Neuro-Hormonal Integration of Metabolism: Challenges and Opportunities in the Postgenomic Era

Vay Liang W. Go, Yu Wang, Hong Yang and Wai-Nang Paul Lee

David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, Calif., USA

Introduction

Humans are multicellular organisms designed to provide continuous nutrition to all constituent cells by means of nutrient homeostasis through genomic-nutrient-metabolic interaction. This process is highly regulated and integrated through neuro-hormonal control processes at various levels of organization. Metabolism at the cellular level is primarily regulated by cell-signaling pathways and substrate environments for specific metabolic events. This is achieved through the regulation of futile substrate cycles within the cell by substrates and signal-sensitive gene expressions. Metabolism at the intercellular level is primarily regulated by paracrine, autocrine, hormones, and other neurotransmitters that alter the functional state of metabolic networks within individual cells and the cell-to-cell relationship. At the organism’s physiological level, metabolic regulation is achieved through complex neuro-endocrine circuitry, and its integration with nutritional signals that translate these interrelationships into nutrients and energy homeostasis [1]. Over the last century, tremendous progress has been made at the physiological level in the following areas: feeding behavior; major function of the digestive processes in the gut and gut-brain-endocrine axis; hypothalamic and autonomic pathways and neurotransmitters in regulating hunger, satiety, and energy metabolism; endocrine control of metabolic function of organs involved in energy homeostasis (brain, gut, liver, muscle, and adipose tissue), and altered metabolic pathways and/or control system failure that can lead to diseases such as obesity, metabolic syndrome, diabetes mellitus, cancer, and other disorders. This has been the subject of various recent workshops sponsored by Nestlé [2–5].
Parallel to the milestones of the above developments, at the beginning of this new century genomic research and the achievements of sequencing the human genome heralded the beginning of the postgenomic era. Nutrients, which serve as energy-yielding substrates and macromolecular synthesis, have acquired a mechanistic regulatory function in the gene [6, 7]. Nutrient-gene analysis occurs at various levels (genome, transcriptome, proteome, metabolome, physione/phenome, and populome), with the development of novel so-called ‘omic’ technologies to generate appropriate metabolic phenotypes or biomarkers. The objective of this review will focus on the role of nutrients in the neuro-hormonal regulation of food intake and metabolism, and the application of genomic, proteomic, and metabolomic techniques in the investigation of the regulation of metabolism, and challenges and opportunities in metabolic and nutrition research in the postgenomic era. With nutritional genomics, proteomics and metabolomics, investigators can now simultaneously elucidate and analyze thousands of genes involved in multiple metabolic pathways on the biological effects of nutrients on cell function and global gene expression and its consequences on their neuro-hormonal regulatory mechanisms in health and disease.

Role of Nutrients in the Neuro-Hormonal Regulation of Food Intake and Metabolism

Nearly a century ago, Pavlov’s [8] experimental work confirmed earlier independent, clinical work by Beaumont [9] and Cabanis [10] demonstrating that the brain influences gut function. Subsequently, Langley [11] provided the concept of the autonomic nervous system and the notion of an enteric nervous system embedded in the gut wall, distinguishing it from the parasympathetic and sympathetic divisions. With the advances in anatomical and electrophysiological techniques, the isolation and characterization of regulatory peptides and neuropeptides and their receptors, and the development of immunoassay techniques [12], we have witnessed an explosion of information and increased appreciation of the brain-gut axis and its interrelationship in the regulation of gut function and control of energy homeostasis, and its alteration in various disease stages, including cancer and metabolic disorders like diabetes mellitus obesity and cancer cachexia [13–15].

Our understanding of the hypothalamic control of energy homeostasis has increased greatly since the discovery of gut and hypothalamic neuropeptides that affect food intake and energy balance. These neuropeptides include: cholecystokinin (CCK), α-melanocyte-stimulating hormones, agouti-related protein, cocaine- and amphetamine-regulated transcript, melanin-concentrating hormone, neuropeptide Y, and proopiomelanocortin and others [15, 16]. The recent discovery that adipocytes are an endocrine organ that secretes leptin demonstrates that adipose tissue not only participates in the regulation of fat
metabolism but also plays a role in the regulation of food intake and nutrient homeostasis. Circulating leptin is transported by a saturable system in an intact form to the brain, where it influences hypothalamic cell groups orchestrating facets of food intake regulation and energy homeostasis through interaction with the Ob-Rb splice variant (long form) of the leptin receptor [17, 18]. By studying these molecules and their neuronal systems, receptors and interactions, we are beginning to unravel the circuitry between peripheral gut and adipogenic signals and afferent neural and hormonal circulatory pathways and hypothalamic effector pathways that regulate gut and adipose functions in fed and fasting states.

Evidence now exists that nutrients have acquired a mechanistic and regulatory function in addition to the traditional concept as constituents of diet that serve as a significant energy-yielding substrate and as a precursor for the synthesis of macromolecules or components in normal cell differentiation, growth, renewal and repair. Nutrients could influence and regulate gene transcription, translation and post translational metabolic processes [6–7]. Moreover, they could regulate the release of gut neuroendocrine peptides that regulate motor, secretory and absorptive function, as well as the release of a metabolic hormone, insulin. The neuropeptides released, such as CCK, could then act in both the circulation and vagal neural pathways, and interact with leptin peripherally in addition to its central action. Our studies, using an in vitro rat stomach-vagus preparation, provided electrophysiological evidence that CCK can modulate certain gastric vagal fibers, leptin can also act peripherally to increase gastric vagal afferent activity, and that CCK modulates the sensitivity of gastric afferents to leptin. These findings prompt us to investigate whether such an interaction between leptin and CCK has an implication in the regulation of food intake [19–21]. The dual CCK-leptin signals exert their synergistic interaction to reduce food intake through CCK-A receptors. The satiety effect induced by leptin plus CCK may involve sensory signals beginning with the activation of capsaicin-sensitive vagal afferent fibers that terminate centrally in the nucleus tractus solitarius (NTS). The information is relayed to hypothalamic sites, of which the paraventricular nucleus (PVN) seems to be the primary target, to integrate signals and orchestrate appropriate food intake alterations (fig. 1). In addition, leptin, being a long-term adiposity signal, may also increase the efficacy of CCK through interactions initiated at peripheral gastrointestinal sites and/or at dual sites with central leptin sensitizing the PVN to respond to inputs generated by the short-term satiety factor, CCK [22–24]. The role of other gut neuropeptides on the peripheral actions on the neural vagal-sympathetic fibers need to be further investigated.

The vagus nerve is critical in mediated the central control of gastrointestinal pancreatic and hepatic functions and insulin secretion [25]. The vagal efferent regulation on gastrointestinal functions is tightly regulated by blood glucose concentrations (fig. 1). The dorsal vagal complex (DVC) neurons are glucose-sensitive neurons that are activated by hypoglycemia. Evidence has now accumulated that the medullary vagal-regulatory pathways respond to altered
Blood glucose levels, demonstrated by hypoglycemia activation of neurons in the PVN and DVC [25–27]. Microinjection of glucose into the DVC prevented the hypoglycemia-induced gastric response, indicating a direct influence of glucose levels on the DVC neurons [28]. Acute glucose deprivation by 2-deoxy-glucose induces Fos expression in nitric oxide-positive neurons in the NTS and dorsal motor nucleus (DMN) as well as in the catecholamine neurons in the ventrolateral medulla A1/C1 and dorsal medulla C2 and C3 areas [29]. Electrophysiological studies suggest that some DMN neurons may have an enteroreceptor function detecting the change in glucose concentration in their environment. However, another study found that glucose had no direct excitatory effect on DMN neurons. The NTS neurons transmit information on local glucose availability as well as peripheral glucose metabolic signals received.
from the vagal afferents toward hypothalamic structures, including the PVN, via ascending adrenergic and non-adrenergic pathways [30, 31]. Recently, we also found that activation of raphe pallidus neurons increases insulin through medullary thyrotropin-releasing hormone in vagal pathways [32].

It is well established that neuro-hormonal pathways in the brain, gut and adipose tissues play a key role in nutrient metabolism and fuel homeostasis, and it is also now established that nutrients, i.e. glucose, free fatty acids and amino acids, can regulate and modulate neuro-hormonal factors that affect its metabolism at the cellular, organ-system, and whole-body levels. Most of these accomplishments were done by understanding the anatomy and cellular physiology and biochemistry, endocrinology, neurology, and nutrition science investigating the metabolism of nutrients and establishing the specific single nutrient metabolic and its control regulatory system. Now that we are entering the postgenomic era with genomic technology, we can analyze this complex multiple nutrient metabolism and its control regulatory system simultaneously, from gene expression to metabolic flux to metabolic phenotype affecting cell cycles and growth, development, and apoptosis [33].

**New Approaches in Investigating Nutrition Metabolism in the Postgenomic Era**

Watson and Crick discovered the structure of DNA more than 50 years ago [34]. Twenty years thereafter, recombinant DNA technologies were well developed and in 2001 the Human Genome Project and Celera Genomics produced the first complete draft of the human genome [35, 36] which subsequently gave way to the so-called ‘postgenomic’ era.

Parallel to the investigation of nutrient metabolism and its neuro-hormonal regulatory mechanism during the last century, advances have been made in the technological development in genomics, proteomics, and metabolomics and its information processing.

Genomics employs either classical DNA-sequencer technology or more advanced techniques such as DNA arrays [37]. Microarrays are able to reveal gene expression patterns containing several thousands of genes simultaneously, allowing one to analyze variations in DNA and RNA and obtain genetic information on the heterogeneity in gene-coding regions or control elements. Transcriptomics, also called expression profiling, mainly utilizes fluorescence-based detection systems to determine mRNA expression levels in a biological sample by means of polymerase chain reaction (PCR) techniques and Northern blot analysis or by the sequence-specific annealing of an immobilized capture oligonucleotide with the corresponding fragment obtained from a tissue sample on a DNA microchip [37]. This expression profiling allows concurrent analysis of the mRNA of a few up to thousands of genes. Genetic polymorphisms related to chronic diseases such as diabetes
mellitus, obesity, and cancer and its connection between genetics and lifestyle and environmental factors, including diet, can now be investigated.

Proteomics allows a huge number of proteins in a cell or organ to be identified and changes in their expression pattern or level to be determined. Proteome analysis requires the isolation of proteins from a sample, their separation by two-dimensional polyacrylamide-gel electrophoresis and staining of the proteins in the gel [37]. A computer-based comparison of gels allows the pattern of protein expression to be determined. The identification of the proteins of interest showing increased or decreased expression levels requires the isolation of the protein from the gel, its digestion with trypsin or other proteases with the generated peptide fragments then subjected to matrix-assisted laser desorption/ionization time-of-flight mass spectrometry analysis to determine the fingerprint of peptide masses that are characteristic of a given protein [37]. Data base comparison with known DNA sequences/amino acid sequences identifies the protein. Mass deviations of the measured peptide fragment mass from the expected amino acid sequence may give indications of post-translational modifications such as phosphorylation, glycosylation or myristylation [37]. Currently, new proteomic technologies are being used clinically in early detection, therapeutic targeting, and patient-tailored therapy [38].

Functional genomic and proteomic techniques can also be applied to enzymes involved in nutrient metabolism [39]. The multi-step pathway from genome to phenotype and the complex process of gene function identification ensures ongoing technological development and research of metabolic pathways and metabolic flux analysis, or metabolomics [7, 40]. A specific metabolic phenotype associated with nutrient metabolism regulatory mechanisms in maintaining fuel homeostasis and normal and abnormal cell function can now be investigated concurrently. Technologies used for metabolic profiling enable the stable isotope approach, which is composed of measuring expression, transcription, and activation of metabolic enzymes [39] to reveal the metabolic characteristics of normal as well as abnormal cells.

Genomics, proteomics, and metabolomics have transformed biomarkers of nutrient-gene interaction from a reductionist concept of one ideal biomarker into a holistic one in which several regulated genes and metabolites can be measured at the same time (fig. 2). Nutrition researchers need to understand the methodological, demographical, environmental, and dietary characteristics of individuals as well as populations as they relate to genetic damage and the molecular epidemiology of health and disease. In response to a need for new tools to study the complex interactions in biological systems, separation, detection, and computing techniques are now merging concurrently [41].

In addition to the technological development, genetically modified animal models developed by gene targeting, transgenic and knockout techniques are currently widely used. Most of these investigations have been focused on genes of metabolic enzymes of glucose and lipid metabolic pathways, including those of the regulatory signaling pathways, to examine the new functional
changes caused by the new genomic constraints in the metabolic network. The systemic knockout (KO) mouse for fatty acid oxidation is now available for pyruvate dehydrogenase [42]. Long-chain acyl-CoA dehydrogenase [43] and very long-chain acyl-CoA dehydrogenase [44], and similarly, tissue-specific knockout models of insulin resistance/diabetes have also been developed. These include MIRKO (muscle-specific KO of insulin receptor) [45–47], LIRKO (liver-specific KO of insulin receptor) [48] and β-IRKO (β-cell-specific KO of insulin receptor) [48, 49]. Undoubtedly more gene-target animal models will be developed to investigate the various metabolic pathways of nutrient metabolism. These models have also been used to investigate optimization problems in integrated physiology, permitting the understanding of the genotype/phenotype correlation.

The new research focus on the neuro-hormonal regulation of metabolism in the postgenomic era includes: investigation into the biological complexity of the genetic architecture; signaling networks and the regulatory dynamics of cellular processes such as cell cycle and apoptosis; metabolic networks and control of flux of substrates, and integrative multi-investigations, multidisciplinary approaches with a high degree of interplay between researchers in metabolic networks, and computational and modeling scientists.

Fig. 2. Technologies of genomic, proteomic, and metabolomic and biomarker analysis involving each step. The sites where neurohormonal control and nutrient regulates the steps of gene expression, as well as the biomarkers to be investigated.
Challenges and Opportunities in Metabolic Research in the Postgenomic Era

In the postgenomic era, biomedical research has undergone a fundamental shift in both technical and conceptual approaches. This occurs at all levels of biological organization, including genetic circuitry and expression in the cells, quantification of cellular processes, including metabolic flux and response to environmental factors and regulatory mechanisms, and integrated activities of tissues and organ function in spatial and temporal orders. As the metabolic phenotype includes the whole organism, these challenges are substantial, and must also take into account the relationship between the above biological events and variable environmental, dietary, and life factors.

Recognizing these complexes, the scientific community and government research-funding agencies developed a research program and direction to address the so-called ‘systems biology’. The goals were to analyze in parallel data in RNA, proteins, and metabolites generated by the new genomic technologies from complex biological samples, developed by appropriate informatics tools, and to link gene response, protein activity, and metabolite dynamics and determine molecular function. The National Institutes of Health (NIH) developed a roadmap initiative to address these complex issues, and the National Institute of General Medicine is encouraging applications to their Centers of Excellence in Complex Biomedical Systems to assemble large teams of investigators from diverse backgrounds, including experimental biology and the computational disciplines of engineering, physics and computer science, to develop a new theoretical framework with a high degree of interplay between computational, experimental, modeling and simulations approaches [50–52]. Such center programs have now been established. In addition, two new initiatives have been developed by the NIH: The National Center for Biomedical Computing seeks a partnership to produce, validate, and disseminate tools, and computational environments that will be useful to a broad spectrum of biomedical research across the nation. The NIH and metabolomic technology development programs encourage the development of highly innovative and sensitive tools to identify and quantify cellular metabolites and their fluxes at high anatomical, spatial, and temporal resolution. All the new Federal initiatives will, hopefully, turn the massive data generated by the new postgenomic technologies into knowledge that will allow researchers to effectively address the interface of diet, metabolism, and its regulatory pathways and control mechanisms, by which diet and nutrition-metabolism can promote health and disease prevention.

Conclusions

In the postgenomic age, nutrition and metabolic sciences are undergoing a renaissance that serves as a catalyst for the study and understanding of
the integrative systems biology of all living organisms. Consequently, the complexities of the interactions among genotype, diet, lifestyle, and environment will lead to changes in the current practice of medicine, where functional imaging technologies will be coupled with genomic, proteomic, and metabolic technologies to generate appropriate integrated data for personalized medical health data, yielding personalized nutrition recommendations and/or genetic therapies, or individualized and specialized treatments (fig. 3).

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**References**


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Discussion

Dr. Basu: Clearly there is no question that I share your views and concerns. All these receptor knockout mice or whatever animal models you looked at, they are just basically short stories. They are the tools that hopefully will be able to integrate, and I would use the term integrative physiology. Ultimately it has to boil down to the human being and how we interpret the various data that we get from different studies in animals into the pathophysiology that occurs in the human being.

Dr. Go: I agree with you but I have to add a word of caution. When you start looking at some of those knockout mouse models, you knockout one enzyme and look at the consequences for the other pathway: some of them are overexpressed, some of them are underexpressed. In a sense knockout mice are in an abnormal state, so I don't know how to interpret the data to determine what normality is. That is my problem at this moment. Dr. German, do you agree with that?

Dr. German: I agree. Coming from the genomic mentality, I think one of the things that we tend to believe is that there will have to be sufficient knowledge to predict how someone should eat and exercise, etc., for the rest of their lives, and the value of putting in place technologies for assessment is that you do them just like any other aspect of our lives, we check routinely whether they are working well, so it won't be necessary to be able to predict a health trajectory from birth to death. You will basically be able to make a recommendation that one can check a year later and see how, in a more comprehensive holistic sense, a metabolism is proceeding on that advice and if it is not going in a direction that you like, you can readjust it. One important thing I recognize is that by putting in place these approaches you can guide people and so your bioinformatic requirements won't be quite as devastating as perhaps you are thinking.

Dr. Go: For me it is still very devastating because I still don't know how to analyze and interpret microarray results.

Dr. James: I have listen to these two talks and it is very nice to end on such an optimistic note, but I must say that I have two concerns. One, I have been very impressed being on research councils for the UK and also in the European system. The genomic has actually been, as my good colleague McFarlan of Oxford says grotesquely, overselling it, and it is overselling itself, and he is very conscious of the limitation of our knowledge, and I think it is rather good that you are putting on this different dimension. I must say that I think the genomic clan in England is a golden triangle consisting of a brilliant group of academics, and the genomic world is getting to the point where a huge assignment of resources of major research councils is exclusively devoted to it. In a special meeting on fetal metabolism McFarlan, who is an expert on thalassemia, told me that they came on thalassemia by virtue of happenstance where they realized that they had this wonderful phenotype with the gorgeous single gene. There was a problem and then the problem was that of course they went to different parts of the world and discovered that thalassemia as a blood disease has a very different manifestation. Then they went to another part of the world and found that these children had a third type, and then they went on to the fourth type. Now they have actually begun to find different specific gene aberrations interacting through this array. He concluded
that we have got to be very careful because if you try to go out in one way from the
genomic analysis, it will be extraordinary difficult to predict the clinical manifestations
of the disease which looks totally different in these different circumstances, and con-
versely you have to have the phenotype beautifully documented before you can have
any hope of suddenly being able to identify the genotype. So I think that the genomic
story is being oversold. On the other hand I think it has got the world in a total strange-
ble hold and therefore I hope your dreams of metabolomes and so on come through. We
must have been dreaming in conjunction because 3 years ago I wrote a paper for the
European scientific community on the genomics of gene manipulation. We identified a
way in which we could look at proteomic interactions to begin to look at all sorts of
things. In other words if you are going to get your metabolome going, I hope you have
some very trusted multibillionaire friends because I think it is going to be tough.

Dr. Go: I agree with you, this is what I call multibillion dollar research and devel-
opment. All my research has been in clinical research, clinical trials, interventional
studies, and I have a hard time at this point looking at how to apply this new technol-
ogy to my research. For example, if I need to understand diet, what I eat, and how that
will impact on the metabolism in my body, I can’t do it in the reductionist approach, it
has to be done in the holistic approach. The holistic approach is basically what the new
technology has promised to deliver in looking at nutrient–gene interactions. I am still
having problems with how to apply these new tools to human research. I am not as
optimistic as Dr. German, I am more realistic and try to be cautious with regard to the
holistic approach that the new technology will bring to new systems biology. That is
why I am more cautious but at the same time optimistic to learn how the new tech-
nological approaches could be applied to our research. So I am going to take a realis-
tic and pragmatic approach to this.

Dr. Sitges-Serra: I really enjoyed your talk, particularly when you underlined the rel-
evance of the interpretation problem that we have. Perhaps it is time to remember a nice
thought that Bergson, a French philosopher, gave: he said imagine a hand in a sand bag,
you are a sand grain and you cannot understand what is going on but if you are the hand,
it is so much simpler to understand. So what we really need is a kind of new paradigm,
a new theoretical paradigm to interpret data. Perhaps you rely too much on technology.
I would also rely on interdisciplinarity because what we have seen in the last 3 days is
how useful interdisciplinarity is in helping us understand the whole complexity of things.
It is amazing that philosophers are becoming mute because they are coming to analyti-
cal thinking which has even less and less to say, while scientists are going into a so com-
plex issue that we need more philosophy to interpret our data. So we are kind of crossing
our disciplines in a very interesting way, and I think that the future is also for interdis-
ciplinarity. It is a pity to see these thousands of people attending meetings in super spe-
cialties not reaching any conclusion because they are really thinking mechanistically and
only in their specialties. So that should come to an end and we should promote inter-
disciplinary meetings in which cardiologists meet with endocrinologists and public
health people and surgeons and basic biologists just to encourage interpretation,
because if we don’t approach facts in a multidisciplinary way we won’t be able to inter-
pret no matter how complex the technology will be, that is also my view.

Dr. Allison: I support what Dr. James has said. Not only has all the scientific fund-
ing being hijacked by these people who are looking at smaller and smaller updates, but
the corollary of that is that academic appointments go to people who are looking at
smaller and smaller bits and these people are then asked to teach medical students
and we practically haven’t got any whole-body physiologists left. So we are teaching
the students about molecular biology and so on, and then they are asked to go and
deal with a whole person, we are getting increasing super specialization and we get
notes about a patient who has been investigated by 6 different departments who have
all failed to make a diagnosis. I am reminded of an old lady who came to see one of my colleagues and she said: ‘Professor, I have been to see all these special doctors about my special bits, but it is not the special bits I am worried about it is the bits in between’.

**Dr. Go:** I fully agree with you. I am a member of the UCLA Curriculum Development Committee. We are solving the problem by creating new courses called doctoring 1, doctoring 2 and doctoring 3, and putting it all together in human and clinical medicine. What used to be physical diagnosis, history taking, is now called doctoring 1. I think this was the problem – that I saw the translational side of current human genomic research. I fully agree with Dr. Sitges-Serra. We have to be able to integrate the results of new technological approaches to clinical medicine.

**Dr. Allison:** No computer has yet been invented with the capacity for intellect and imagination of the human brain.

**Dr. German:** You said it is going to be expensive, but I think we should separate genomics and I think the emphasis on genomics is inappropriate, especially for nutritionists. We are not really in the genome business, we are in the post-genome business, and that is something that is a field we can change. We can change the way we interact with the environment. You talked about the money, but the Surgeon General in the United States has gone on record saying obesity is costing the Americans, just the American economy, USD 1 hundred billion a year. That is a lot of money to address the science. As I said, people put far more investment into the mobile phone than they do into monitoring our health; they feel that mobile phones are more valuable technology than health. The question is why. Why don’t we say let’s invest in this, and build the necessary knowledge. I think the key problem for the nutrition community is the lack of biological knowledge. If we measure something what does it mean, that is the science that has to be built. I think it is not reductionist, I think it means to do mechanistic science but joined together so that we can look at each point in context. That is going to mean you are going to measure things, it is certainly going to be more expensive to measure. Is it going to cost USD 1 billion a year? I doubt it. If we do it we will save USD 1 billion.

**Dr. Go:** I think the key point is that we use technology to create a new knowledge basis. But from my personal interest, creating the new knowledge is far more important, but at the same time I am open minded to use the new technology to create that knowledge, and whether that knowledge is what we are looking for to apply for health promotion and prevention still needs to be determined.

**Dr. Steenhout:** I like the term ‘personalized medicine’, but I will ask a very provocative question. Are those technologies evolving so rapidly that we cannot think that people will also want to personalize the conception of their children, and what does it mean in terms of ethical aspects?

**Dr. Go:** There are a lot of ethical issues. This is why schools of medicine and schools of public health in the United States now have departments of bioethics because somewhere along the line we need to address this issue. When we start using genetic material, there are certain precautions that we need to worry about. I think down the road we actually are practicing personalized medicine. Now genomic technology is used to fingerprint your genetic profile. This technology can also fingerprint the food you eat and be able to investigate your gene–nutrient interaction at different stages of your life cycle. So, in a sense, using new technology based on old knowledge or new knowledge being created characterizes who we are and how we respond to what we eat and determine our metabolic phenotype. But the issue that you raised has become a real ethics issue which we are now being confronted with. That is why I hate to sit in the Human Subject Committee because I don’t have the full knowledge of how to handle ethical issues in research that deals with genetic material and new technology.

**Dr. James:** The question on ethics is an entirely appropriate one, and isn’t it fascinating that you don’t want to go on that committee. You have one of the most powerful intellects in the United States, you have an enormous educative capacity and,
just as you highlighted, I have a problem in ethics because as I understand it we have a range of intelligent cautions and the average surprisingly happens to be a hundred. It is a fundamental issue because I disagree partly with this concept of individualized, personalized processes for several reasons. Look at the nature of human society, the extraordinary importance of having an environment which is conducive to societal welfare because the implication, and it is almost a caricature of what we have in England and the United States, is the idea that everything is individualized and that is a misunderstanding. The great societies of the past were not based on that concept although individual responsibility was important. But the current evidence of obesity is that we probably have between perhaps 200 genes involved to determine the propensity to becoming fat, and 50% of the explanation for the variance across a population comes from the effects of these genes interacting with the environment. So it is not simply environment and it is not just simply genes. But there are beautiful studies in *New England Journal of Medicine* showing that genes actually influence behavior. My behavior now looks both in terms of the way I eat and the characteristic style in which I eat, and also the propensity that I have to do exercise. Now, Dr. German, I am suffering from all these genes and because my IQ is only 95 you are now imposing on me that I should understand that this little print that I could get in 5 years time is going to tell me what the spectrum is with this mathematical formulation of the gene expression of these 200 genes. On the basis of that, actually I need a few more genes to be able to know if I am on a high- or low-salt diet and my trans-fatty acids will or will not do something for me, and my insulin resistance is a bit troubling. At present if you go to Australia, which is the only place I know where it has been done, and ask a consumer to chose a food on the basis of what they think is good in their crude understanding, you have two conflicting concepts. In other words you have a food that is high in saturated fat but it is low in salt which is good, the average consumer cannot cope with the integration of balancing that risk. So how are we going to cope? I know that I have 14 genes to make me either be active or not active, and like particular foods or not and so on, I mean it is madness. Therefore I would propose that functional genomics is actually the new nutrition of the molecular biology running out of things to do and that is good. But I think that when we come to the ethics of society we are going to have to follow the philosophical line and say let’s pull back a bit and, if we go into disciplinary mode, we begin to realize that the family, as Dr. Basu was saying, is terribly important because that is what the evidence shows. We have to use different dimensions of evidence and what affects those families, it is actually the environment and civilization in which they live. So I think we will have to go not simply from the genome to the metabolome but to the understanding of what is conducive in food, in other terms to an appropriate state of being which is conducive to mankind.

Dr. Go: I fully agree.

Dr. Sitges-Serra: Let’s touch another interesting topic concerning the same issue. One of the problems of funding and publishing is that the editorial and funding policies have been stuck with the clinical trial issue. It is really clear that maybe we can now consider the clinical trial as an almost obsolete approach to nutritional investigation or research. Maybe it is in a certain sense the final good tool of mechanistic medicine, looking at the single factor and trying to do this analysis with a single variable differing from two populations. But things become more complex. You again need the experts’ opinion, and the epidemiologists were saying that expert opinion comes at the end of the evidence. But now we are starting to see the reverse, an expert opinion is essential to criticize a clinical trial and a clinical trial per se says nothing if it is not appropriately analyzed. So are we approaching a kind of, at least in nutrition research and maybe in other fields too, much less privileged position for the clinical trial?

Dr. Go: Dr. Rock will remember that she and I recently participated in a symposium on diet and cancer prevention in the post-genomic era at the National Cancer Institute. The auditorium was full of people, and Dr. Rock and I were on the podium,
trying to figure out an answer to the question you just asked. What I basically said was
that I am not abandoning any of the tested ways of doing clinical research, my position
is to build it into it. A good example right now is the European Prospective Investigation
into Cancer and Nutrition project. It is a prospective study of over 5,000,000 people in
10 European countries. The National Cancer Institute plans to investigate and apply
this new genomic technology to this project.

Dr. Rock: I can comment on something else too. I think what Dr. James is trying to
get us to do is to think in terms of not and either/or, but it is taking this and putting it
into the framework of public health and people. Is that right? Because what is missing
here is that this reliance on technology does not really take us into the grocery store.
I disagree with Dr. German because I don't think there is any way we are going to make
broccoli taste like ice cream. But within the context of culture and public health that
is really what is missing here that all of the genomic knowledge in the world isn't
necessarily going to give us guidance in terms of public health policy because of the
diversity of individuals. We are basically using population-based data to drive the advice
we are giving people. We have to look from a more global and environmental perspec-
tive even though this doesn't mean we throw this out, that just helps us understand it.

Dr. James: I think that is true but it also has very important implications on the
Cochrane analysis. If you think about the major issues, it is extraordinarily important in
this dimension because if you look at what is happening in the food business across the
food world, across the globe, the rate of change is fantastic. Are you going to tell me that
we have to wait for a true understanding of whether the genomic differences between
the Japanese and the Finns are really the explanation for the astonishing differences in
heart disease, which of course I totally disagree with. Are we then going to go for the
genomic patterns of the Icelandics and the Japanese and the South Americans and so
forth? I think we have got to be really quite careful about this because if you then take
the logic through there and say we need Dr. Rock's gorgeous trials of practicalities, it is
going to be about 100 years before we can give even generally sensible advice. So I actu-
ally have a completely different perspective in the public health dimension where we are
actually going to have to partially revert the judgments recognizing that most of the huge
public health gains that have been of enormous benefit to mankind have come before
the evidence, as we would understand it, was there. The question is are we going to pro-
duce or can we move so that we can take on both views, where we can monitor what is
happening, be highly refined in what we do, and have a better analytical accretion of
information so that we can adjust far more effectively when we make mistakes, as we
have done in public health in the past. I think it is an enormous challenge.

Dr. German: I think it is important to recognize that there is an overemphasis on
genomics and yet there are very few scientific bodies that have the confidence to be
able to say that genomics won't predict everything. I think you missed the subject I
tried to raise: that we are not what our genes say we are, throughout our lives we
definitely change. I think the geneticists miss this and it is up to this scientific body to
continue to point out the importance of environment including diet to the varying
expression of genotype. You can't make one measurement when someone is born
because genotype won't predict what they are going to do for the rest of their lives.
We do need to measure people, we have to guide the health to a certain extent.
Traditionally we achieved a successful way of eating based on empiricism and, like it
or not, we have eliminated a lot of that knowledge from communities. Now we have to
define some way to put it back and I would say the technologies that are becoming
available on metabolism allow us to do that with more confidence. But the knowledge
and guidance for individuals will not be based purely on genetics. Nutritional sci-
etists are the body that has to broaden that perspective and hopefully get the money
to build the necessary knowledge beyond genetics.

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