June 2003 Issue | Kathie Swift, MS, RD Canyon Ranch in the Berkshires

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Welcome to Functional Medicine Update for June 2003. We have been talking about “functional medicine” for several years. Why have we chosen “functional medicine” instead of “integrated,” “complementary,” or “holistic” medicine? We chose the term “functional medicine” because it seemed to be independent of discipline. Everyone can rally around this term. Who would not want to practice functional medicine? The function we seek to improve is related not only to physiological, cognitive, emotional, and physical function, but also to the concept of being functional in and of itself.

The British Medical Journal recently published an article titled “What Should We Say to Patients with Symptoms Unexplained by Disease? The ‘Number Needed to Offend.’ ”1 I owe Dr. Lev Linker thanks for this article. Years ago in medicine, “functional” was a pejorative term that generally referred to an unexplained or psychosomatic disorder. I predicted this definition would change, and “functional” would become an operative term that described physiological and physical function related to early warning signs of later-stage pathologically definable disease.

Re-Exploring “Functional”
We should not be limited by previous understanding of the word, and this BMJ article re-explores the term “functional.” Working with patients, investigators reviewed a series of terms that could be related to conditions unexplained by a specific organic cause. These words included signs and symptoms of a complex nature that were incapable of unequivocal, precise definition.

Included among the terms were “symptoms in the mind,” “hysterical,” “psychosomatic,” “medically unexplained,” “depression-association,” “stress-related,” “chronic fatigue,” and “functional stroke.” What terms might best define these conditions associated with diffused symptomatologies? Investigators spoke to physicians who had reviewed those terms. The physicians were not pleased with the term “functional.” They felt “medically unexplained” would be better. The authors of the article state:

“Many diagnostic labels that are used for symptoms unexplained by disease have the potential to offend patients. Although ‘medically unexplained’ is scientifically neutral, it had surprisingly negative connotations for patients&ldots;.

“Conversely, although doctors may think the term 'functional’ is pejorative, patients did not perceive it as

such. As expected, ‘hysterical’ had such bad connotations that its continued use is hard to justify, although it is the only term in this list that specifically excludes malingering&ldots;.

“Many of the available labels did not pass this basic test, but ‘functional’ (in its original sense of altered functioning of the nervous system) did. This label has the advantage of avoiding the ‘non-diagnosis’ of ‘medically unexplained’ and side steps the unhelpful psychological versus physical dichotomy implied by many other labels. It also provides a rationale for pharmacological, behavioral, and psychological treatments aimed at restoring normal functioning of the nervous system. We call for the rehabilitation of ‘functional’ as a useful and acceptable diagnosis for physical symptoms unexplained by disease.”

It is interesting, in the evolution of medical literature, to see what we talked about 10 years ago rise up on the radar screen. The term “functional” may be redefined in light of the patterns of genetic and proteomic expression which lead to the interface of the term “functional” with a paradigm shift that is occurring, a revolution in medicine. We now recognize that disease emerges from the interaction of the gene and its potential to be expressed in its environment. It is host-environment medicine.

An article titled “Host-Environment Medicine. A Primary Care Model for the Age of Genomics” appeared in the Journal of General Internal Medicine.2 The authors state, “Rapid developments in genomic and proteomic testing promise to impact the way in which clinicians assess disease risk and drug selection in their patients.” These would become individualized to the patient and become personalized medicine rather than medicine for the averages.

The authors of this article add, “Because most diseases result from host-environment interactions, however, primary care providers will need to avoid the trap of biological determinism by examining the important role of environmental factors in their clinical assessments and interventions.”

Mendelian Determinism

These authors were describing Mendelian determinism, according to which we have recessive and dominant characteristics in our genes, and we can do little to get out from under those characteristics. Our genes for cancer, diabetes, heart disease, rheumatoid arthritis, or a bad life were determined by our parentage, and we can do nothing about it.

These biological deterministic concepts are now being replaced by the recognition that genes are expressed, and proteins and metabolomic effects are expressed in different ways depending on the environment in which individuals find themselves. We are starting to realize we have much more plasticity in our genes.

A Paradigm Shift

The authors of the article in the Journal of General Internal Medicine explain the application of the host-environment concept to the development of genomics and proteomics. They believe it will shape a different medicine that is more focused on the function of the individual based on that interaction, rather

than on diagnosis.

We are witnesses to a major paradigm shift in medicine. The concept of the primacy of diagnosis, based on histopathology, is reaching the point of diminishing returns. We are witnessing the emergence of a precedent set of events. We recognize that functional changes occur as a consequence of the interaction between the genome with its environment, producing an outcome through proteomic and metabolomic effects seen in reshaping the phenotype of the individual well before the onset of histopathology.

Most doctors begin to intervene with their patients at the stage of chronic, complex disorders. Our Clinician of the Month, Kathie Swift, will talk about these disorders later in this month's edition of FMU. We are witnessing a transition in medicine that may be second only to the revolution caused by Pasteur's discovery that invisible microbes can cause disease.
As a consequence of this paradigm shift, the entire pharmaceutical industry is in transition. We are seeing the emergence of pharmacogenomics, techniques to try to evaluate how drugs are metabolized by unique, different genotypes of cytochrome P450 and phase 2 conjugation enzymes.

A review article in Progress in Drug Research is titled "Drugs, the Human Genome, and Individual-Based Medicine."3 The author, Dr. Jay Glasel, discusses the paradigm shift in pharmacology and the medical application of pharmaceuticals that will focus more on individual genotypes as we move toward individualized medicine.

Single Nucleotide Polymorphisms
The genetic basis for the concept of individual medicine comes from recognizing that not all of our genes are expressed simultaneously. Different agents in the environment, including drugs, may influence the expression of those genes. People can vary through single nucleotide polymorphisms (SNPs), of which nearly 2,000,000 variations in the 30,000 to 40,000 genes of the human genome have been identified.

There is a greater amount of variation in functional capability than we previously understood. If Dr. Roger Williams—father of the concept of biochemical individuality—were alive today, he would probably be saying, "I told you so."

Assessing Individual Responses
Individual responses are where the action is. Many traditional studies describe a group of the average, with a mean and standard deviation. These studies may have lost the real specificity of cohorts within those group aggregates. An outcome might emerge among the cohorts that is entirely different from the average. Cohorts might have been more or less responsive to a particular therapy.

When we make particular associations based on the rule of averages as laws or maxims that become standard clinical practice, we assume everyone will respond in ways similar to those in the studies. We don't look at the variations among cohorts within these studies with unique characteristics to respond in different ways. It would be interesting to go back and reinterpret all the medical literature upon which decision-making is based, and look at the cohort analysis of different genomic types. We might be amazed at how it would change the conclusions we derived about medicines that work and don't work, and which therapies are more cost-effective than others because they generalize to the mean. As a consequence, these studies lost the specificity of the individual. Dr. Glasel reviews the history of individual patient responsiveness, where the pharmaceutical industry is going, and how SNPs may

influence the way that medicine evolves to be individualized in the future.
That leads to the question of the role of nutrition in the series of environmental variables that influence gene expression, proteomic outcome, and metabolomic function. A landmark article, titled "Nutrigenomics: Goals and Strategies," appeared in Nature Reviews.4 The term "nutrigenomics" is a coined term that appeared in Webster's Dictionary as of last year. It is the application of genomic tools, or looking at the way the human genome is expressed as a consequence of nutritional signals or nutritional impact on gene expression.

The authors of this article state, "Nutrigenomics is the application of high-throughput genomic tools in nutrition research. Applied wisely, it will promote an increased understanding of how nutrition influences metabolic pathways and homeostatic control, how this regulation is disturbed in the early phase of a diet-related disease and to what extent individual sensitizing genotypes contribute to such diseases."

Nutrition as Information
Have you ever considered nutrition as a signal? We typically think of nutrition as a means of preventing scurvy, beri-beri, pellagra, xerophthalmia, rickets, kwashiorkor, and marasmus, maintaining proper body weight, handling hedonic satiety issues, making sure you have enough albumin, and that you are not anemic. That is the traditional view of nutrition.

Now we know that food is more than just those variables; it is actually information. The food we eat creates an information mosaic, a portfolio of information that is picked up by receptor sites. It is transmitted to the genes, which express their messages in cell-specific ways unique to that individual. The result is a different phenotypic outcome in that cell that, over weeks, months, years, and decades of living, eventually leads to a reprogramming of that individual's phenotype so he or she looks, feels, and acts different. Thus we become, in part, what we eat.

Fat Stores Reveal Dietary Habits
If you were to analyze the subcutaneous fat of an individual, you could determine what he or she had been eating, based on the reservoirs of omega 6, omega 3, partially hydrogenated trans fats, and saturated fats. Michael Oliver and others have published work on the influence of fat on metabolism in Sweden, Scotland, and London. They found differences in metabolic activities depending on a subject's eating habits with respect to the type of fats in their diets.5

That measurement is the gross level. If we looked at the molecular level, the cell physiological level, we would be able to see changes in cell phenotype as a consequence of altered diets unique to the individual in his or her diet response.

Gluten Sensitivity and Nutrigenomics
A gluten-sensitive individual who carries HLA SNPs would be a good example of this concept. Gluten is a friendly molecule for most individuals. In those with genetic susceptibilities in the HLA system, however, it is an unfriendly molecule. It imparts dysinformation and creates an alarm reaction in the gastrointestinal mucosa. That alarm reaction activates Th1 and Th2 lymphocytes in the gastrointestinal-associated lymphoid tissue (GALT) and increases the risk of both localized and systemic inflammation. The phenotype changes depending upon the information from the diet. That is nutrigenomics that is washed through the genetic uniqueness of the individual.

The concept of nutrigenomics represents a paradigm shift that is inextricably connected to the concept of personalized medicine, toward which mainstream medicine is moving. We are seeing the term "functional" evolve from a pejorative term to become an operative definition of the precursors of later-stage pathologically definable disease, altering physiological, phenotypic, metabolic, or proteomic function, or genomic expression.

The Systems Biology Approach

Nutrients in this theme are seen as dietary signals detected by the cellular sensor systems that influence gene and protein expression and, subsequently, metabolite production. What has often been called the "systems biology approach" is the combination of all those factors. To understand human functioning, you have to understand the interaction, or interplay among genomic expression, protein synthesis and activity (proteomics), and metabolomic function that controls the phenotype of the cell. It is this combination that gives rise to the trajectory of the way that cell, tissue, organ, organ system, or body will ultimately be traveling over time.

This is a very different model of medicine from the histopathology-based model in which most members of the medical community were trained. The former model relies on medical taxonomy, describing the damage in a cell from a normal cell to an abnormal cell, or a normal tissue to an abnormal tissue, using some kind of a technology. It could be retinography, electron microscopy, nuclear magnetic resonance, or CT scanning to provide some way to examine the difference between a normal and a damaged tissue.

Broadening the Perspective

We are well along the road toward understanding genomic expression, proteomic outcome, and metabolomic control levels of the cell that precede the onset of visual changes in many of the cells, tissues, and organs associated with pathology. This dramatic change in view requires us, when we speak to patients, to have a broader perspective of the variables in their lives. We have to understand their attitudes, beliefs, and environment. We need to know what they eat and drink and how they exercise. All of these factors influence and signal their genetic sensors and subsequently alter their phenotype. Dietary variables are unique to that person's genotype.

An example of this new model is the concept of folic acid and its relationship to the homocysteine cycle or the folate cycle. We have discussed one of the more common polymorphisms in the folate cycle: the methylenetetrahydrofolate reductase (MTHFR) polymorphism. One common example of this polymorphism involves a substitution of C for T (cytosine for thymine) at the nucleotide position 677 in the sequence of the gene that encodes the synthesis of the messenger RNA for the enzyme MTHFR. This is the MTHFR 677C®T polymorphism.

MTHFR Polymorphism and Dietary Folate

A recent general population study reported in the American Journal of Clinical Nutritionreviewed the effect of folate intake on plasma folate and homocysteine concentrations.6 The authors found that individuals with the MTHFR polymorphism, at moderate or low level of folate intake in their diet, have increased homocysteine levels and lower levels of plasma folate. The authors conclude, "At any folate intake level, TT subjects have lower plasma folate concentrations than do CT and CC subjects. Yet at high plasma folate concentrations, tHcy concentrations in TT subjects are as low as those in CT and CC subjects." This means those with the MTHFR polymorphism high plasma folate concentrations may need higher levels of folic acid in their diet to overcome this genetic uniqueness

This discovery may have implications for function, not just cardiovascular function that we often ascribe to elevated homocysteine, but perhaps also cognitive function and early-stage dementia. The authors of another study, published in the American Journal of Clinical Nutrition, found that homocysteine levels, when even marginally elevated, were associated with decrements in cognitive function in a group of healthy individuals living in an elderly community in Italy.7 The authors conclude, “Elevated plasma homocysteine has an independent, graded association with concurrent cognitive impairment as measured with the Mini-Mental State Examination in healthy elderly community dwellers.”

This study found, from low to high homocysteine levels, an increasing risk of cognitive impairment, when measured with a standard psychometric questionnaire (MMSE). Therefore, levels from 4 to 7 to 8 picograms per mL of homocysteine might be considered to be in the normal range. Levels above 8 would be in a higher-risk category. I should mention that clinically, a level below 4 is also a higher risk to homocysteine-related problems. A homocysteine level that is too low also suggests folate trap with insufficiency of 5-methyltetrahydrofolate going on to S-adenosylmethionine (SAM). Homocysteine levels that are either too low or too high can be harmful.

These changes occur well before the onset of megaloblastic anemia in a person who ends up with a hematological aberration. These cognitive impairments and functional changes that occur with borderline elevated homocysteine occur in the absence of overt hematological changes. Often, when a clinician is looking for a diagnosis of folate deficiency, he or she will miss the insufficiency relationship.

Supplementing to Improve Homocysteine Status

One might wonder what differences would exist between administering 5-methyltetrahydrofolate or folic acid as a supplement. That question was the topic of another paper in the American Journal of Clinical Nutrition.8 The title of this paper is “Comparison of the Effect of Low-Dose Supplementation with L-5-Methyltetrahydrofolate or Folic Acid on Plasma Homocysteine: a Randomized Placebo-Controlled Study.”

The only challenging part of this study is that the investigators did not stratify to MTHFR genotype. It was a combination of all different types—the wild type plus the polymorphisms of MTHFR. The reason that is important is because the majority of the population has the wild genotype with a specific average need for folic acid. The MTHFR TT types, for instance, have increased need for folic acid to overcome that genetic uniqueness. Therefore, the sensitivity they might have to folic acid and homocysteine would be higher. A study without stratification would necessarily decrease the sensitivity to those individuals in the statistical minority carrying the polymorphism of MTHFR of the TT-677 type.

Preferential Benefits from 5-methyltetrahydrofolate

This randomized, placebo-controlled trial used 100 mg of folic acid versus an equal molar amount of 5-methyltetrahydrofolate to look at plasma homocysteine levels. Researchers found the 5-methyltetrahydrofolate lowered homocysteine by 14.6 percent, whereas the same dose of folic acid lowered it by 9.3 percent. Folic acid was about 45 percent less effective at the 100 mg dose in what was a population-based collection of different genotypes of MTHFR.

Even in the gross levels, the 5-methyltetrahydrolate would appear to have a statistically significant advantage, dose per dose, over folic acid. We would like to see a study that stratified for MTHFR TT-677 genotypes to evaluate the sensitivity of folate versus 5-methyltetrahydrofolate in that group. For certain

genotypes, we are starting to see that higher levels of folate, and perhaps even preferential forms of folate, might be more desirable for reducing the risk of homocysteine-related dysfunctions that cut across gynecology, obstetrics, oncology, cardiology, neurology, psychiatry, pediatrics, and reproductive biology. These are the various systems associated with abnormal folate chemistry and poor methylation reactions.

Assessing Functional Changes

I have been discussing unique ways of assessing functional changes that occur at the genomic, proteomic, and metabolomic levels. This field is still in its infancy in the development of the assessment methodology. A number of authors have speculated that a decade from now, clinicians will have tools available to integrate these concepts into treatment algorithms based upon this system's biology approach

Today, however, we are still trying to do our own pattern recognition by collecting data to the best of our ability, knowing there is a limitation on the expense we can incur to accumulate all the information. How do we do these assessments? What biomarkers should we use for evaluating nutrition status and functional physiology?

We will continue to discuss those questions. That theme will be woven throughout the remaining six months of FMU this year as we look at biomarkers for assessing physiological function and how that interrelates with nutrigenomics.

With that longer-term objective, we can move to the first chapter of this story, titled "Biomarkers for Assessing Nutritional Status."9 The results of a recent symposium on this topic were published in a supplement to the Journal of Nutrition, Vol. 133, page 873-1024. I will touch on a number of these articles now, and then I will come back and fill in the gaps with more specifics during the remainder of this year.

First of all, what are we trying to evaluate? A nutritional biomarker can be any biological specimen that is an indicator of nutritional status with respect to intake or metabolism of dietary constituents. It can be a chemical, functional, or clinical index of status, and by integrating different bits of information, we start to develop a pattern. That pattern gives us higher degrees of specificity and more assurance that our conclusions or the hypotheses that lead to those conclusions are justified.

Pattern Recognition

One bit of information, in and of itself, always has a high error opportunity because an infinite number of curves can be drawn through a single point. To understand a trend or draw a conclusion from multivariate contributions, we need to collect multiple data points. The comprehensive physical and health history becomes a sine qua non for good pattern recognition. Family history is very important. Then we need to establish functional indicators, looking at physical and emotional function. We need to look at biological parameters, explore noninvasive ways to assess function, and then integrate all of those factors into a profile that results in a pattern.

That pattern would be like a thumbprint; for instance, if we examined just one whorl on the thumb, we could not identify an individual. But if we looked at enough of the picture of the thumb and could recognize a pattern, we could do so. A retinal exam would be another way of looking at it. We are trying to find the lowest common denominator of variables required to develop the understanding of that pattern in the individual.

Evaluating Dietary Variables

The biomarkers can be broken down into validation of the specificity, precision, and accuracy of the methods, and their reproducibility. When we examine dietary variables, we always want to start by understanding what the person is eating. I am amazed when I talk to clinicians who are performing functional or nutritional medical assessment to find that some of them say they didn't ask what the patient ate. They just made an assumption. It is very important to do dietary evaluation with either a food frequency questionnaire or a diet diary, some instrument that allows you to understand what that individual is eating, relative to his or her genetic susceptibilities and characteristics and the outcome in the phenotype.

We are going to be evaluating some biomarkers that have precision, sensitivity, accuracy, and reproducibility. When woven together they can start to form a mosaic of understanding of the individual.

Let's look at some examples of the use of the laboratory.10 Rather than go through the signs and symptoms and the nutritional evaluation from a whole-organism perspective, let's look at the laboratory. Biomarkers of physiological status provide suggestions that relate to environmental variables that influence genetic, proteomic, and metabolomic function. Like the error and variation associated with any kind of measurement, we need to consider the magnitude and impact of the biological and laboratory variables when using these biomarkers. We need to know the range of specificity.

I am surprised when I hear people talk about ideal blood sugar levels. Sometimes they state that fasting blood glucose should be a specific number. I have done those analyses, and I know the range of ideal is actually narrower than the variability of the test itself on repetitive analyses. If we use only a very narrow range, we would ultimately end up just measuring the scatter of the test; we would not be looking at any physiological variables. We need to know the range of sensitivity, precision, and reproducibility of the test before we begin to define an optimal level or optimal range of a specific analyte.

Sources of Biological Variation

Biological variations can arise from obvious genetic differences from person to person, and whether a person is well or sick. If sick, how sick is that individual, how dysfunctional? What environmental variables may be at play that relate to the alteration in the particular biomarkers we are using? Serum lipids provide an example. If a person ate a large deli pizza in the last two hours, that pizza will have a significant effect on the outcome of serum lipid analysis, and it may very well affect the clinician's decisions. We have to know what the standard is by which we are measuring and what perturbations might have altered the data we are going to be analyzing.

Many simple variables in a standard blood test can be used for assessing aspects of nutritional status. An example is blood urea nitrogen (BUN) and creatinine ratio. That is a simple assay in a standard blood test that we often use as a measure of kidney function and kidney clearance indirectly. However, we now know that variables related to protein sufficiency can influence BUN-to-creatinine ratios.

Sources of Variation in BUN-to Creatinine Ratio

Protein malabsorption or maldigestion can influence that ratio, as can inappropriate intake of protein. If a person has a BUN-to-creatinine ratio less than 10, might he or she have a problem with dietary protein intake? Is something going on related to maldigestion or malabsorption of protein?

You would want to correlate that with the dietary history to see if the patient is getting adequate protein. Does the protein the patient eats contain the proper balance of essential amino acids, or is it an unusual or unbalanced type of protein? Does the patient have an underlying chronic gastrointestinal dysfunction relative to small bowel mucosal function that could relate to altered amino acid absorption? Could chronic pancreatic insufficiency be related to poor protein digestion and assimilation? All of these questions would come into play when you start to develop a pattern of various questions that might lead you to a better understanding of why that person had a low BUN-to-creatinine level.

Variables in Protein Utilization

A number of variables influence protein digestion, protein assimilation, and amino acid utilization. These variables have to do with appropriate acidity of the chyme. If a person has atrophic gastritis, with low stomach acid secretion from the parietal cells, or has pancreatic insufficiency, he or she may be a protein malabsorber. In this case, you will find a very high level of excreted nitrogen and undigested protein in the patient's stool.

These processes of looking at the gut as a bioreactor and as a place where various nutrients are broken down from large to small and then absorbed become part of our overall evaluation of a patient's nutrition and physiological status. Again, urinary nitrogen is a useful biomarker for dietary protein intake. This was described in one of the articles in the Journal of Nutritionseries I mentioned previously.11

Biomarkers of Fatty Acid Intake

Plasma lipids are a major determinant of aspects of fat intake. The chylomicrons are generally cleared postprandially, actually within the first couple of hours after eating. Various lipoproteins bind different fractions of cholesterol and triglycerides. It is important to recall that the control of plasma lipids is complex. We are dealing with both a lipoprotein fraction, which is controlled by neuroendocrineimmune function, and a fat fraction. Measuring cholesterol in the blood, we are not just measuring cholesterol; we are measuring it bound to a lipoprotein whose synthesis and transport are controlled, basically, by a variety of endocrine, neurologic, and immunological factors.

If we really want to look at fatty acid intake, we have to examine things like plasma fatty acids to look at composition of the various fats. Red cell membrane fatty acids would tell us a bit more about the type of fat. Or we could do subcutaneous fatty acid analysis, as I mentioned earlier. Now we can start breaking things down into the omega 6 or omega 3 fatty acid families with the saturated acid families. We can understand the relative balance of arachidonic acid to omega 3 fatty acids to see if the individual has a proinflammatory potential. The normal ratio of arachidonic to omega 3 fatty acids is somewhere in the range of 3.2 to 6.6. Significantly elevated ratios of arachidonic to EPA may indicate potential imbalances in precursors to the omega 3-derived prostanoids versus the omega 6-derived prostanoids.

We can use fatty acid analysis; we can use whole blood plasma analysis of lipoproteins. We need to remember that when we are measuring cholesterol or triglycerides in the blood we are also measuring lipoproteins, which are influenced by neuroendocrineimmune function. This is discussed in the Journal of Nutrition.12

Assessing the Folate Cycle

We have tools in our standard assessment that allow us to assess methylation nutrients—the folate cycle. We have the hematology red blood cell number, the hematocrit, intracellular hemoglobin levels, and the

MCV, the mean corpuscular volume. Elevated MCV can be a sign of macrocytosis, which is suggestive of B12 insufficiency. You then start looking at alterations in the 1-carbon methylation.13 Similarly, if you had a low-grade anemia, you might start looking at B12, folate, and the other folate-containing nutrients, B6, and trimethyl- or dimethylglycine.

As I pointed out earlier, one should not use this solely as an assessment tool for insufficiency of the folate cycle. You need to go to metabolic markers such as homocysteine or methylmalonic acid to understand it. Vitamin B2—riboflavin—has also been added to this family of folate-dependent nutrients, so we would look at the folate, B12, B6, riboflavin, dimethylglycine connection. That all relates to the concept of S-adenosylmethionine. In the absence of metabolite assays, you might actually be misled if you did not see an elevated MCV.

That is the first chapter in our assessment. We will come back and talk about other nutritional assessments in future issues of FMU. Let's turn to Side II.

INTERVIEW TRANSCRIPT

Clinician of the Month
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JB: I recently discovered, with some chagrin, that we have never interviewed a registered dietitian as Clinician of the Month in almost 21 years of FMU. This month, making up for that omission, we are privileged to have Kathie Swift, a registered, licensed dietitian/nutritionist who earned her master's degree in nutrition at Arizona State University and has done post-graduate work through the Institute for Functional Medicine training programs. She has been nutrition director at Canyon Ranch in the Berkshires for more than 10 years and is actively involved in developing a program, "Nutrition Intelligence," combining food and nutrition guidelines, which was presented at the White House Conference on Complementary and Alternative Medicine.

It is a privilege to welcome you to FMU, Kathie. Thank you for talking to us about the complicated interface of nutrition and medicine, and the dietitian's role in that interface.

KS: Thank you, Jeff. I am honored to participate in this interview. I appreciate the knowledge I've gained as one of your students during the last decade. It is timely that we are discussing the successful integration of nutrition into medical practice. Just in the last few months a number of key articles and major moments in the field of nutritional medicine have appeared that affect the present and the future. If I might just name a few, there was an excellent article in the Journal of the American Dietetics Association on key trends affecting the nutrition profession, including the boom in technology.14 We will all have to become information masters of medicine and nutrition.

The trends include the crisis in obesity, the global food supply, and changes in the American society—changes in the population, values, modern lifestyles, work life, technology, and a desire on the part of health seekers who come to our offices. Also, in January, the US Preventive Services Task Force

presented evidence strongly recommending dietary counseling for adults with high cholesterol and other risk factors for chronic diseases such as cardiovascular disease.15 That was a major publication.

Evidence-Based, Outcome-Based Medicine

In the past few years we have seen a strong need for evidence-based medicine, which is the wonderful marriage of not just clinical evidence from randomized controlled trials, but the integration of our clinical expertise and our experience. In health care today everyone is concerned about cost-effectiveness and the efficiency in which we operate.

Another mandate we can discuss is sharing outcomes as part of a physician/nutritionist team. The supplement to the April issue of the American Journal of Clinical Nutrition was entirely devoted to the nutritional guidance of family doctors.16 All of these are critical papers and information sources that we should be devouring.

RD/MD Integration

JB: One of the articles in that supplement of the American Journal of Clinical Nutrition in April 2003 you mentioned talks about the RD/MD interface and how the registered dietitian can work with the medical doctor to create a unit of expertise within the practice. What do you see as the positives and some of the challenges that integration presents?

KS: The task force paper and other papers that are being published confirm the benefits of the team approach. Various constraints, time being the most critical, make this partnering essential in today's medical practice.

From my own experience, we need a dietitian/nutritionist with excellent communication skills who has continued to improve his or her clinical knowledge base, especially in the evolving areas of genomics, functional foods, and nutritional supplements. As for the work of the nutritionist in complementary care, the dietetic practice group at ADA is a great example of dietitians with these types of skills. It is the nutritionist's responsibility to look toward the future and be aware of key trends.

Building a Critical Partnership

Some physicians are already interested or knowledgeable in nutrition. I have encountered physicians who are and many who are not. Sometimes I've had to drive the interest in nutrition in some settings, and there are many ways to do that. Today, with the internet and all the information that is available, it may be less challenging than it was many years ago.

The other thing that is happening is that the patient may be the agent of change because of technology. We know the physician is expected to be knowledgeable about the latest and best available in evidence-based information. I believe I read in one of the articles I mentioned in the American Journal of Clinical Nutrition, that about 6000 new articles are published in the literature every week, with over 1000 new guidelines published annually. The authors clearly feel it is impossible for either doctors or nutritionists to work alone. The partnership is critical.

Continuing to Learn

An essential part of achieving that objective is continuing to educate ourselves. You know the old saying, "You cannot begin to learn what you think you already know." My personal philosophy for integrating

nutrition into medical practice is to let my heart be my guide. I have had to take my brain on the ride, keep my eyes open, and keep reminding myself that patience is the key. We have to remember that even small changes are built upon over time. Sometimes we approach this very idealistically and we want everything to happen at once, but small accomplishments represent progress.

We began at Canyon Ranch by bringing in outside experts. I brought in experts like yourself, Dr. Leo Galland, and Dr. Sid Baker, to educate the nutritionists and the physicians. These experts presented the leading-edge concepts in medicine, and to anyone with a scientific background they made perfect sense. There wasn't as much time spent having to convince people, but one of the challenges certainly comes from the skeptics.

Honoring Skepticism

Another thing I have always kept in mind is honoring healthy skepticism where science and medicine are concerned. The integration here at Canyon Ranch was challenging, but we now have what I believe is one of the premier models for nutrition and functional medicine in the country and probably in the world. Some of our most brilliant discussions were generated because we had some skeptics on the team. The medical/scientific analysts kept the questions coming. Once you get the engine started, building on small increments, it all comes together.

Looking back, our origins in developing this were very elementary. At the time, I didn't even have a computer. At Canyon Ranch, we always favored what we called the "high touch" versus a "high tech" approach. Since those beginnings we've evolved to a more computerized technology.

Giving Free Samples

One interesting thing the physicians, my colleagues, and I did to integrate nutrition was to provide samples of our services. This is something every professional should strive to do. Everyone loves freebies, and our skills and services are no different. I would do a nutrition consult with a physician or a physician's family member, perhaps with one of his or her children, or with one of the nurses—anyone whose eating habits the doctor was interested in improving.

Nutritionists and doctors who are interested in integrating their services on a more functional basis need to be able to walk in someone else's shoes. We need to experience something in order to feel it, live it, and be able to talk about it. We call that the "Jacuzzi effect" here at the Ranch. It's a major marketing force that remains alive and well today—word of mouth. So many times, a nutritionist may be working with a patient who can be the sales person for nutrition services, whom an article referred to as an "information broker." That person shares his or her positive experience; how he or she managed to lose 25 pounds, improve arthritis, or reverse insulin resistance through nutrition counseling. A successful client will bring more into the fold. We periodically have what we call "sampling fairs" of all our health and healing services for other employees, so everyone knows and can talk about his or her experience. I think that's critical.

Serving Community

Another thing we can all do as professionals is serve our communities. Years ago I was a clinical nutrition director in a very progressive hospital in central Louisiana. I wanted to start a program called Community Health Update to educate the community on various nutrition topics. The administration predicted doom and gloom. It wouldn't work; they had tried it before; previous attempts had failed. That's always a good challenge. But I believe that like all things in life, there's a season for everything.

I made sure that I put together a group of engaging presenters who were passionate about being on a panel to discuss nutrition and medicine. It worked. In fact, it was so successful they had to turn people away. Even now, getting out in our communities and providing our services is important, whether it's the YMCA or the local hospitals. This practice has after-effects that elevate the integration of nutrition into medicine as more people become interested. When there is public interest, it is in high demand. I can't stress enough the importance of networking.

Building Visibility

We need to make ourselves visible in our practices. The physicians at Canyon Ranch see the nutritionist every day. However they can make that happen, whether it's morning rounds or weekly meetings together, the sharing is critically important. It works both ways. If I come across a new article, for example, on oats in the gluten-free diet, and I'm not sure if the doctors saw it, I share it. That builds trust and mutual respect and ensures collaboration and cooperation.

Many integrative medicine practitioners have told me their programs failed because of the challenge of turf battles. I read an article on Medicare reimbursement for diabetes and the whole medical nutrition therapy field, which I believe said it well: "Nothing good will be derived from engaging in a debate that pits one professional group against other professionals. We all have a valuable role to play in delivering the highest quality care to patients." Whether it's a naturopath, a chiropractor, an acupuncturist, a family practice physician, or a nutritionist, we all have unique skills and we have to honor and appreciate our backgrounds.

Interacting Experts

The interaction I've had with my colleagues is singularly the most important thing that has contributed to my continuing to learn and grow. When I have a complex patient, someone with sleep issues perhaps, I know there's someone I can rely on who has expertise I may be lacking.

It is important to appreciate our own strengths and admit that none of us is an expert in everything. Some of the more complex patients we work with have a multitude of lifestyle issues, including polypharmacy, stress, social issues, or family dynamics. We all need to appreciate that building better integrative, multidisciplinary teams is the best way to serve patients.

Creating a Financially Viable Practice

JB: Over the years that I've known you I have observed your ability to create alignments and work with groups to create better outcomes. The way you have done it is different from the stereotypes some people carry regarding registered dietitians. They see dietitians as hospital-based individuals who deal with meal planning or food exchanges. Clearly, a "registered dietitian" can be engaged in a number of different pursuits, from individual clinical nutrition to institutional nutrition.

You have been effective in building alliances. You have also created an opportunity for financial viability because the best programs will ultimately fail if they are not self-supporting. Would you explain how you have been able to pull together a financially viable integrated program?

KS: As in any profession, not all dietitians have the same skills and capabilities. An article in a recent ADA journal described dietitians as multidepartmental managers. We've got to appreciate that in any profession, we have people with multiple skills and others who are best because of their specialty areas.

Some wonderful things are emerging in the field of dietetics. I mentioned the different dietetic practice

groups. That's a great example. There's going to be a new one with specialists in weight management. In complementary care, the dietitians are better versed in functional medicine, supplements, and functional foods. This will help physicians; it will help other healthcare professionals who want to learn more about potential referrals and networking. You may want to seek out a dietitian with this particular skill level, such as a sports nutritionist. We can't all be experts in every single area.

Seeking New Opportunities

The fact that my husband was in the military presented me with an opportunity and a challenge. We moved every few years. I was able to gain experience in many different capacities. I was a clinical nutrition director and an outpatient nutrition director in a hospital that was like a mini spa. My office was in a demonstration kitchen where I held cooking classes and classes for children. We had a health food restaurant. This was back in the 1980s. I lived in England where I was exposed to Healing Touch and aroma therapy. That's another pearl. Registered dietitians must keep looking for new things and bring an adventurous spirit to the profession.

Now, with the web, any physician, patient, or healthcare professional can log on to the American Dietetic Association's website, eatright.org, to find a dietitian in any area. It's very important for a doctor, a patient, or anyone else to do their investigative work. I give clients here at the Ranch, if they want a referral, a list of questions to ask the dietitian they might find via the web, to make sure the individual has these special skills, whether it be advanced skills in functional medicine or some other area.

Dietetic Success Stories

JB: What areas in your experience in the practice of dietetics are particularly likely to yield good outcomes or be particularly effective? These would be what I refer to as "slam dunks."

KS:

Being here at Canyon Ranch has been the ultimate experience in integrative medicine. First, the successes can happen with any condition if you've got a good physician/nutritionist partnership and support system, and if the patient is willing to commit to making changes. The props we use include the intention, the coaching, the training, the practice, the skill building, and the tools we give the patient. These tools are critical because they are very personalized educational materials.

As I look around my office, I see food models, plates, containers, and all sorts of visual props. We need to be creative in the way we counsel people. A teenage girl will relate better to a lipstick or a nail polish bottle as a visual aid compared to a sports enthusiast, for whom a golf or tennis ball works much better. I use food products, labels, supplement bottles, pedometers. If I'm going to coach someone in trying to increase his or her activities of daily living through more movement, and I talk about a pedometer, the patient wants to see one. That's another thing I would encourage. Our offices for nutrition counseling become interactive centers where patients can get involved. They like that.

Insulin Resistance

Our physicians all agree we've had great success dealing with insulin resistance. That could be a "slam dunk." It is critical to pick a person up in the earlier stages on the pathway to pathology, before the later stages develop. We have to keep that in mind with better diagnostic testing. Here, probably the testing we do most often would include the two-hour glucose insulin challenge test, CRP, homocysteine, lipid profiles, and thyroid profiles, in addition to routine basic blood work. Others in our top ten are IgG and

IgE antibodies, red blood cell mineral levels, detoxification profiles, urinary organic acids, and hair analysis.

If there are dietitians listening who are not familiar with these tests, I strongly encourage them to further their training in functional medicine, especially with all the wonderful resources that your group, Jeff, has provided, and your course, Applying Functional Medicine in Clinical Practice. Insulin resistance is absolutely a success story. We call it the trifecta—the dyslipidemia and inflammation.

Slam Dunk Success Stories

We've had great results with PMS with such simple things as changes in diet and nutritional support. I can't tell you how many women with severe PMS can be helped with just some simple changes in diet and taking high potency multivitamin/mineral supplements.

Another area in which we have had tremendous success is with patients with complex problems such as chronic fatigue, fibromyalgia, or various inflammatory processes, where we have used a more high-tech approach and investigated food intolerance. We have picked up a lot of people with gluten intolerance, and that has been a major "slam dunk".

Just this week, I followed up with someone who had Crohn's disease for many years and it was hard for us to believe that this had never been investigated. That patient has experienced a dramatic improvement with using a medical nutritional food product and a good elimination diet. Those are some of our major "slam dunks."

A Combination Approach

Another interesting thing I heard at a recent conference, Dr. Cindy Geyer, one of my colleagues here, reported on some cases we've worked on together using what we call low-tech, moderate-tech, and high-tech approaches. I'll be talking about these at the May symposium. I'll give you a quick low-tech approach example. A client presented with severe daily headaches and fatigue. The simplest thing we did was to have her eliminate an artificial sweetener. That was a very simple "slam dunk."

A case of a moderate-tech approach was a person who presented with severe hypertension, weight gain (she felt she was a heart attack waiting to happen), and joint stiffness. We did some lab tests looking for insulin resistance or inflammation. Because of the medications she was on, we also looked at certain nutrient levels and we uncovered a B12 deficiency. With brief intervention, one nutrition counseling session, one medical session, and a phone follow-up, nine months later the woman had made significant progress, just by increasing her daily movement activities and switching to a nutritionally intelligent core diet of fruits, vegetables, fish, nuts and seeds, and some nutrient repletion.

Nutritional food and nutritional therapy can do incredible things. Part of the success we've had is due to our excitement and passion about what we do. Our physicians are excited about learning and studying functional medicine and integrating some simple things into their practices. If we're passionate about what we do, the movement can spread and the patient is on the receiving end of health restoration.

Masterful Skills

JB: This has been an inspiring discussion. The skills you've developed and the masterful way you use them to bring other disciplines into the vision and create opportunities for improved outcome are a model

for the rest of us. Thank you for sharing both your procedural point of view and how you have used your philosophical and emotional energy to create great change. We'll look forward to checking back with you and what's going on at Canyon Ranch in the Berkshires.

From the Lab to the Clinic

astrointestinal Restoration with Pro- and Prebiotics

I close with a follow-up to Kathie Swift's excellent comments about some of the "slam dunks" that are useful in practice. One of those is the concept of gastrointestinal restoration using probiotics. Two review papers on this topic appeared recently, one in the *Lancet*[17] and the other in *Current Opinions in Clinical Nutrition and Metabolic Care*.[18] The latter review covered age-related effects on intestinal microflora, with a decrease in anaerobes and bifidobacteria populations and an increase in enterobacteria.

These reviews explain that changes are associated with reduced intestinal immunity and increased intracellular permeability in the GI mucosa, which becomes a portal of entry for partially digested materials that may activate the immunological system, and that these changes may be associated with altered immune function in older-age individuals. The authors in the latter review are focusing on age-related effects, but it is important to point out that these conditions of altered gut flora and altered immunological function of the enteric immune system can occur at any age, depending on the circumstances of the environment. Antibiotic exposure, drugs, alcohol, and various types of toxic environmental substances may endanger the integrity of the flora and result in alterations in gut-associated immune function.

Benefits of Probiotics
In summary, the authors suggest that changes in intestinal microflora may play clinically important roles in individuals with altered immunological function. They urge investigation to determine if an individual may have altered gut immunological function and/or permeable gut, and they recommend probiotic supplementation to benefit individuals with these conditions and improve gut immune function and the gut commensal environment.

In the *Lancet* paper, the authors point out that the human gut is a natural habitat for a large and dynamic bacterial community. There are about 3 ½ pounds of bacteria of hundreds of species living in our gut, and there is a constant turf warfare going on over who gets what bit of real estate. A substantial part of these bacterial populations are as yet undefined, so there is a lot yet to be understood about the dynamics between the bacterial flora and the gut-associated immune function. However, even at the point of our present understanding, the relevance and effect of these bacteria and a host of physiology and pathology issues seem to be well documented.

Gut Microflora
Major functions of the gut microflora include metabolic activities that result in salvage of energy and absorbable nutrients—production of butyrate in the large bowel, for instance. Butyrate is colonocyte fuel and is used for colonocyte replication and appropriate gene expression. Intestinal epithelia have important nutritional effects on immune structure and function. They also protect the colonized host against invasion by alien microbes that in imbalanced or disturbed microflora can become foe rather than friend.

Gut flora might also be an essential factor in certain pathologic disorders, including multi-system organ failure, colon cancer, and inflammatory bowel disease (IBD). These disorders may start early on as increased inflammatory bowel disease, particularly the diarrhea-dependent form of irritable bowel syndrome (IBS).

Pro- and Prebiotic Supplementation

Nevertheless, bacteria may be useful in the promotion of human health by oral probiotic and prebiotic supplementation. These substances, which are the natural food of the friendly bacteria, include fructans, which are metabolized selectively by the symbiotic bacteria. *Arabino galactans* is another good example of a specific substrate for these friendly bacteria; it leads to the starvation of unfriendly bacteria and the survival of friendly bacteria.

Pro- and prebiotics together represent a fundamental treatment in the effort to restore proper GI immune function. This is good medicine. It relates to pediatric atopic disorders, infant diarrheal disorders, and asthma-related disorders. These are systemic inflammatory conditions associated with altered immune function. Pro- and prebiotics can also be beneficial in localized digestive disorders like IBD, Crohn's disease, or certain forms of IBS.

The IBS Connection

The IBS connection is a little more complex. The authors of a recent review in the *Archives of Internal Medicine*concluded there was no connection between alternative therapies and the remediation of irritable bowel.[19] However, I think if we look in more detail at the specific genotypes and their relationship to microflora in the gut, we will find well-defined interrelationships between the diarrhea-predominant form of IBS and altered gut flora.

The use of pre- and probiotics is a fundamental form of therapy from the lab to the clinic. That ends this month's *FMU*. We will see you in July.

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