

DIABETES—ASKING THE RIGHT QUESTIONS

Mark A. Hyman, MD

Mark A. Hyman, MD, is the editor-in-chief of *Alternative Therapies in Health and Medicine*. (*Altern Ther Health Med*. 2006; 12(5):10-13.)

It ain't what you don't know that gets you into trouble. It's what you know for sure that just ain't so.

—Mark Twain

In science, as in life, we receive answers to only the questions we ask. How is this true in the explosive increase in diabetes worldwide? How might diabetes be a model for a new way to diagnosis and treat chronic complex illnesses? Unfortunately, we are married to definitions and risk factors and not exploring more fruitful lines of inquiry. We are mired in asking the wrong questions, much like the religious sages of the middle ages who wondered how many angels could dance on the head of a pin. What is the correct definition of diabetes or insulin resistance or metabolic syndrome or pre-diabetes? Should we be excited by the latest drug therapy or gene discovery in diabetes? What about CAM therapies? Should we be assessing old or new therapies as “green drugs” to control blood sugar or lipids? Are these useful questions or simply distractions from the more important question of how to deal with diabetes from a cultural, social, political, etiologic, and comprehensive systemic, biological perspective?

Does asking the wrong questions distract from the larger notion of discovering the causes of disturbances in the dynamic continuum of our metabolic equilibrium and their remediation? Does asking the wrong questions deflect from inquiry into the critical processes of restoring self-regulation to our complex biology? I would argue that the answer to these questions is yes.

Understanding that illness has purpose and that disease is generally rooted in the body's attempt to correct underlying imbalances or dysfunction, we can seek to not alter, block, or interfere with normal metabolic processes, but to learn how to enhance, facilitate, and promote normal function. Symptoms are clues to deeper molecular, metabolic, and psycho-spiritual problems. They are welcome signposts guiding us to the imbalances, dysfunction and causes of illness. Symptoms are not enemies to be silenced, but friends that can orient us in the maze of metabolic accommodations resulting from the collision of genes, environment, and lifestyle we call disease.

So how do we reorient ourselves to more effectively address

the biggest worldwide epidemic threatening our species, an epidemic that threatens our children and shortens our life expectancy for the first time in history?¹ One billion people worldwide are overweight; 300 million are obese. One in 3 children born today will have type 2 diabetes in their lifetime. The rates of diabetes are increasing exponentially, both in developed countries and in developing worlds. In 1985, an estimated 30 million people worldwide had diabetes. In 2000, 150 million were “afflicted.” It is estimated that by 2025, 350 million will have diabetes.² The World Health Organization (WHO) estimates that 2.5% to 15% of annual health budgets are spent on diabetes-related illnesses.³ Despite advances in diagnosis and pharmacologic therapies, the crisis continues unabated.

Perhaps we are thinking about the problem in old ways, and we need to reorient from treating the disease of diabetes and focus on the underlying metabolic dysfunctions that arise from lifestyle choices and cultural habits that destine a pharmacological approach for failure. Treating a patient who does not exercise; eats a nutrient-poor diet that includes white flour, refined sugars, and trans fatty acids, and that is low in fiber, omega 3 fatty acids, and phytonutrients; and who does not sleep enough with the latest peroxisome proliferator-activated receptor (PPAR) agonist or statin can be likened to pushing an enormous boulder up a mountain.

The diabetic constellation of hypertension, dysglycemia, dyslipidemia, visceral obesity, inflammation, oxidative stress, mitochondrial dysfunction, and coagulopathy is the tip of a much larger iceberg.⁴ While we may have to temporarily lower elevations in blood pressure, lipids or glucose, this cannot be our long-term strategy. We can chip away at the tip of the iceberg or dive deep to find the proximal causes rooted in our way of living, eating, sleeping, and moving our bodies, in the way we have left the source of the natural conditions that sustain life. Our ancestors did not need scientists, nutritionists, the media, or diet books to tell us what to eat to sustain human life. Unfortunately, we now need these things because we are lost in the supermarket forest, unsure of what items to hunt and gather to nourish our bodies appropriately.

We study each symptom or manifestation of disease in isolation, sometimes seeking to combine treatments in a new “polypill”⁵ (statin, beta-blocker, ACE inhibitor, aspirin, folate) that can reduce the burden of disease. This approach fails to recognize that thousands of variables and dynamic alterations in disease come from a very few original causes—this principle is the foundation of biological or functional medicine. The “poly-

meal” (wild salmon, wine, dark chocolate, almonds, fruits, vegetables, and garlic) might be a more effective and sensible solution with greater benefit.⁶

The simplicity of this perspective is founded in 2 guiding clinical notions. First, find and remove or correct the obstructions to normal biological function (and they are few—genes, dietary inputs, toxins, infections, allergens, and stress). Second, provide the more natural conditions (necessarily unique to each individual) for proper biologic and psycho-spiritual functioning (they are also few—quality protein, fat, carbohydrates, vitamins, minerals, phytonutrients, conditionally essential nutrients, water, air, sleep, rhythm, love, community).⁷ The name or definition of disease and the treatment of disease become less important than correcting the internal milieu that gave rise to symptoms. We cannot escape the exigencies of being born into the animal world, dependent on nature and each other in order to thrive.

SIDETRACKED BY THE NAME

A recent pair of editorials in the *American Journal of Clinical Nutrition* argued the merits and limitations of the various definitions of metabolic syndrome, a precursor to diabetes, and a significant disease risk factor unto itself. Gerald Reaven, the physician who first coined the term “Syndrome X,” later called “metabolic syndrome,” believes that while this appellation is useful in research, the concept has no clinical utility.⁸ It distracts, he says, from the more important task of identifying and treating each risk factor separately and aggressively—control the blood pressure, the lipid profile, the inflammation, the coagulopathy, and the glucose metabolism—and applies equally to metabolic syndrome or diabetes.

The World Health Organization, the Adult Treatment Plan III (ATP III), and the International Diabetes Federation all have different definitions of metabolic syndrome, including with varying importance abnormal fasting or post glucose load glucose, high-density lipoprotein (HDL) and triglyceride levels, blood pressure, and obesity or waist circumference. While this homogenization of definitions may have academic utility, it is not particularly helpful in working with the single patient in a clinical setting. The problem with names and labels is that they abort the thinking process. They abort thinking about the state of a person’s individual constitution—their unique genetic constellation interacting with their nutritional, immune, endocrine, or overall metabolic state—what has been referred to as the biological terrain or internal milieu. That terrain might be a better starting part for clinical disease management than attempting to match a patient to an existing or new International Classification of Diseases (ICD-10) definition. Many patients will not fit into the box of diagnosis. Some may have normal lipids or glucose but severe hyperinsulinemia, or central obesity, but normal glucose metabolism. They also may have different precipitating causes from dietary indiscretions to inflammatory or toxic etiologies layered upon a sea of genetic variation.

Grundy, in an accompanying editorial, makes the argument for an understanding that recognizes the interaction of all aspects of the “syndrome”—dyslipidemia, dysglycemia, hypertension, vis-

ceral obesity, inflammation, and coagulopathy—as a unifying principle that can help in early pattern recognition of metabolic derangement. Grundy reminds us that, “Whereas single-disorder organizations and sub-specialties may find it difficult to embrace risk-factor clustering as a new prevention paradigm, its reality makes a move in this direction virtually inevitable.”⁹ Perhaps treating the risk factors is less important than treating the patterns they form at their root.

Taken in isolation, any study—whether basic science or translational clinical research—provides a limited guide for clinical care. Yet when considered together, patterns, themes, principles, and guiding concepts emerge. The National Institutes of Health (NIH) New Roadmap initiative recognizes the importance of systems thinking, patterns, and networks of function in disease and health. And the NIH is supporting basic research in this area. Yet the gap between basic sciences, epidemiology, and clinical care is vast because our approach to chronic conditions like diabetes is focused on treating downstream effects, and not a comprehensive view of the causes and their remediation. If the disease is primarily a lifestyle, nutritional, and metabolic disorder, why do we seek new drugs or employ outdated dietary recommendations from organizations such as the American Diabetes Association, which ignores the reality that the content of food is equally important as the calories?

BEYOND THE NAME: SEARCHING FOR MEANING AND ORDER IN CHAOS

So what do we know about the causes of diabetes or metabolic syndrome? What do we know about the various factors that influence its expression? And what do we know about the ways to influence genes and metabolism that reorganizes the abnormal patterns of function that appear clinically—the hyperinsulinemia, dyslipidemia, inflammation, oxidative stress, mitochondrial dysfunction, coagulopathy, hypertension, and central obesity? Is there a way of thinking and treating the patient in the clinic that addresses all of these problems simultaneously without addressing any one of them individually or directly? The answer, I believe, is yes.

I propose that diabetes is a clinical model for a problem that is endemic to clinical medicine—treating the symptoms, not the cause—and that understanding how to improve the biological terrain; optimize nutrient status; improve gene expression through specific nutrients and phytonutrients; and regulate immunity and metabolism via lifestyle interventions such as diet, exercise, stress management, and adequate sleep collectively can have a much greater impact than any pharmacologic treatment.

What does the evidence indicate might play a role in the development of insulin resistance, metabolic syndrome, and type 2 diabetes? A key epidemiological study by Willett et al assessed the collective effects of an improved dietary pattern (low glycemic load, high cereal fiber,¹⁰ high polyunsaturated and monounsaturated¹¹ fatty acids, low trans fats); moderate to vigorous exercise 30 minutes per day; no current smoking; and the consumption of half an alcoholic beverage per day. It was esti-

mated that in the 84,941 women followed in the study, 91% of all diabetes could be prevented.¹²

There are hundreds more genes that help us adapt to starvation than to excess calories. Learning to influence gene regulation and expression through dietary, lifestyle, and environmental influences on PPAR and nuclear factor kappa binding (NFkB) and other key receptors and transcription factors is critical.

Over 35% of our calories come from 2 engineered foods foreign to human genes and biology—the genetically novel epic monocultures of corn and soybeans that infuse nearly all industrial foods produced through commercial agriculture or food processing.¹³ These industrial foods have untoward effects on human physiology and metabolism. They alter and become our cellular structure. Eating whole foods, native in design and beneficial to gene expression and cellular functioning is more sensible (and scientifically sound), than forming our cells and tissues of recently developed material that is biologically questionable.

The information in food and the science of nutrigenomics¹⁴ is a more useful guiding paradigm in the treatment of disease than understanding food as simply a source of energy, with all calories being equal in their metabolic effects. The research points in quite a different direction.

The quality and source of fat, carbohydrate, and protein qualitatively and quantitatively influences all the biological systems involved in insulin resistance and type 2 diabetes. Plant-based whole-food dietary patterns can prevent or even reverse underlying pathologies and metabolic dysfunction.¹⁵ Dietary fatty acid composition also plays a critical role—eliminating trans and saturated fats and increasing omega 3 and monounsaturated fats improves all parameters of diabetes and metabolic syndrome—the hyperinsulinemia, dyslipidemia, inflammation, oxidative stress, mitochondrial dysfunction, coagulopathy, hypertension, and central obesity.¹⁶ Carbohydrate quality is equally important—low-glycemic-load and -index carbohydrates with a high fiber content have similar benefit.¹⁷ Adequate protein nutrition also plays a role in glucose metabolism and can improve skeletal muscle function and reduce post-prandial lipids, insulin, and glucose and ghrelin secretions.¹⁸ Elimination of red meat from the diet improves microalbuminuria and fatty acid profiles in people with diabetes.¹⁹

Dietary fiber has salutary effects on weight, lipids, and glucose metabolism and is equivalent to sulfonylureas in lowering glycated hemoglobin.²⁰ Micronutrients such as chromium, zinc, magnesium, biotin, vitamin D, the B vitamins, and antioxidants also might play a key role in modulating the various components of metabolic syndrome.²¹ Conditionally essential nutrients such as lipolic acid, coenzyme Q10, and carnitine also play a physiologic role in metabolic syndrome.²² Phytonutrients such as the carotenoids,²³ almonds,²⁴ soy, and phytoestrogens²⁵ influence gene expression, favoring insulin sensitivity, and reduction in lipids, oxidative stress, inflammation and coagulopathy.

Other key lifestyle factors affect our metabolic equilibrium as well. Exercise alters skeletal muscle metabolism and improves glucose uptake, reduces low-density lipoprotein, raises HDL,

lowers blood pressure, and reduces inflammation and oxidative stress.²⁶ Autonomic dysfunction with sympathetic over-activity exacerbates insulin resistance and lipid and glucose metabolism and promotes central obesity.²⁷ Therefore, techniques to enhance parasympathetic and reduce sympathetic activity, such as yoga or meditation, can have protective or even therapeutic benefit in metabolic syndrome and diabetes.

While these therapies may have a small or limited benefit when studied in isolation, when taken together to approximate the more natural conditions, foods, and activities with which we evolved, they can dramatically help prevent and treat the sentinel disease that is a central cause of the accelerating epidemic of degenerative diseases including cardiovascular, neurodegenerative, and neoplastic conditions that afflict our aging population and our children. Disease is not a natural consequence of life to be accepted, but a reflection of the loss of the natural and evolutionary conditions necessary for self-regulation and healing. It is the body's best attempt to restore balance given a difficult set of circumstances. Learning to restore our capacity for self-regulation and metabolic equilibrium is the hope of the next generation of medical scientists and practitioners.

REFERENCES

1. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med.* 2005;352(11):1138-1145.
2. International Diabetes Federation. Diabetes prevention. Available at: <http://www.idf.org/home/index.cfm?node=264>. Accessed July 20, 2006.
3. International Diabetes Federation. The costs of diabetes. Available at: <http://www.idf.org/home/index.cfm?unode=3B9691D3-C026-2FD3-87B7FA0B63432BA3>. Accessed July 26, 2006.
4. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA.* 2002;287(19):2570-2581. Review.
5. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ.* 2003;326(7404):1419.
6. Franco OH, Bonneux L, de Laet C, Peeters A, Steyerberg EW, Mackenbach JP. The Polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. *BMJ.* 2004;329(7480):1447-1450. Review.
7. Hyman M, Baker SM, Jones DS. Functional medicine and biochemical individuality: a paradigm shift in medicine. In: Jones DS, Quinn S, eds. *Textbook of Functional Medicine*, Gig Harbor, Wash: Institute for Functional Medicine; 2006:55-63.
8. Reaven GM. The metabolic syndrome: is this diagnosis necessary? *Am J Clin Nutr.* 2006;83(6):1237-1247.
9. Grundy SM. Does a diagnosis of metabolic syndrome have value in clinical practice? *Am J Clin Nutr.* 2006;83(6):1248-1251.
10. Montonen J, Knekt P, Jarvinen R, Aromaa A, Reunanen A. Whole-grain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr.* 2003;77(3):622-629.
11. Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. *Am J Clin Nutr.* 1998;67(3):577S-582S.
12. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med.* 2001;345(11):790-797.
13. Pollan M. *The Omnivore's Dilemma*. New York: Penguin Press; 2006.
14. Phillips C, Lopez-Miranda J, Perez-Jimenez F, McManus R, Roche HM. Genetic and nutrient determinants of the metabolic syndrome. *Curr Opin Cardiol.* 2006;21(3):185-193.
15. Jenkins DJ, Kendall CW, Marchie A, et al. Type 2 diabetes and the vegetarian diet. *Am J Clin Nutr.* 2003;78(3):610S-616S. Review.
16. Salmeron J, Hu FB, Manson JE, et al. Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr.* 2001;73(6):1019-1026.
17. Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am J Clin Nutr.* 2004;79(5):774-779.
18. Gannon MC, Nuttall FQ, Saeed A, Jordan K, Hoover H. An increase in dietary protein improves the blood glucose response in persons with type 2 diabetes. *Am J Clin Nutr.* 2003;78(4):734-741.
19. de Mello VD, Zelmanovitz T, Perassolo MS, Azevedo MJ, Gross JL. Withdrawal of red meat from the usual diet reduces albuminuria and improves serum fatty acid profile in type 2 diabetes patients with macroalbuminuria. *Am J Clin Nutr.* 2006;83(5):1032-1038.
20. Chandalia M, Garg A, Lutjohann D, von Bergmann K, Grundy SM, Brinkley LJ. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med.* 2000;342(19):1392-1398.
21. Triggiani V, Resta F, Guastamacchia E, et al. Role of antioxidants, essential fatty acids,

carnitine, vitamins, phytochemicals and trace elements in the treatment of diabetes mellitus and its chronic complications. *Endocr Metab Immune Disord Drug Targets*. 2006;6(1):77-93. Review.

22. Henriksen EJ. Exercise training and the antioxidant alpha-lipoic acid in the treatment of insulin resistance and type 2 diabetes. *Free Radic Biol Med*. 2006;40(1):3-12. Review.
23. Coyne T, Ibiebele TI, Baade PD, et al. Diabetes mellitus and serum carotenoids: findings of a population-based study in Queensland, Australia. *Am J Clin Nutr*. 2005;82(3):685-693.
24. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. *JAMA*. 2002;288(20):2554-2560.
25. Bhathena SJ, Velasquez MT. Beneficial role of dietary phytoestrogens in obesity and diabetes. *Am J Clin Nutr*. 2002 Dec;76(6):1191-1201. Review.
26. Klein S, Sheard NF, Pi-Sunyer X, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies. A statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Am J Clin Nutr*. 2004;80(2):257-263. Review.
27. Rosmond R, Dallman MF, Bjorntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. *J Clin Endocrinol Metab*. 1998;83(6):1853-1859.