Textbook of **Functional Medicine**

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Chapter 3
Why Functional Medicine?

- ***Importance of Improving Management of Complex, Chronic Disease***
- ***Our Aging Population and the Centrality of Diet, Lifestyle, and Environment***
- ***Functional Medicine Incorporates Genomics***

Importance of Improving Management of Complex, Chronic Disease

David S. Jones, MD and Sheila Quinn

The Larger Context

Despite the fact that non-genetic factors that are *modifiable*—including diet, overweight, inactivity, and environmental exposures such as smoking—account for 70–90% of mortality in the U.S.,[1] physician education, training, and reimbursement are most often focused on treating disease using drugs and surgery rather than comprehensive patient-centered treatments focused on the individual. For example, as reported in a study published in the *British Medical Journal*,[2] clinical questions in primary care can be categorized into a limited number of generic types and frequency. The four most common question types were:

1. What is the drug of choice for condition x?
2. What is the cause of symptom x?
3. What test is indicated in situation x?
4. What is the dose of drug x?

This shortsighted approach to health care should give us all cause for serious concern, because it is perpetuating a system that is far too costly and increasingly ineffective for the prevention and management of chronic diseases whose root causes are to be found in a much more complex perspective on patients' lives.

A Critical Problem

The gap between emerging research in basic sciences and integration of new knowledge into clinical practice is often astonishingly large—particularly in the area of complex, chronic illness.[3] This is one of the reasons that today's healthcare providers are not adequately trained to manage the increasing burden of complex, chronic disease.

The 20th century took on—and, to a great extent mastered—the challenges of providing health care for acute conditions (injury and life-threatening illness). Knowledge and technology grew apace, and so did costs; measures no one thought possible 100 years ago have become readily available. Organ transplants, re-attachment of severed limbs, life-support systems, new drugs, infection control procedures, laparoscopic explorations and surgeries—the list is extensive. But at the same time that our healthcare system was becoming dependent on advances in acute care, other influences were superseding acute conditions as the greatest threats to American health: increasingly stressful and sedentary lifestyles,[4,5,6] industrial pollution[7] of air, water, and earth[8] leading to devitalized (and sometimes dangerous[9,10,11]) food, overconsumption (rising rates of obesity) but undernutrition,[12] and fragmented family and community ties (social isolation[13,14,15]). These influences have helped to create an overwhelming burden of chronic disease that we do not yet train our healthcare providers to treat or prevent effectively.[16] Among other contributing factors:

- Disease prevention has too often been conceptualized as immunization and early diagnosis, an approach that is far too limited. Effective prevention

of chronic disease today requires understanding individual genetic vulnerabilities (20–30% of chronic disease risk) and the effect of lifestyle upon those individual variations (70–80% of the risk).
- Physicians highly trained primarily in conventional diagnosis and treatment (drugs, surgery, radiation) are not well qualified to apply prevention-focused interventions such as nutrition, diet, and exercise to help patients minimize their risk of suffering from one or more of the major chronic diseases in America (heart disease, diabetes, autoimmune disease, mental illness, and cancer).[17]
- In addition to prevention strategies, many complex, chronic diseases are very responsive to dietary and various lifestyle interventions.[18] But clinicians without these skills are literally at the mercy of the pharmaceutical industry. "Doctors are taught about drugs by agents of the pharmaceutical industry, which works hard to persuade them to select the newest and most expensive medications—even in the absence of scientific evidence that they are any better than older, less costly ones."[19] Or, we would add, even in the presence of evidence that many non-drug interventions are therapeutically effective and significantly less expensive.[20,21]

Increasing Economic Burden

The American healthcare system is predicated on a huge myth—that the more a society spends on health care, the better the health of its population will be. We justify having—*by far*—the costliest healthcare system in the world by deluding ourselves that we therefore also have the best health in the world. However, our romance with ever newer and more expensive drugs, technology, and surgeries has not achieved what we have been led to expect. Consider just a few of the many significant statistics available on this subject:

National health expenditures:
- increased 69% between 1990 and 2000, to a per capita cost of $4,637, which is 68.5% higher than our closest competitor (Germany) and more than 2½ times as much as the UK;[22,23]
- increased at a rate 4–5 times that of inflation in most years of that decade (a time of relatively low inflation in other industries);[24]
- were disproportionately affected by the cost of prescription drugs, which were responsible for 21% of the cost increases in Year 2000, while representing only 9% of total spending;[25] and
- are expected to rise to $3.1 trillion over the next 10 years (from a level of $1.4 trillion in 2001).[26]

What does the American public get for this exorbitant price tag?
- A nation with 43.6 million uninsured in 2002[27] (while every other westernized nation provides basic coverage to all its citizens).
- An excessively high serious medical error rate (highest among U.S., Canada, the UK, Australia, and New Zealand), including (in 1994) 160,000 deaths from adverse drug reactions (ADRs).[28]
- An unacceptable portion (45%) of Americans failing to receive "indicated care"[29] including, notably, preventive care.
- A healthcare system that is thought by many to be "in imminent danger of collapse."[30]

Add to this volatile mix, the projection that one-third of the people born in the year 2000 will eventually have diabetes[31]—perhaps the most costly of the chronic diseases when all its comorbidities and secondary complications are considered[32]—and we believe that no further evidence is necessary to justify a sea change in our approach to health care. There will be many ideas about the best changes to consider, but this textbook is being written, in part, to ensure that all those who are interested in the assessment, prevention, and treatment of chronic disease know what functional medicine has to offer.

There are, of course, other powerful societal drivers for the problems described above. Among them are the demand for fast and easy, high-fat, high-sugar foods; the demand for expensive testing (such as CAT scans or MRIs) and expensive drugs; the increasingly sedentary nature of most jobs (tied to a desk) and personal lifestyles (centered around television and other passive entertainment experiences). It is important that all sectors share the responsibility for empowering healthful choices—the individual and his/her family, the workplace, the residential and civic communities, the marketplace, and the healthcare system. This book addresses needs that exist within the healthcare system, but does not in any way discount the vital influence of other elements of society. We do, however, call upon clinicians to let their voices and their work be stronger and more insistent in the call for prevention and health, rather

than concentrating their formidable knowledge, intelligence, and skills on after-the-fact interventions.

Functional Medicine and the Chronic Care Model

In the inaugural issue of the *Annals of Family Medicine*,[33] the lead editorial focused on the need for a new paradigm for the primary care disciplines. The present intellectual framework[i] taught in our medical education system fails to address the web-like interactions of multiple comorbidities for chronically ill patients. The power of organ-system medicine and the scientific research based on this model have brought us to the doorstep of the 21st century where, despite huge advances in disease detection, pharmacology, and surgical interventions, we are ill-equipped for the century's greatest challenge—an aging population with ever-increasing rates of (largely preventable, often reversible) chronic disease. The dominance of the existing heuristic (rule of thumb and experience) and reductionist model has fragmented medical care into specialty and sub-specialty care, which drives costs upward[34] and conflicts with the need for a comprehensive, integrated approach to chronically ill patients with multiple comorbidities.

In Grumbach's insightful editorial, *Chronic Illness, Comorbidities, and the Need for Medical Generalism*,[35] he opens: "It is said that when students enter medical school, they care about the whole person, and by the time they graduate, all they care about is the hole in the person. Current medical education inculcates many of the dominant values of modern medicine, reductionism, specialization, mechanistic models of disease and faith in a definitive cure." He suggests that the dominant paradigm now being taught is most applicable in the context of acute illness (e.g., trauma and infection). However, the dominant illnesses of the 21st century are and will be the chronic diseases (e.g., diabetes, heart disease, arthritis, and dementia, among others). In this context, the reductionist model fails to address (what he believes is) the most germane issue: "Cure is rarely possible, but improved functional status with amelioration of symptoms of pain and dysfunction and longer life (health span) through a thorough understanding of secondary prevention is possible." He goes on to describe the paradigm shift in the intellectual matrix needed for integrated care for the chronically ill:

> These studies demonstrate the futility of reductionistically carving up patients on the basis of individual conditions and sending them to the diabetes program on Monday, the cardiac program on Tuesday, the arthritis program on Wednesday, and the depression program on Thursday. What is needed is a model of care that addresses the whole person and integrates care for the person's entire constellation of comorbidities. This generalist approach does not deny the value of specialty care, which can offer expertise and unique services to the care of patients with chronic illness. But the generalist approach affirms a central role for the primary care clinician as the coordinator and integrator of specialty care and other referral services, working in partnership with the patient and other health care personnel to optimize overall physical functioning, mental health, and well-being.[36]

IFM has been an innovator in this field for more than two decades. Functional medicine is not a unique and separate body of knowledge, but it does represent a different way of applying the scientific and clinical information that emerges from the research literature and from the clinical practices of many disciplines. Functional medicine emphasizes a definable and teachable *process* of integrating multiple knowledge bases within a pragmatic intellectual matrix that focuses on functionality at several levels as the key to health. Functional medicine uses the patient's story as an essential tool for integrating diagnosis, signs and symptoms, and evidence of clinical imbalances into a comprehensive approach to improve both the patient's environmental inputs and his or her physiological function. It is a clinician's discipline, and it directly addresses the need to transform the practice of primary care.

Functional medicine can substantially improve the existing Chronic Care Model,[37] which comprises six basic elements to foster productive interactions between patients and providers:

1. Patient self-management support;
2. Delivery system design (team-based delivery of care);
3. Decision support (consistent with scientific evidence and patient preferences);
4. Clinical information system (organizes individual patients and patient populations to receive appropriate levels of care);
5. Organizational support; and
6. Community support.

[i] The intellectual framework and filter taught and then used by primary care practitioners will, from here on, be called the intellectual matrix.

The strength of the Chronic Care Model is the acknowledgment that optimal care relies on healthcare team building involving the top levels of the organization as well as the caregivers, and integrating support for patient self-management. However, what is missing and central to success in this effort is an intellectual matrix that can filter research and clinical evidence to achieve a coherent focus applicable to the *unique* set of signs and symptoms presented by the *individual* patient. No such matrix now exists outside of the functional medicine model. The Chronic Care Model is still grounded in the heuristic, organ-system based, reductionist thinking that is inadequate to the task.[38] As presently configured, that model will run into the same wall: chronic illness and multiple comorbidities are difficult to handle because the *fundamental, underlying clinical imbalances* have not been clearly delineated as the starting point for understanding chronic, complex illness. Even the coordination of resources as described in the Chronic Care Model will inevitably fall significantly short of the goal if the focus of this integrated collaboration is not properly identified. Functional medicine helps to identify the proper focus from a multidisciplinary, patient-centered model that all caregivers can learn and apply.

The Chronic Care Model appears to assume that the best we can do for a patient with chronic disease and comorbidities is to minimize the progression of the disease through the consistent and complete application of existing standards of care. There's no implicit or explicit anticipation of actually restoring health, and no recognition that unless we can restore health (to varying degrees in different patients), the huge impact of chronic disease on the healthcare system and the economy will be virtually unchecked. One might summarize the problem in this manner:

- if assessment and treatment are not fully integrated with prevention,
- if therapeutic interventions are not expanded to include a primary emphasis on diet, exercise, and lifestyle,
- and if health and disease are not perceived as existing on a continuum, along which the patient's placement can move towards health (even in the presence of significant chronic disease and comorbidities),
- then the emphasis is always going to be on palliative care, and the costs are always going to be excessive.

Functional medicine directly addresses the restoration of health, looking for common factors among various symptoms, diagnoses, and comorbidities that can be affected by intervening to improve function at the cellular level and the organ level. The functional medicine matrix takes into direct consideration the patient's lifestyle and diet, genetic predispositions, and core clinical imbalances, seeking a multifactorial and individualized approach that will reach beneath symptoms to restore function and generate momentum toward health. Too often the patient care process is seen as complete when a diagnosis is achieved and a drug is prescribed. In functional medicine, the diagnosis is the beginning of the journey, and the patient's past and continuing story is the central driver.

Our Aging Population and the Centrality of Diet, Lifestyle, and Environment

David S. Jones, MD and Sheila Quinn

Healthy Aging Matters

Researchers have estimated "the cost to our society resulting solely from the triad of coronary heart disease, diabetes, and obesity alone is nearly half a trillion dollars!"[39] Since most of the chronic disease burden occurs in the last decades of life, the importance of healthy aging can, therefore, hardly be overstated. However, it isn't an aging population, per se, that increases the economic burden on the healthcare system. It's an older population that has either more disease, or more years of life with disease, or both. Booth et al.[40] point out that "the advances made against modern chronic diseases over the past 30 years have come to a halt." Today in North America and most of the westernized world, people are living longer and, for many, those additional years are filled with the cost and effort of managing multiple chronic diseases. We have no idea whether or not there is an upper limit to life expectancy—all past predictions about such limits have been exceeded, in a steady, linear climb of about 2.5 years per decade for the past 150 years.[41] So, we may as well assume that the upper boundary will continue to advance, which means we will be providing expensive, intensive healthcare services to a growing number of older citizens who will be living with more heart disease, more diabetes, and

more arthritis, cancer, and other complex chronic diseases for 30–40 years, rather than 10–20.

At least, that's what current projections indicate. There are many who believe, however, that a different goal is within our reach: "In the ideal case, the healthy citizens of a modern society will survive to an advanced age with their vigor and functional independence maintained, and morbidity and disability will be compressed into a relatively short period before death occurs … ."[42] There is research to support this hypothesis: "Not only do persons with better health habits survive longer, but in such persons, disability is postponed and compressed into fewer years at the end of life."[43] And, even more to the point, successful aging is often the result of factors under at least some personal control: "our weight, our exercise, our education … our abuse of cigarettes and alcohol … our relationship with our spouse, and our coping styles can [all] be modified. A successful old age … may lie not so much in our stars and genes as in ourselves."[44]

To be sure, there is much about the process of aging that we cannot yet understand or control. Aging is certainly associated with increasing incidence of disease and disability on a population-wide basis. However, research is making it increasingly clear that there are many behaviors (diet, exercise, stress reduction)[45,46,47,48] and treatments (antioxidants, essential fatty acids, minerals, certain amino acids, the B vitamins, and much more)[49,50,51] that can counteract the functional decline that leaves us vulnerable to disease and disability as we age.[52] Functional medicine helps to bring this knowledge into clinical practice, both for prevention and for treatment.

Centrality of Diet and Exercise in Prevention and Treatment

A healthcare system that is primarily dependent on the prescription pad for therapeutic success will inevitably be far more costly in the long run[53] than one that brings lifestyle and environment to the fore. Diet, exercise, stress reduction, and active lifestyles are the most effective—and least costly—tools for lifelong disease prevention; there are numerous studies that validate this assertion, providing data on everything from pancreatic cancer[54] to sarcopenia[55] to very costly diseases such as heart disease and diabetes.[56,57] (We do not mean to discount the huge impact of broad societal influences such as a strong economy, an educated and well-compensated workforce, and supportive communities, but discussion of those issues is beyond the scope of this book.) Research is emerging in a continuous and expanding stream to demonstrate the therapeutic effectiveness of lifestyle interventions for the treatment of many chronic diseases.

Using type 2 diabetes as an example can help us understand more clearly what's at stake. Consider the following facts:

- The incidence of diabetes is rising rapidly—it's a red flag bearing the message that something important has gone awry.[58]
- "100% of the increase in prevalence of type 2 diabetes and obesity in the U.S. during the latter half of the 20th century must be attributed to a changing environment interacting with genes, since 0% of the human genome has changed during this time period."[59]
- Diabetes is being diagnosed in ever younger patients—so we will be paying for their care for many, many more years if we don't act now.[60,61]
- It is a very costly disease. In 2002, the total cost of diabetes was $132 billion/year—$92 billion in direct medical costs and $40 billion in disability, work loss, and premature mortality.[62] This is a 35% increase over the 1997 total.[63] In just five years, we added $34 billion/year to the healthcare budget from diabetes alone. (If this doesn't scare us, what will?)
- Diabetes has many genetic links and new information is emerging all the time about how those can be identified.[64,65,66] Clinicians will increasingly be paying attention to genes at risk through ethnicity and family history, thus bringing genomics (environment acting on genes) into play.[67]
- Diabetes increases the risk of many other chronic diseases, including various neurological conditions,[68,69] heart disease,[70,71] kidney disease,[72,73] stroke,[74] and cancer.[75,76] Today's growth in the incidence of diabetes will lead directly to increases in many other diseases as the diabetic population ages.
- For most type 2 diabetics, the disease can be prevented, delayed, or reversed.[77,78]

It's hard to read this condensed set of facts about diabetes and not wonder, "What's gone wrong?" This is a (mostly) preventable disease, about which a great deal is known; it causes great human suffering if not prevented;

it costs us tens of billions of dollars each year; and it's now hitting our children. What is standing in the way of turning this around? It's certainly not a lack of information—even a quick search of the literature turns up hundreds of relevant research articles in every field from endocrinology to epidemiology to psychology.

At the risk of offering an oversimplified explanation, one reason seems intuitively obvious: We do not have a healthcare system, or healthcare practitioners, with the skills, time, and will to do what needs to be done. We have a healthcare system that forces practitioners to focus on seeing the most patients in a day, for the smallest investment of professional time and effort, with quick access to drugs (and highly vulnerable to pharmaceutical industry pressure and patient demands). This scenario cannot help but obscure the real answers to the problem.

Functional medicine offers a way to change this scenario. Practitioners can begin approaching patient care from a different perspective, with a broader set of tools, and with an empowered patient as ally and partner. Helping the doctor—and the patient—to fully understand the critical factors that affect functionality, aging, disease, and health over a lifetime will help create a more cost-effective healthcare system, and lead to longer health spans for our citizens.

Functional Medicine Incorporates Genomics

Jeffrey S. Bland, PhD

Genomics—The Genetics-Environment Interface

April 25, 2003 represented the 50th anniversary of the publication describing the structure of DNA, in the journal *Nature*, by Watson and Crick.[79] That classic paper contained the prophetic comment, "It has not escaped our attention that the specific pairing (of the DNA bases) we have postulated immediately suggests a possible coping mechanism for the genetic material." This paper, and companion papers that appeared in the same issue of *Nature* by Wilkins, Strokes, and Wilson, and Franklin and Gosling, created a paradigm shift in medicine that has taken 50 years to be integrated into its curriculum. **The concept that disease mechanisms originate at the molecular biological level and are related to intricacies of interaction between the environment and genes and their expression heralded a new age in medicine.** The seeds that were planted then are only now coming into bloom.

Rabinowitz and Poljak commented in 2003 that we are seeing the emergence of a new primary-care model built on the molecular medicine discoveries of the last 50 years.[80] This primary-care model integrates the concept of host/environment interaction in framing a better understanding of the origin of disease and its potential treatment, individualized to the patient. Until very recently, we have tended to believe that diseases are "hard-wired" into our genes as a consequence of genetic uniqueness. This belief has caused us to forget or overlook the important variable of environment and its role in modulating the expression of genes. As these authors point out:

> These (molecular genetic) developments, however, raise the concern that both physicians and patients could fall into a trap of biological determinism, believing that one's genetic and metabolic makeup far outweighs the role of environmental factors in disease. Such thinking fails to acknowledge that most health outcomes are the result of interactions between host factors and environmental factors.[81]

Although the human genome contains only between 30,000 and 35,000 genes, millions of variations of these genes, called single nucleotide polymorphisms (SNPs), exist within the gene pool. These polymorphisms occur as variations in which the least common allele is present in at least 1% or more of the population. Researchers have found that when these SNPs are present in a gene it means a person has two different genes coding for the same function. Only recently have we understood that many of these SNPs lead to differences in the phenotype of an individual, and that how these differences may be expressed depends upon environmental factors.

One major environmental factor that modifies gene expression is the individual's nutritional status. Both macro- and micronutrients can influence the expression of genes, the translation of the genetic message into active protein, and that protein's ultimate influence in controlling metabolic function.[82,83,84,85,86]

The effective integration of these concepts into the educational model so that patient assessment and treatment can be personalized to the patient's own genetic uniqueness represents a great challenge for modern medicine. It has been postulated that medical nutrition education is very near a "tipping point" that will herald rapid changes in the existing system vis-à-vis these exciting concepts.[87] Functional medicine has been addressing

these issues and training clinicians to understand and use the concepts for many years.

(According to Gladwell, the tipping point is the moment when an idea, trend, or social behavior crosses a threshold, "tips," and spreads like wildfire.[88] Broad examples from medicine include the discovery of the polio vaccine, the identification of insulin as a treatment for type 1 diabetes, the 1964 Surgeon General's Report on the health effects of cigarette smoking, and the McGovern Committee and the 1979 Surgeon General's Report on Health Promotion and Disease Prevention. Another tipping point may be the changes stemming from the Human Genome Project that are leading to a new definition of medical nutrition education.)

As evidence that we are near the tipping point in medical education, Tel Aviv University recently incorporated into its medical curriculum a course titled "Introduction to Pharmacogenomics: Towards Personalized Medicine."[89] As investigators learn how different individuals metabolize substances based on their genetic uniqueness, we learn more about the important roles specific nutrients play in modifying the expression of metabolic patterns in the individual. Diet, lifestyle, and environment have significant influence on the way an individual can metabolize specific substances based upon his or her genetic uniqueness. We are seeing the first applications of genomic medicine in the area of pharmacogenomics. Pharmacogenomics is defined as the unique metabolism of various substances based on an individual's genetic uniqueness. A great deal of research is being done to study individual variations in reactions to drugs and that body of research will contribute enormously to our understanding of personalized medicine.

Nutrigenomics

Linus Pauling was a pioneer in alerting physicians to the importance of nutrients in modulating physiological processes at the biomolecular level and ultimately giving rise to the phenotype of health or disease. The interface between genomics and nutrition is now defined as the field of "nutrigenomics." As Kozma observed:

> Information from the Human Genome Project will dramatically change health care for the dietetic and nutrition discipline. Approaches to risk assessment including obtaining family history, diagnosis, prevention, early intervention, and management of nutritional issues will evolve through the application of nutritional genomics. Dietetic and nutrition specialists will increasingly require knowledge of genomics, gene-environment interactions, the expanding role of pharmacogenomics in drug and food therapies, and genetic applications to clinical practice.[90]

The development of nutrigenomic concepts will assist clinicians in understanding the varied responses of different patients to specific nutritional therapies. An example is the wide inter-individual variation in blood lipid and lipoprotein responses to dietary change.[91] A diet that is low in fat and high in unrefined complex carbohydrate may in one individual be effective in lowering total blood lipids. In another individual with a different genotype, however, the same diet may actually increase specific members of the lipid and lipoprotein families. Similarly, some individuals, when placed on a higher-protein, low-carbohydrate diet, may have reductions in their blood lipid profiles, while others may have elevations of blood lipids on the same diet.

Fogg-Johnson and Kaput provide a good restatement for us to consider:

> Effects of the Human Genome Project are surfacing in anticipated and unanticipated areas. One of the key discoveries from the project is the existence of individual differences in gene sequences that result in differential response to environmental factors, such as diet. Those genetic differences, single nucleotide polymorphisms (SNPs, pronounced snips), are the key genetic enabler of the emerging scientific discipline called nutrigenomics or nutritional genomics. … The science of nutrigenomics is the study of how naturally occurring chemicals in foods alter molecular expression of genetic information in each individual.[92]

Since approximately 1990, nutrition research has undergone a gradual shift in focus from epidemiology and physiology to molecular biology and genetics. This shift has resulted in a growing realization that we cannot understand the effects of nutrition on health and disease without determining how nutrients act at the molecular level. Müller and Kersten note: "There has been a growing recognition that both macronutrients and micronutrients can be potent dietary signals that influence the metabolic programming of cells and have an important role in the control of homeostasis."[93]

In every respect, the transition occurring within medical nutrition is epic in its impact and scope. Nutrition-focused practitioners are at a pivotal point in the history of their practice. Kauwell's observations are particularly pertinent: "Armed with the findings of the Human Genome Project and related research, dietetics practitioners will have the potential to implement more

efficient and effective nutrition intervention strategies aimed at preventing and delaying the progression of common chronic diseases."[94]

Genomics and Proteomics: Importance for the Future of Nutrition Intervention

A central feature of this paradigm shift in medical nutrition is the recognition that not all genes within the human genome are expressed in every cell simultaneously. Instead, the expression is selective to the cell type and cell environment. The study of the synchronous activation of families of genes to yield various proteins that ultimately regulate metabolic function is called "proteomics."

A large body of information exists about the number of genes, chromosomal localization, gene structure, and gene function. Scientists are only now beginning to understand the orchestrated way the proteins expressed from these genes control metabolism.[95] For example, researchers have found that in some cells only 50% (approximately) of the genes transcribed to form the specific messenger RNA (mRNA) are translated into active proteins. The action point in the control of cellular physiology is therefore the combination of genetic transcription (expression), active protein formation, and control of metabolism that has been termed the "phenome."

The phenotype of the cell is a complex process or system of interacting events related to genetic expression, protein synthesis, protein activation, and metabolic regulation. By evaluating genetic expression through the production of specific mRNAs, the synthesis of specific proteins from those mRNAs, and ultimately the effect of those proteins on metabolic function, we can establish biomarkers of health and disease. From this understanding, we can evaluate the role of specific nutrients on this process in the individual patient. Although this may at first seem to be a daunting task, new screening technologies and powerful systems of bioinformation analysis are emerging to hasten the day when such interventions are a real option in clinical care.

Toward a Systems Biology Approach

As we write in 2005, the systems biology approach[ii] for analyzing individual effects of nutrients on function is not yet available, but a number of clearly identified relationships that connect specific SNPs, nutrient sensitivity, and disease risk are now understood. Petricoin and Liotta predicted in 2003 that clinical applications of proteomics, which involve the use of molecular genetic technologies at the bedside, will result in patient-tailored therapies.[96]

Work at the Institute for Systems Biology in Seattle, Washington, has demonstrated the success of an integrated system for understanding cellular physiology based on the interaction of genomic expression, proteomics influences, and their role in controlling metabolism.[97] Although this work is in its early stages, the "proof of concept" that a systems biology approach can be used for evaluating the impact of genetic expression, proteomic activity, and their roles in controlling metabolism, supports an optimistic perspective for the future of personalized and functional medicine.

Upstream vs. Downstream Medicine

In the last few decades, much medical research has focused primarily on discovering specific molecules that inhibit enzyme function "downstream" in a complex physiological process. The search for molecules with the selective ability to inhibit specific enzyme-mediated steps, such as angiotensin-converting enzyme inhibitors (ACE inhibitors), selective serotonin reuptake inhibitors (SSRIs), H2 blockers, and selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), has succeeded in fueling the growth of the multi-billion dollar pharmaceutical industry (not without serious consequences for some patients with some of these drugs).

Genomic and proteomic research has begun to demonstrate, however, that rather than blocking specific enzymes downstream in a complex biological system associated with a specific disease, it can be even more effective to develop new approaches that would selectively regulate the expression of various alarm molecules upstream in the metabolic process that are associated with the disease. The emphasis of such research is to identify tissue-selective "upstream" modulators of

[ii] Systems biology seeks to explain complex biological systems, such as the cell, through the integration of many different types of information.

genomic and proteomic expression. The objective is to identify ways to normalize the functional changes associated with early disease risk without adversely affecting other tissues engaged in similar metabolic processes.

The Rise of Personalized Medicine

This revolutionary shift in thinking suggests that substances consumed in the diets of various cultures for thousands of years may have profound influence on gene expression and proteomic outcome. It may also help explain the epidemiological observations that certain diets are associated with reduced disease risk. As Willett pointed out, the integration of extensive epidemiological research with the discoveries being made in nutrigenomics will give rise to a new personalized medicine using diet, lifestyle, and environment as principal tools in both prevention and treatment of specific chronic diseases.[98] Burke wrote, "Evidence is now emerging of the complex interactions between genes and the environment in the causation of many diseases, and the study of the interactions represents the next important step in genomic research. Efforts to understand the molecular mechanisms that underlie complex diseases will build on insights and strategies developed in the study of single-gene diseases."[99]

From these concepts, new clinical tools and programs are emerging to help apply medical nutrition in ways that will make it more effective in improving patient outcomes, and that approach is a key component of the functional medicine model, and thus an urgently needed element in modern clinical care.

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