Effects of food on metabolic regulation and disorders

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Nestlé is the world's largest food company and supplies ~1% of all dietary choices. Today's food marketplace is arguably the most complex, dynamic, highly competitive and exciting of human endeavours. The food supply is changing. Advances in commodity genetics combined with industrial processing have extended the yield, caloric content, nutritional quality and safety of agricultural materials used as food ingredients. As the largest food producer globally, Nestlé is committed to ensuring the highest nutritional quality of its ingredients and products. This paper provides an overview of the work Nestlé is doing in the field, illustrated by examples of our published work, and highlights the areas that are actively under investigation at the Nestlé Research Center in Lausanne, Switzerland.

Nestlé's work in food composition

Today, humans consume diets with remarkably diverse compositions. Nestlé has spent >100 years studying the quality and safety of food ingredients, including proteins and amino acids (from plant and animal sources), carbohydrates (glucose, simple sugars, complex polymers of different sugar backbones and polysaccharides), lipids (triacylglycerides as fats and oils from plants and animals, complex membrane lipids and sterols), polynucleotides, nucleic and organic acids, and vitamins and alcohols, as well as the secondary metabolites of plants and microorganisms, including carotenoids, flavonoids, anthocyanins, complex polysaccharides, oligosaccharides and conjugates. However, studying these components as isolated ingredients does not necessarily provide the means to understand complex foods. Nestlé is therefore applying its world leading scientific expertise in food structure and nutrition to understand diet and metabolic health.

The challenges to understanding the implications of food composition for metabolic regulation are encyclopaedic, yet some important principles can be discerned. Depending on the dose, all dietary components affect metabolism and metabolic regulation to some extent. Nestlé research has found that varying amino acids in different proteins affects their metabolism and processes as diverse as glucose metabolism, insulin sensitivity, adipose regulation and food-intake control, and that varying the fat composition affects lipid metabolism, glucose metabolism and insulin resistance[1]. Different simple sugars (such as glucose and fructose) and their polymers (both digestible, such as starch and glycogen, and indigestible, such as oligosaccharides) produce varying metabolic responses[2]. Finally, non-essential exogenous plant and microbial metabolites, ranging from simple organic acids, amines and polyamines to flavonoids and pigments, interact with human metabolic regulation[3].

On the basis of our research, we believe that no single food component can be understood in isolation. The overall balance of foods within the context of a particular individual (with regards to factors such as lifestyle and age) can be appropriate or deleterious to health. Furthermore, health itself varies and dietary compositions that are balanced in one metabolic situation might be unbalanced in another. For example, a diet that fuels the metabolism of a performance athlete for long endurance events[4] could be deleterious to an overweight sedentary individual who is developing insulin resistance[5]. The problem is yet more complex, as foods with the same basic compositions have different metabolic effects depending on their structures. Although the nutrition community as a whole is pursuing the role of diet composition in metabolic health, few researchers are establishing the role of food structure in scientific detail. It is clear that this area needs more investigation. Nestlé is therefore actively pursuing this goal.

Nestlé's work in food structure

We now know a great deal about the basic biomaterial properties of foods and their complex structures[6]. Unfortunately, little is known about the relationships between complex food structure and gut physiology. Food ingredients consist of the molecules of agricultural commodities (that is, cultivated plants and livestock) and their supramolecular structures, both of which can be altered by processing (Fig. 1).

Food structures influence metabolic processes in the humans who consume them, but we are only just beginning to understand how. The ligands of minerals, associations of biopolymers, colloidal states of lipids and integrity of cellular plant materials all affect the dynamics of digestion, gut sensing and signalling systems, and the absorption and bioavailability of nutrients, substrates, fuels and bioactive molecules.

Structures that are formed spontaneously by the components of food within the intestine also affect digestion. Understanding the molecular processes of self assembly involves a practical application of the field of nanoscience[7]. As an example, the basic food polymers, proteins and polysaccharides, are thermodynamically incompatible in aqueous solution and spontaneously separate into two discrete phases: a protein-rich aqueous phase and a carbohydrate-rich aqueous phase[8]. How these discrete phases form, guide digestion and dissociate within the intestine remain poorly understood.

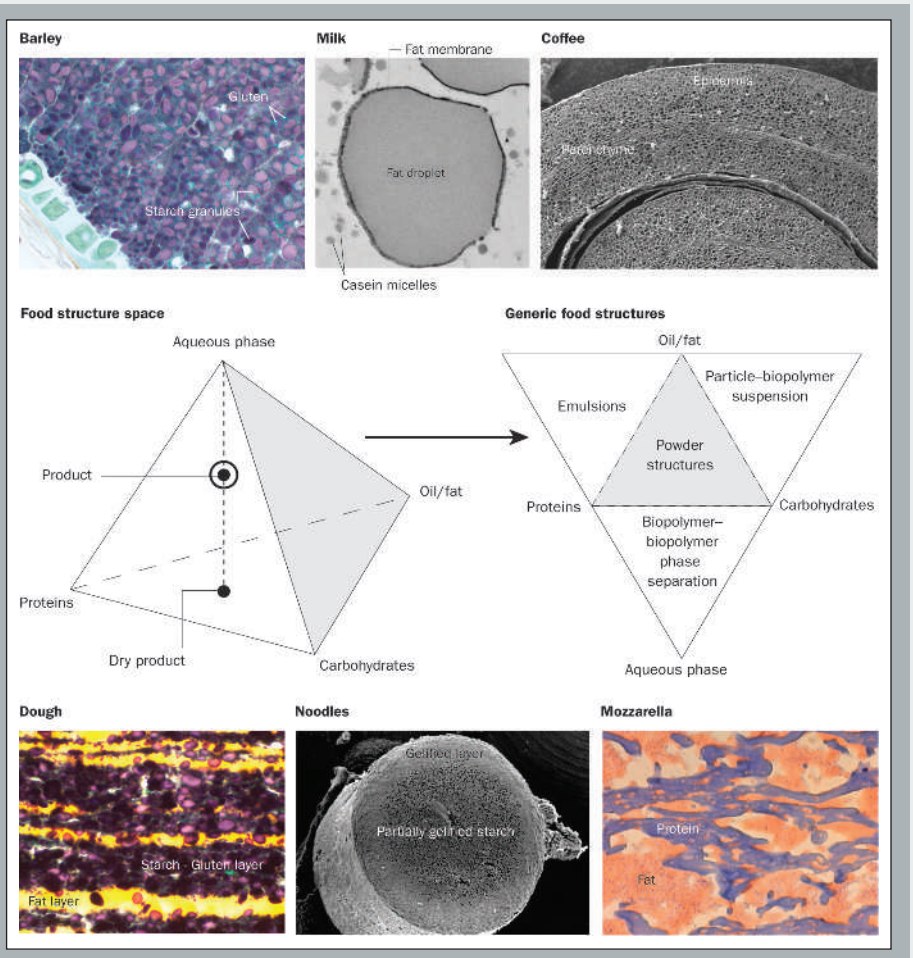


Figure 1 | The physics of food structure
Food ingredient biopolymers interact in water to form various complex structures. Gels, fibres, emulsions and foams are explicitly formed during food processing and preparation. These structures contribute to the stability, shape, texture and organoleptic quality of the final foods, and are an indispensable part of the value of products such as bread, dough, pasta, cheese and ice cream. The goal of cuisine is to gain control of the structure of complex foods (whether by individual chefs or industrial process engineers). Traditionally, this means that it is necessary to dissociate the specific biological functions of agricultural biomolecules (enzymes, muscle fibres and so on) and to gain the general material properties of their polymer classes; for example, proteins and polysaccharides share with synthetic polymers their phase-separating behaviours in aqueous solutions[8]. Food processing transforms the ingredient composition into distinct assemblies that control attributes of the product (for example, appearance, colours, flavours and texture). All possible combinations of the food constituents (proteins, carbohydrates, lipids and water) can be represented as a tetrahedron signifying the overall generic space of food structures. In foods that are primarily water, the biopolymer structures are dispersions or suspensions mirroring the multicomponent and multiphase nature of foods. In semi-solids and solids, the structures are also describable as heterogeneous composite biomaterials. This simplified diagram shows that the process of changing a given food composition involves a series of structures formed from a fusion of generic structures. Our goal now is to understand the relationships between food structure and nutritional functions.

One question that begs asking is "Is food structure beneficial to health?" — in other words, is it better to digest and absorb food components rapidly from a simple homogeneous fluid or slowly from a complex organized matrix? This could take decades of comparative studies to answer. However, it is also possible to look to evolution for clues. Nestlé has spent many years studying human milk, which evolved under the constant Darwinian selective pressure to provide complete nutrition to infants. Milk is an obligate fluid secreted from the mammary gland, and might therefore be expected to be a non-structured source of rapidly released nutrients. In fact, studies have shown that most of its components are delivered conspicuously slowly by the infant's intestinal absorption processes — in some cases ingeniously so. The major milk protein casein is easily digested by infant proteases due to its lack of secondary structure. Nevertheless, casein micelles self-assemble into complex curds within the stomach of an infant in response to the action of the rennin enzyme. As a result, the proteins exit the stomach slowly[9]. Glucose is present in milk as lactose, which is a nonabsorbable disaccharide. Therefore, glucose is absorbed only as quickly as it can be digested and released by an infant's lactase enzyme. The example of human milk demonstrates that rapid bioavailability might not be the optimal means to deliver nutrients. Accordingly, the processing that controls food structure is important to the quality of human diets.

Nestlé's interest in the gut

The human gastrointestinal tract is an inspiring organ (Figs 2,3) with prodigious length, surface area, cellular diversity, signalling capacity and metabolic activity. It is the largest immune organ and the second largest neurological organ in humans. It harbours 10 times more bacterial cells than all the cells in the rest of the human body combined. Additionally, it has extraordinary capacities to physically propel, mechanically manipulate, enzymatically digest and actively absorb nutrients from even the most intractable biological matrices. Its quantitative capacity for transport and absorption is even more impressive considering how selective this process is. Interestingly, the absorption of calorie rich, nonessential components (including lipids, carbohydrates, proteins and even alcohol) is not downregulated by the intestine regardless of the state of energy excess. All of these processes require the coordinated regulation of considerable genetic investment along the intestine[10].

The ability to sense nutrients was a requirement of simple organisms early in cellular evolution. Yet taste and smell are only a part of the overall signalling induced by foods. Not surprisingly, in addition to its digestive and absorptive functions, the gastrointestinal tract plays a role in sensing and signalling as part of the physiology of energy metabolism. Nutrient ingestion generates afferent signals from the gastrointestinal tract to the brain that adjust food intake, and glucose and energy metabolism.

Nestlé's attention to energy metabolism

Energy metabolism and its appropriate regulation are a prerequisite for good health. Understanding how energy is stored and utilized in healthy conditions, as well as those of energy-balance deregulation (such as obesity and type 2 diabetes), is a focus of Nestlé's current research. This knowledge is being applied in infants to prevent predispositions towards fat gain and type 2 diabetes later in life, in adults to aid weight loss and promote weight maintenance, and in individuals of all ages to prevent the complications of obesity (that is, insulin resistance and diabetes).

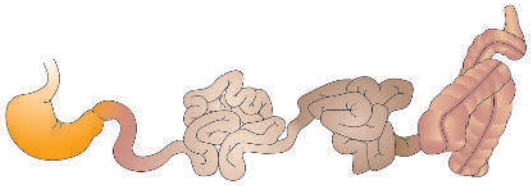
The growing prevalence of obesity has renewed our interest in understanding the role

of dietary factors (including lipids, proteins and carbohydrates) as early determinants of childhood obesity[11], as well as the predisposition to diet-induced metabolic disorders in adulthood. Nestlé research addresses targets including proteins in infants[12] and excessive carbohydrate intakes in adults[13] using models ranging from healthy humans to cell cultures[14]. The act of eating promotes energy consumption, and the thermic effects of food itself and energy expenditure are important to overall energy metabolism.

Nestlé's focus on individual variations in metabolic state and dietary responses

Although a disturbingly high percentage of the population suffers from metabolic disorders, it is notable that many individuals in the same environment do not. Why do some people accommodate their metabolic regulation to variations in diet and lifestyle? We are actively working to combine imaging and metabolic profiling as the cornerstone for future health assessment (Fig. 4). If people vary in their responses to diet, we need to know how scientifically.

Nutrigenomics is beginning to assign the genetic basis of differences in human responses to diet[15]. However, genotype is not the only way in which individuals within a population differ with respect to dietary responses. Diet itself, lifestyle, life stage and health status all influence dietary requirements and metabolic responses to foods. Metabolic disorders cause changes in physiological states and perturb normal responses to diet, as do



Peptide secretion	Stomach	Duodenum	Jejunum	Ileum	Colon	Other	Influence of diet
Control of meal size and motility							
Gastrin	G cells						↑Peptides, amino acids ↑Ca
Gastrin-releasing peptide (GRP)						Neurons	↑Fatty meals ↑Whole proteins
Cholecystokinin (CCK)		I cells				CNS Neurons	↑Dietary fat ↑Proteins after digestion ↑Dietary fibers ↑High fat, low carbohydrate might reduce CCK-induced satiety
Motilin		M cells				CNS	↑Meal ↑Fat ↑Acid ↑Alkali
Somatostatin			D cells			Pancreas CNS	↑Mixed meal ↑Fat ↑Protein ↑Sucrose
Neurotensin				N cells			↑Fat (four carbons, minimum fatty acid chain length) ↑Alcohol
Control of glucose homeostasis/adiposity							
Ghrelin	A cells					CNS	↑Fasting ↓after food intake ↓Dietary carbohydrate ↓Psyllium fiber ingestion Conflicting evidence with effect of dietary proteins
Gastrin inhibitory peptide (GIP)		K cells					↑Emulsified fat. Hydrolysed triglycerides (not triglycerides) ↑Long chain fatty acids (not short chain) Administration of surfactant that blocks the formation of chylomicrons completely blocks GIP release by fat ↑Sugars that utilize the sodium-dependent glucose transporter (glucose, galactose, sucrose)
Glucagon like peptide 1 (GLP-1)				L cells		CNS	↑Mixed meal ↑Digestible fat ↑Carbohydrates
Peptide YY (PYY)				L cells		CNS	↑Energy intake (total calories) ↑Fat, protein, carbohydrate ↑Gastric acid
Neuropeptide Y (NPY)				Neurons		CNS Pancreas	↑Protein meals and other nutrients and by cholinergic reflexes ↓Anticholinergic agents
Leptin						Adipocytes	↑Carbohydrate-rich meals

Figure 2 | Cells within the stomach, proximal small intestine, distal ileum and colon all sample the gut. Complex meals induce the secretion of cocktails of peptides to digest and absorb nutrients. The integration of the various control systems that signal ingested calories, control meal size, signal adiposity and give pertinent input throughout the brain is still far from being understood. The thickness of rows indicates the intensity of peptide secretion. An upward pointing arrow (↑) indicates that the release of the gut peptide is increased by the specified food or nutrients. A downward pointing arrow (↓) indicates that secretion of the gut peptide is decreased by the specified food or nutrients. CNS, central nervous system.

the intensity, duration and frequency of exercise, as well as stress[16]. Throughout history, humans have shown a remarkable ability to adapt and survive in differing environments. Modern humans are exposed to a variety of diets and willingly engage in extremes of physical activity, ranging from being relatively sedentary to highly active.

The environment that an individual is exposed to can alter the expression of genes, in some cases for long periods of time[17]. Genetic imprinting, programming or, more generally, metabolic memory can alter the physiological responses of an individual to different lifestyles and diets. Food choices early in life can potentiate genetic predispositions — that is, induce epigenetic susceptibility to particular diseases, including hypertension, obesity and diabetes. Nestlé research has also demonstrated the benefits of adaptive responses to various environments, including athletic training, which in turn affects the value of diets tailored to an athlete's unique metabolic demands[16].

Nestlé's vision for assessing individual metabolic states

Humans differ in their metabolism, responses to diets and predispositions to metabolic disorders. Is it possible to measure these differences and act upon them? Biomarkers of diseases as clinical diagnostics are a cornerstone of disease management. Yet such markers rely on the presence of a diseased state. Preventing metabolic disorders before they damage health will require a new generation of diagnostics or metabolic assessors that are accurate enough to measure the varying metabolic status of healthy individuals, and to guide their dietary and lifestyle choices.

Measuring genotype alone cannot determine existing, or predict future, metabolic health. The alternative is to measure metabolism directly. Nestlé research has pioneered the applications of metabolic profiling to nutrition[18]. Mass spectrometry combined with various high-throughput separation techniques can identify thousands of metabolites and complete networks as a step towards human metabolomics. If metabolites could be measured quantitatively in individuals, a person's status could be compared to that of the healthy population and their own history, thereby achieving a fundamental change in the routine assessment of personal health[19]. Measures of metabolites and peptides, including those responsible for gastrointestinal sensing and metabolic signalling, could be fitted to models and used to assign individual alterations to biochemical pathways regardless of whether they were caused by genetic variation or environmental effects. Nestlé and its academic and industrial partners are developing much needed high-throughput technologies to enable the scientific community to assemble large legacy databases appropriate for data mining, in order to more fully understand metabolic disorders, and their progression, reversal and ultimate prevention[20].

We appreciate that using metabolic profiling to build knowledge that will monitor and guide individual health raises important issues. The first is quantitation — specifically, accuracy and precision. Currently, there are insufficient standards to routinely quantify the hundreds of metabolites that even a minimal approach to health status measurement would require. The second is the importance of context — that is, annotating the subjects who are the sources of the metabolic data. Rather than biasing the outcome by including only diseased individuals and disease endpoints, multiple aspects of health (such as physiological, neurological, genetic, anatomical, behavioural, cognitive and other dimensions in normal individuals) should be included. The third concerns food itself. If food structure is important to metabolic health, it must be described. If response to diet is critical to metabolic health, it must be measured. Metabolism must be assessed not simply in the fasted state but also in the fed or postprandial phase; the changes in metabolism during this phase reflect the capacity of an individual to process a meal through the complex regulation of sensing, digestion, absorption and signalling, all of which are involved in energy homeostasis. The molecular imaging technologies that are revolutionizing clinical medicine hold great promise to compliment research on food and its physical dynamics in the gut with research on metabolism and the measurement of metabolic profiles.

Nestlé's work in determining food as a solution to metabolic disorders

The power of nutrition research and food processing to solve health problems is illustrated by the successes in identifying essential nutrients, recognizing their absolute requirements, and retaining, enriching and fortifying the food supply to prevent deficiency diseases. However, metabolic disorders will need different solutions.

Nestlé's food and nutrition research is tackling metabolic disorders and considering all possible strategies that might reverse the devastating consequences of unbalanced diets. Of course, food is involved in metabolic disorders — it is the fuel of metabolism. Yet a great deal of scientific knowledge about food and metabolism is lacking. The Nestlé Research Center has long recognized that science is best pursued as a collaborative enterprise. We have therefore engaged the research community through hundreds of collaborations, consortia and taskforces. To address metabolism and its consequences, Nestlé has actively collaborated with more than 1,000 scientists and 100 academic institutions over the past decade. Nestlé has taken an active role in bringing together researchers in basic metabolism and those at the forefront of nutritional research by hosting annual international nutrition symposia in Lausanne. The outcomes of these symposia have promoted scientific networks, stimulated collaborations and helped to guide research visions. Following the first symposium on "Personalizing Diet and Health", scientific consensus concluded that human health assessment was becoming

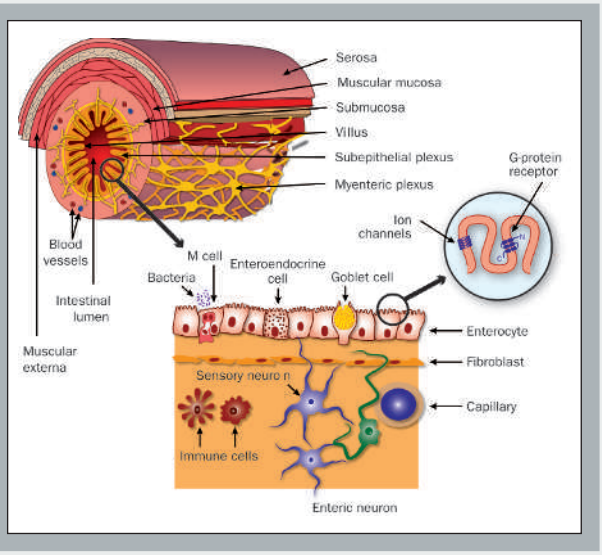


Figure 3 | Transversal nutrient sensing mechanisms in the gut
The gastrointestinal tract responds to changes in its luminal contents, and the gut wall also senses the bacterial population. In response, the enteroendocrine system secretes >20 hormones. The enteric nervous system, which comprises >108 neurons and 70–80% of the body's immune cells, achieves bacterial sensing, mechanical (osmotic stimuli, heat and acidity) sensing, luminal (apical membrane of epithelial cells) sensing and cellular sensing; in addition, after transcellular or paracellular passage, it achieves sensing of ion channels (direct gating), metabolic signals or cues and G-protein receptors, and integration of luminal sensing (neuroendocrine cells → gut brain signalling and immune cells → immune signalling.

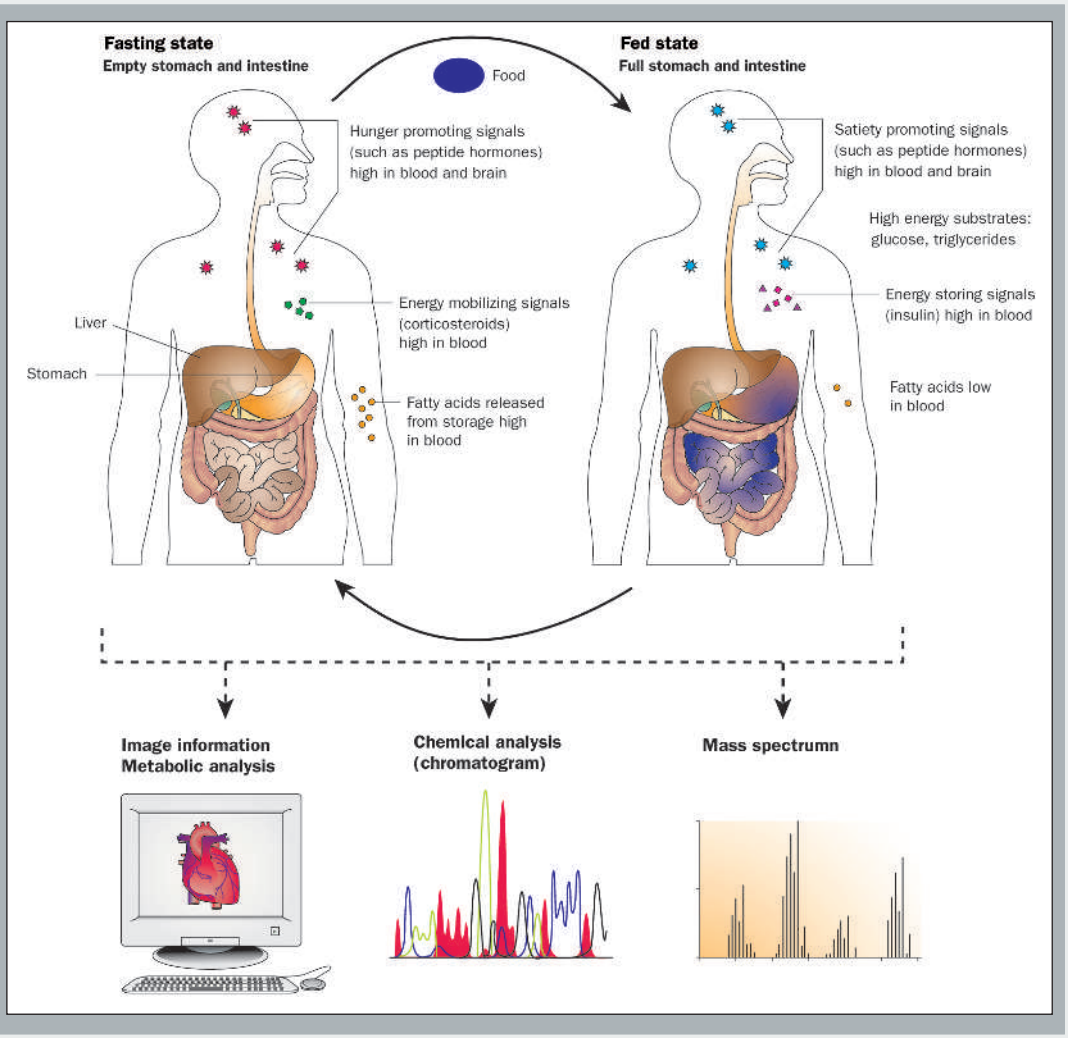


Figure 4 | The dynamics of food and metabolism
Metabolic regulation is a continuous process varying from fasted to fed states. Levels of metabolites rise and fall in response to the influx of nutrients from foods, as do the signalling systems that stimulate appetite and mobilize energy in times of need, and inhibit eating and direct energy-rich molecules into storage in times of surplus. The combined molecular-imaging and metabolic-profiling capabilities available today due to revolutionary advances in analytical sciences provide an unprecedented opportunity to accurately monitor these processes. If brought to practice as part of routine health care, these tools would similarly revolutionize the diagnosis, treatment and prevention of metabolic diseases.

necessary. After the second symposium, entitled "The Next Energy Crisis: Metabolic Health", it became clear that aggressive steps were needed to manage individuals with existing metabolic disorders. Nestlé is currently working to extend this strategy to prevent metabolic disorders before they occur.

The implications of metabolic disorders for long-term health, as identified by scientific research, confirmed by clinical evidence and interpreted by scientific experts, are alarming. Those individuals who are at risk of metabolic disorders need to know so and early. This is the role of public health. Nestlé is now looking to address the critical challenges raised by this knowledge. Once assessed, how will individuals choose foods with the dietary compositions, structures and quantities that are appropriate? How can the complex agricultural and food marketplace change to provide them? There will be no simple solutions. Unquestionably, greater knowledge of foods, and their compositions and biological effects, will be needed. The diversity in the marketplace that is available for individual choices in taste, texture and flavour must extend to variables that relate to metabolic health. Nestlé is committed to providing the scientific research and technologies necessary to meet this challenge.

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