet in terms of quality and quantity has to be contextualised to the living conditions and lifestyles of individuals and groups. Although general statements can be made about these needs, the idea that a single ‘prescription’ will be fit for purpose under all circumstances is unlikely to hold. One objective of nutrition research is to gain a better understanding of the nature of the supply that best fits the demands under any particular circumstance, and to characterise diets that adequately meet that purpose. The objective of the profession of nutrition is to understand how to apply that generic and specific knowledge from one context or individual to another.

Failing to meet the demand

The demands for nutrients and energy are very variable, and the diets that can meet those demands also vary widely. When the demands are adequately satisfied by diet, the result is health. If the supply fails to meet the demands over an extended period, then ultimately ill-health will be the consequence. The period of time over which this becomes obvious may be very variable, depending on the particular circumstances, from minutes and hours to months or years. In practice, the imbalance between demand and supply will in due course lead to an alteration in the partitioning of nutrients to different tissues and/or functions. This is most simply identified as changes or progressive alterations in the structure of the body. Body shape, size and composition are the simplest summary articulation of the adequacy of the diet to meet the body’s needs over extended periods. Thus, the simplest routine measures of the shape and size of the body, height and weight, are summary statements of the historical adequacy of the diet to meet an individual’s needs. The relationship between height and weight, relative to reference norms, is the basis for all anthropometric markers of nutritional status that are used in individuals and in populations to mark well-being, risk and outcome. Measures of body habitus in structural terms are also closely related to the functional capabilities of the body. Thus, measures of body shape and size are used to indicate functional state in broad terms, but may be severely limited in this regard at the extremes or important critical times (see later in this chapter).

Ultimately, the foods we consume provide the components from which all of the needs of the body are met. Some of these are derived directly from the chemicals contained in the food, or made available to the body from the food following digestion and absorption. Others are made within the body from the chemicals contained in the food to meet the specific needs of the body. The pathways for the endogenous formation of compounds can be tightly regulated. Other components are made available to the body from the microbiome in the intestinal tract; again, this process may be regulated, controlled or influenced directly by the needs of the body itself. People consume widely different diets, without regard to their composition in terms of energy and nutrients, and the body’s regulated metabolic processes modify the pattern ultimately available within the system.

The energy and nutrients required by the body are made available in stages. Following digestion in the gastrointestinal tract, simpler compounds become available for the body to absorb. Protein is needed in the diet, but as a source of amino acids rather than as the native protein. It is only available in a useful form when the individual amino acids contained within the dietary protein have been released by digestion and incorporated into the amino acid pool of the body itself. Similar considerations apply to all macromolecules. One aspect of dietary quality is the extent to which the pattern of simpler molecules generated following digestion matches the body’s pattern of need, or the extent to which further metabolic interconversion might be required to meet this pattern more effectively. Ultimately, the energy needs of the body are met through the oxidation of macromolecules. As balance is maintained, the energy released is derived from a similar pattern of macromolecules to that taken in the diet. The actual processes associated with the achievement of balance for lipid, protein and carbohydrate are still unclear, but are absolutely dependent on the dynamic processes of turnover that enable regulation.

For individual nutrients, achieving balance, or regulation of the body pool, may be achieved in very different ways. For monovalent cations such as sodium or potassium, absorption is virtually complete, and regulation is predominantly at the level of excretion through the kidney. At the other extreme, for a divalent cation such as iron, regulation of the amount in the body is almost entirely at the level of absorption. Thus, it is not appropriate to expect to increase the body content simply by adding more to the diet, without an appreciation of the factors that regulate absorption and excretion. For other divalent cations such as calcium, the control is more complex, with regulation both at the level of absorption and at that of excretion, as well as elaborate controls on the endogenous interchange between different body compartments and tissues. It is possible to identify general classes of nutrient handling, related to the chemical, physical and biological function of individual nutrients. The important consideration is that regulated absorption and excretion contribute to matching the availability of nutrients to the body's needs.

An intake that is inadequate to meet the needs of the body constrains function, leading to problems associated with deficiency. An intake that is in excess of needs has to be disposed of or excreted in a safe form, and if the capacity to do this is exceeded then the excess that cannot be excreted represents a metabolic stress in its own right. For energy and each nutrient there is a range of intake that meets the needs of the body without the risk of either inadequacy or excess, and this is associated with health and minimal, or no, stress. One important overriding protection is the change in appetite in relation to the adequacy of the diet in meeting the body's needs. One consequence of a deficiency in the diet of a specific nutrient is eventually loss of appetite. Being presented with a poor-quality diet is often associated with loss of appetite, and this combination can lead to metabolic disequilibrium, and ultimately death. This has resulted in the identification of an important fundamental principle in nutrition: limiting nutrients.

Limiting nutrients

The idea of limiting nutrients was first defined in 1840 by J. von Liebig, who stated that the rate of growth of a plant, the size to which it grows and its overall health depend on the amount of the scarcest of its essential nutrients that is available to it. This concept has now been broadened into a general model of limiting factors for all organisms, including the limiting effects of excesses of chemical nutrients and other environmental factors. The identification of limiting nutrients has been the important basis for the determination of nutrient requirements, and for the classification of nutrients in the diet as essential (indispensable) or non-essential (dispensable). Replenishment of the diet with the nutrient that is lacking immediately reverses the constraint, leading to improvement in appetite and return of normal structure, function and behaviour.

The great success of nutrition research over the past 100 years has been to gain a better determination of the body's needs for energy under a range of circumstances, and of the absolute requirements for individual nutrients and their relative proportions. One powerful approach was to determine the effect on the body when a single nutrient was excluded from the diet. It was possible to determine that for many components, their absence from the diet, or their presence in limited, inadequate amounts, led to adverse consequences. The more obvious extreme responses were seen within a very short period of the poor-quality diet being consumed, with loss of appetite, reduction in weight and altered body composition. Examples here would be the dietarily indispensable amino acids. At the other extreme, for some nutrients of which there was a significant store, such as vitamins A or B12, changes might not become manifest for weeks or months. For others, such as iron, copper or magnesium, dietary inadequacy might be ameliorated in the short term by adaptation. Tissue reserves were drawn on, albeit at a functional cost, and the metabolic cost only became obvious over extended periods of time. The ability and ease with which the need for any individual nutrient could be determined vary across this wide spectrum of response, and hence the approach used differed accordingly.

Thus, the lack of availability of energy or any single nutrient can act to limit function, either as a substrate or as a specific co-factor. This can lead to some complex interactions. For example, there is an important and well-established interaction between the energy and protein content of the diet. At marginal levels of protein imbalance, an increase in energy intake will re-establish nitrogen balance; at marginal levels of energy imbalance, an increase in protein intake may re-establish energy balance. This general relationship applies to all nutrients under what is known as Kleiber's law: if the energetic efficiency of a diet is improved by the addition of a single nutrient, that nutrient was limiting in the diet. For diets of poor quality that are deficient in a particular nutrient, growing animals consume a greater amount to maintain an equivalent rate of weight gain. Addition of the deficient nutrient improves the efficiency with which the energy is utilised from the diet. These nutrient–energy interactions can also be demonstrated for nutrient–nutrient interactions. This is why a reference such as the DRV is defined as the amount required to maintain health in otherwise healthy individuals, *on the assumption that* the requirements for energy and all other nutrients have been met.

If a diet lacking a sufficient amount of an individual nutrient is consumed in excess of the needs for energy, some of the excess may lead to thermogenesis and be lost as heat, but more usually it is deposited as tissue. As a nutrient limitation is likely to constrain lean tissue deposition, the likelihood is that the excess energy will be retained as adipose tissue.

Endogenous formation: Proteins and amino acids, building blocks and regulators

Dietarily indispensable components may be organic or inorganic. Inorganic ions or molecules, such as potassium, sodium, chloride, iron and zinc, have to be provided pre-formed in the diet, although they may be an intrinsic part of an organic molecule. The indispensable nutrients derived from organic molecules might be expected historically to have been found in normal diets in amounts adequate to meet metabolic needs, as throughout evolution there can have been no selective advantage in maintaining the pathways for their formation, and loss of these pathways did not incur any survival cost.

Dietarily non-essential, dispensable components may not need to be provided pre-formed in the diet, but they are nevertheless an absolute requirement for normal metabolism. It may be that they can be omitted from the usual diet without incurring any obvious cost in the short or longer term, and examples of this would be non-essential amino acids (dispensable amino acids) or longer-chain polyunsaturated fatty acids. The ability to omit them from the diet without any consequence requires that their precursors are available in sufficient amounts, either from the diet or from metabolic exchange. However, such precursors may be required by the body in amounts much greater than can usually be provided in the diet. In addition, they are often the building blocks for special compounds required in large amounts or they perform important regulatory roles in the body, for example fatty acids to form stable and healthy cell membranes, or the amino acid precursors for DNA and RNA synthesis. Although the capability to make these molecules may exist, the capacity to do so is potentially limited, therefore if the demand is particularly high, it may not be possible to make a sufficient quantity. Under these circumstances these nutrients become 'conditionally essential' in the diet.

The metabolic pathways through which dispensable nutrients are formed within the body are often protected, in order to ensure the capability to support vital processes and to protect cellular integrity. For this reason, it may not be easy to expose a dietary limitation. The extent of this buffering capability in terms of availability is one important aspect of resilience. The buffering may be achieved by trading one important process for another, for instance stunting in the face of inflammation or infection. The pathways that enable the endogenous formation of these nutrients are usually critically dependent on the availability of many other micronutrients, and hence their metabolic availability may be especially vulnerable in poor-quality diets. Limitations in the formation or availability of these nutrients might only be exposed by a stress test.

Thus, dietarily indispensable nutrients have to be provided pre-formed in the diet; dietarily dispensable nutrients do not have to be provided pre-formed in the diet, but the pathways for their endogenous formation must be intact and have the capacity to meet the need. For conditionally indispensable nutrients, the demands can under some circumstances exceed the capacity for endogenous formation. There has been an assumption that the ability to meet the nutrient needs of the body is determined only by the dietary intake and the capacity for endogenous metabolic formation. It is increasingly clear, however, that a significant contribution to meeting the nutrient needs of any individual might be derived from the metabolic activity of the microbiome.

Microbiome

Many species of bacteria have evolved and adapted to live and grow in the human intestine. The microbiome of the gut contains 300–500 different species of bacteria, and the number of microbial cells within the gut lumen is about 10 times greater than the number of eukaryotic cells in the human body. In humans, most bacteria exist in the colon and terminal ileum, but in other animals, such as ruminants or rodents (and other animals that practise refection), there are substantial populations in other parts of the gut. The microbiome and the organisms that comprise it represent an ecosystem in its own right, with complex metabolic interactions within the ecosystem and with the host itself.

It is increasingly clear that cross-talk between the organisms, both metabolically and genetically, plays an important role in maintaining the viability and resilience of both the microbiome and the host. There is energy and nutrient exchange within the ecosystem and hence the ability to make nutrients that can be made available to the host. The presence of this exchange is clearly demonstrated by the dependence of ruminants on a viable and supportive rumen activity. The extent to which this happens in humans is less clear, either for macronutrients or for micronutrients. However, it is clear that it does occur for water and minerals such as potassium, sodium, calcium and magnesium, chloride, vitamins such as vitamin K, and to some extent B vitamins and nitrogen balance. There are other complex interactions, such as the microbial fermentation of non-absorbed carbohydrate ('dietary fibre') to short-chain fatty acids, with direct effects on gut function and more widely on metabolism.

What is undoubted is that the activity of the microbiome is responsive to the nutritional state of the host and can make available nutrients that otherwise would be limiting if dependence for all nutrients was on simple dietary provision, or the host metabolism alone. Thus, it is not clear to what extent variability in an individual's ability to meet a suitable pattern for their own metabolic needs is enabled through a responsive metabolism of the resident microbiome. Indirect evidence suggests that this contribution can be substantial under certain circumstances, and is critical for nitrogen balance.

1.4 The integrated system

Normal growth and development

Growth is an ordered and structured process characterised by increasing tissue mass, complexity, organisation and maturation. Growth is often captured simply as changes in height, weight, relative body proportions and body composition. More refined changes associated with maturation may be captured as bone age or the timing of critical events such as puberty. Nevertheless, even the most sophisticated of these articulations are pale reflections of the complex, regulated processes taking place. The nature and timing of these processes are determined by genetic endowment, and by modified genetic expression related to epigenetic change. They are also regulated by a sophisticated interplay of the hormonal environment. However, ultimately all of them depend on the availability of sufficient energy and an appropriate pattern of nutrients at the appropriate time to enable net tissue deposition of a suitable composition.

The WHO (World Health Organization) growth standards have been developed out of the experience of the growth of normal children from around the world. They show that children grow similarly across all societies given an equal chance of a healthy and a nutritious environment before pregnancy, in the peri-conceptual period and during pregnancy, infancy and childhood. Any constraint on growth reflects adverse environmental conditions. There is a measure of innate variability, but this is small compared with the marked differences associated with environments of different quality. Failure of growth, marked either as wasting or stunting, is associated with functional consequences for every tissue and organ. The growth constraint results in a limitation in acquired functional capacity. It may be sufficiently small to require a stress test to demonstrate its extent, but more significant insults express themselves as readily demonstrable limitations of function, for any system of the body. At early ages these constraints are potentially reversible, but this plasticity is lost progressively with age. In practice, the loss of capacity represents a reduction in the extent of reserves and a decrease in resilience. The decrease in resilience represents greater vulnerability, or loss of allostatic capability, and hence greater susceptibility to all environmental challenges. For any individual with reduced resilience, ill-health is more likely to express itself at an earlier stage or more aggressively for the same environmental challenge. Growth takes place in a craniocaudal direction and, when subject to constraint, the brain tends to be protected at the expense of other organs. Hence, the capacity of the other tissues to support and protect brain function will be determined by the extent to which their own nutritional environment during earlier life has been enabled or constrained.

Adaptation

The ability to maintain function in the face of widely different dietary or other environmental exposures is brought about through a series of processes characterised as adaptation. This is how the body achieves a functionality that is fit for purpose in the particular context. One important characteristic of adaptation is that the processes that change in response to the altered context are reversible. The system reverts to its former state given a return to the previous environment, such as the development of polycythaemia at altitude. These adaptive processes enable and protect vital functions. The ability to respond appropriately is the hallmark of resilience, but it carries a cost, in terms of both energy and nutrients. If the supply of energy and nutrients is not matched to the demand over a period of time, the most obvious consequence is a change in body weight.

Weight loss is a consequence of the body having to meet its energy needs from the oxidation of macronutrients derived from tissues without adequate dietary replenishment. To an extent all tissues lose some mass, but the brunt is borne by muscle and fat. Less obvious is the accompanying compromise in function, with the reserve capacity that represents resilience being sacrificed at an early stage. This loss of capacity applies to all functions to a greater or lesser extent and leads both to increased vulnerability to external challenge and to impaired capability to achieve and maintain homeostasis. This process is known as *reductive adaptation* and is the basis for a greatly increased risk of morbidity and mortality in under-nourished individuals and populations.

At the other extreme, the consistent consumption of a diet that provides energy in excess of needs leads to an increase in weight and body mass. This is most obviously seen as increased adiposity, but there is also an increase in the mechanical and metabolic machinery required to support the increased mass, which can be characterised as *expansive adaptation*.

When the dietary intake of energy and nutrients exceeds requirements, the body responds to reduce the metabolic and physiological burden and avoid toxicity. In the short term, balance may be achieved by lowering intake, reducing absorption or increasing excretion in the urine. The extent to which balance is achieved depends on the magnitude and nature of the excess, but is usually associated with increased metabolic work or a re-prioritisation of metabolism, representing both a challenge and a cost to the system. For example, balance in the face of an excess amino acid intake is achieved through transamination, deamination with increased urea formation and excretion. In the same way, for those inorganic elements where the availability is regulated at the level of absorption – such as calcium and iron – increased faecal excretion will be associated with changes in the local environment within the bowel that may alter the colonic microbiome, change the biophysical properties of the bowel content (e.g. soap formation with calcium salts) or directly increase the potential oxidant load on cells of the gut (e.g. iron).

The capacity to accommodate excess macronutrient intake is limited. In the immediate postprandial period when the rate at which exogenous nutrients appear in the circulation exceeds their clearance and assimilation, normal physiological regulation and control are compromised, with consequent changes in nutrient partitioning, blood pressure and haemostatic responses. This poor metabolic control, or lack of ability to cope with excess, marks an increased vulnerability to disease. Over longer periods, with continued excess, as the capacity of the adaptive responses is exceeded there is increasing dysregulation, loss of resilience and increased vulnerability. This state is marked by increasing weight and fatness, increasing deposition of fat centrally and ectopically within muscles and viscera, elevated concentrations of circulating nutrients and hormones, in both the fasted and postprandial states, chronic inflammation and impaired haemostatic and vascular function, and abnormalities in lipid, amino acid and glucose metabolism. Together, these processes mark expansive adaptation that enables survival, but at the cost of reduced resilience. Diagnostic criteria based on these features (increased waist circumference and poor metabolic control) have been used clinically to identify and treat those with increasing risk of cardiometabolic disease (e.g. 'metabolic syndrome').

The challenge is to gain a better understanding of the underlying pathophysiology and the innate and modifiable factors that contribute to variability in the capacity to accommodate excess. Accumulation of fat within the abdomen as visceral adipose tissue is sometimes, but not always, associated with inflammation. Some individuals may be overweight but have good metabolic control and a lower risk of morbidity and mortality. This may be attributed to better integration and control of the metabolism through a limited number of processes that are very sensitive to the availability of specific micronutrients, especially vitamins, which act as co-factors in the regulation of endocrine control, inflammation and immune competence. Poor micronutrient status in the face of excess macronutrient intake acts as an additional stressor and may explain some of the variability in metabolic dysregulation and associated morbidity in the overweight and obese. Importantly, the ability to maintain metabolic control is linked directly to physical activity and metabolic processes within skeletal muscle. Improved control may be enabled through the disposal of energy via contraction; through the endogenous provision of substrates for metabolism synthesised within and exported from muscle; and through the release of regulatory peptides or myokines that act systemically to influence metabolism in other tissues. The capacity of muscle to contribute to whole-body metabolism may be determined by the mass of skeletal muscle (e.g. organ size), the level of metabolic activity within muscle associated with being physically active, or both. There is a need for a more complete appreciation of the nutritional factors that determine the integration and control of metabolism, and their variation from person to person.

The individual: A component of society as an organised system

The challenge for all societies is to enable and ensure a consistent supply of food to meet the needs of all individuals. This depends on a series of complex interactions, which can be characterised as a food-acquisition system. There is seasonal variation in the quantity, quality and diversity of food available, though in modern societies this is buffered by national, international and global activities of food production and movement. For traditional societies the wider environment and climate play a more dominant role and the degree of resilience is likely to be reduced. The interplay of these factors has a significant role in the development of social and cultural behaviours, the relationship with religious practice and many aspects of how societies are organised. A period of poor nutrition can have an immediate effect on the risk of ill-health or death, and families use a range of mechanisms to protect themselves. However, the cost of employing protective behaviours might have an impact on the entire family for long periods of time, and may even have inter-generational consequences.

By definition, successful societies have managed to secure regular access to food of adequate quality and quantity. The cuisine and traditional food practices have evolved based on accumulated experience and wisdom, determined ultimately by survival and being fit for purpose. These experiences are deeply ingrained in all cultures as patterns of food preparation and consumption. With the monetisation of food and its use as a commodity, these relationships change, so that the processes of food production have become divorced from the practices of food preparation and consumption. Progress in food production, processing techniques and technologies has enabled great efficiencies of land use, preservation, storage and transport over large distances. One consequence of this has been a substantial reduction in the diversity of the diet, however. Reduced diversity leads to a significant risk of a reduced quality of diet because of a greater difficulty in ensuring a match for the varied needs within the population.

Our perceptions of diet quality are directly related to our understanding of nutrient requirements, which are themselves imperfect. The simple observation that obesity is now an increasingly common problem, which appears to evade all attempts at prevention and effective treatment, makes it clear that we do not have adequate control of these relationships. In practice, the most direct way of determining how well the provision from the diet matches needs is to explore the relationship between diet and either markers of risk for ill-health, the development of disease itself or death. This is classic nutritional epidemiology.

The most useful summary statement of an individual's historical and current nutritional status is offered by height, and weight in relation to height, captured as weight for length or height in childhood, or Body Mass Index (BMI) in adulthood. Both a lower and a higher BMI are associated with increased mortality, leading to a U- or J-shaped relationship between BMI and mortality. Increased mortality for people who are relatively lighter is associated with death from chronic lung disease, and for those who are relatively heavier with death from cardiovascular disease, type 2 diabetes and some cancers. A preferred range exists within which risk of ill-health and death is the least. There is a similar U-shaped relationship for the relationship between height and mortality. Shortness is associated with death from cardiovascular disease, and tallness with death from some cancers. These are population statements of risk, but clearly lightness, heaviness, shortness and tallness have important nutritional correlates over the life course.

More complex relationships can be drawn in terms of body composition, body proportions, growth patterns and the timing of maturation, but the underlying importance lies in the fact that cumulative nutritional experience throughout life leads to differences in nutritional partitioning to organs and tissues. These underlying biological processes are linked to susceptibility to ill-health and mortality, although the mechanisms through which these linkages operate are not yet clear. Importantly, what is not known is the extent to which the associations are causally related, either directly or indirectly, or how far they are simply indicative of common underlying factors. Bringing clarity to these relationships through a more insightful understanding of the underlying mechanisms is one very important challenge for nutritional research. This requires an understanding of the nature of the interactions and complexities of each system in its own right at the different levels of organisation, as well as the ability to integrate this knowledge effectively across those different levels.

1.5 Developing nutritional research

Nutritional research embraces factors operating at all levels of organisation, but it also requires the ability to synthesise understanding between the different levels of organisation and across disciplinary boundaries. To achieve this, clarity and consistent use of language are required to enable communication, together with standardised and quality-assured approaches to measurement to facilitate synthesis and interpretation. In this sense, as an integrative science, nutrition represents the meeting place for many different interests and disciplines. Although there has been progress in enabling this exchange, modern technologies offer very significant new opportunities. It is therefore imperative to ensure that commonality of purpose and understanding among the different disciplines are achieved rapidly. For this to happen, nutrition research needs to build on its components to achieve a better understanding of the systems themselves, and of the interactions of both their individual parts and the systems with each other.

These investigative activities can and do take place at different levels of complexity, but accessing any one level, or the interaction between the levels, is challenging. It has not yet been offered in any standard way or with consistency. This has led to problems in carrying out nutritional research that is of high quality and of value in a coordinated way across a range of sectors and activities. The development of 'toolboxes' that are fit for specific purposes should enable and facilitate better and more effective investigation.

Toolboxes

Nutritional science has two defining characteristics: the ability to determine the requirements for energy and nutrients (the nutritional demand); and the ability to determine the extent to which the demand has been met (the nutritional state or status). The assessment of nutritional state, at the level of the cell, the organ, the whole body or the population in humans, animals or plants, is an area of research specific to nutrition and there are specific 'tools' that are used to make an assessment. Most simply, the assessment can be captured in three dimensions: what you eat (a statement about food, diet and feeding behaviour), what you are (capturing the size, shape and composition of the body) and what you can do (the functional competence expressed in terms of biochemical and physiological measures of micronutrient status, performance and functional capacity, and level of physical activity). Each dimension is important, but each in isolation is insufficient to describe nutritional status completely. Therefore, any 'toolbox' needs to include a measure of all three dimensions. There are many different measurement instruments available and the choice among them depends on the specific nature of the question to be addressed and the time, funds and expertise required to quality assure their use.

The level of complexity and sophistication of the toolbox need to be appropriate and proportionate to the question being addressed. For an entry-level toolbox, the tools should be immediately accessible, require the least physical resource and be least likely to impose on volunteers and staff engaged in the study. The information gained will be limited in both amount and utility, but should be sufficient to offer a broad categorisation of nutritional state and to determine whether there has been a change in that state. Detailed information will not be provided on all aspects of dietary exposure, body composition or micronutrient status. At this level, intake may be assessed using short questionnaires on reported appetite or the extent to which eating behaviour is consistent with current dietary guidance (e.g. healthy eating score or index) or dietetic plan. This will indicate the need for further assessment or intervention. Body size and shape may be assessed by simple anthropometry (stature, weight and girth – both current and change), while functional capacity can be assessed using short questionnaires that capture reported activity behaviour (levels of activity or sedentary behaviour) or well-being.

More detailed assessment would require more advanced tools such as a food frequency questionnaire or a multiple pass 24-hour recall questionnaire to describe either the dietary pattern or quantitative measures of reported energy and nutrient intake; bioelectrical impedance analysis or skinfold thickness measurement for assessment of body composition; and measures of muscle function, exercise capacity or conventional biochemistry to assess micronutrient status as a marker of functional state. Greater depth of understanding can be acquired with more advanced analytical techniques characterising patterns of consumption, or taking a multi-compartment approach to the determination of body composition. Isotopic probes can also be used to investigate the flux through metabolic pathways and the function of different physiological systems. It is now possible to take a life systems view combining all measures within an 'omics' approach to provide summative statements on the phenome or metabolome.

Increasing sophistication is associated with increasing cost and invasiveness. Irrespective of the level of complexity of the toolbox, confidence in the measures and their interpretation can only be achieved where measurements are taken in accordance with national governance requirements and conducted within a quality assurance framework. For all measures, there is a need to be able to demonstrate the validity and performance characteristics of all equipment. The individuals making the measurements also need to be appropriately trained using standardised operating procedures (SOPs) and to be demonstrably competent in using objective measures of accuracy, validity and standardisation.

Nutritional research of the future will have to embrace all aspects of the reductionist science that has powered and enabled such remarkable progress in the past, but it will also have to develop much more refined capabilities for synthesising the knowledge gained. This will ensure a better understanding of the systems involved, how they might be regulated, and the interventions that are most likely to achieve change that leads to longer life with better health.

1.6 Conclusion

For research in nutrition to be of great benefit, it needs to provide a base of evidence to improve health promotion, disease prevention and clinical care, drawing on understanding from science to improve practice. A central feature of this activity would be the ability to characterise reliably the nutritional phenotype, its determinants and variability, and to intervene to maintain or improve the phenotype at individual, group and population levels. Achieving this requires an understanding of the determinants of at least three major systems and how they articulate to enable better health. These three systems are the social systems that embrace the social determinants of health; the lifestyle systems that contribute and determine individual behaviours and how they relate to health; and the whole-body human biological system, its regulation and integration.

Nutrition research has to draw on the widest range of approaches and methods available to achieve a better understanding of how the body is enabled to meet its requirements for energy and nutrients. The methods are rich and varied and each gives a perspective on particular aspects of a system. These different perspectives then have to be interpreted and understood in the context of the system as a whole. Integrating understanding within and between systems is not always carried out in a consistent way, and data have not always been collected with a view to facilitating this integration. By their very nature, each of the systems is dynamic, with exchange, turnover, regulation and control representing the hallmarks of achieving stability and healthy function. There are fundamental principles underlying these exchanges and interactions, and consistency of language, together with quality assured measurements, should enable greater coherence in integration within and across different levels of organisation. Within each area of investigation there are also aspects that are inherently variable, such as dietary intake and physical activity, therefore their value can only be determined in the context of the extent to which they better enable the body to meet its inherently variable requirements. Ultimately, nutrition revolves around what the body can do for itself to meet its cellular and metabolic needs, and how this can best be supported through the regular consumption of a sufficient diet of appropriate quality.

This chapter has considered how understanding can be organised to enable better scientific investigation and to comprehend more clearly the nature of nutritional demands, how they might be measured and how they might be adequately met across all contexts. One of the most important objectives of nutrition research is to gain greater knowledge of the nature of the supply that best fits the demands under any particular circumstance. In turn, the objective of the profession of nutrition is to understand how to apply that generic and specific knowledge from one context or individual to another.

Reference

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