THE REAL ALTERNATIVE MEDICINE: RECONSIDERING CONVENTIONAL MEDICINE

Mark A. Hyman, MD

Mark A. Hyman, MD, is the Editor-in-Chief of *Alternative Therapies in Health and Medicine*. (*Altern Ther Health Med*. 2005;11(5):10-12.)

Reductionism is the primary and essential activity of science. Also crucial are synthesis and integration, tempered by philosophical reflection on significance and value ... . To make any progress [researchers] must meditate on the hidden design and forces of the networks of causation.

—E.O. Wilson, *Consilience: The Unity of Knowledge*

Sarah, a single, 29-year-old, nulliparous woman who had been recently diagnosed with moderate to severe cervical dysplasia, cervical inflammation, and human papillomavirus (HPV) consulted me for an "alternative" opinion. After multiple culposcopies, her physician recommended a loop electrosurgical excision procedure (LEEP) to treat the precancerous changes in her cervix. To a young, single woman without children, the risk of cervical incompetence and any threat to her future fertility was unacceptable.

Other than a history of recurrent cystitis, persistent urinary frequency, multiple courses of antibiotics and subsequent yeast vaginitis, the patient had an unremarkable medical history. She worked in Africa in development, had no history of tropical illnesses, and ate a diet of fish, vegetables, and fruits and little sugar, caffeine, or alcohol. She was a non-smoker. There was no history of previous sexually transmitted disease, nor any family history of reproductive or breast cancers. The appropriate conventional approaches to her pathology included cryotherapy, LEEP, or laser treatments. The "alternative approach" did not focus on removing the pathology, but on identifying and correcting functional, genetic, and molecular imbalances.

LOOKING BEYOND PATHOLOGY

Modern medicine is like taking your car to a mechanic who has no idea what's under the hood and is trying to fix the car based on listening to the noises it makes.

—Eric Lander, Whitehead Institute/MIT Center for Genome Research

Pathology is immediately evident upon culposcopic or pathologic examination of tissues; abnormal function and genetic antecedents are often less clear. Proper pathological assessment is essential, but identification of pathology and identifying the "diagnosis" is *the beginning* of the analysis, not the end. "Good medicine" goes beyond the pathological diagnosis to define the mechanisms underlying the origin of the dysfunction. Rather than asking, "What is the pathology?" we asked a different set of questions: "What cellular processes are involved in dysplasia? What genetic polymorphisms may contribute to the abnormal phenotype of dysplasia? What are the biochemical and metabolic indicators or biomarkers of the abnormal function that precede or co-exist with pathology, and how can they be used to guide therapy and follow clinical progress and risk? Can these biomarkers be identified and a preventive therapeutic plan be implemented before the development of cellular atypia? What hormonal milieu initiated or fostered dysplasia? Can any interventions modify the expression of cellular, biochemical, and genetic factors that are the preconditions for pathology? What clinical markers reflect improved function and reduced risk? Do those correlate with reversal of pathology? What biochemical, basic science, observational, and clinical data support an integrative approach to normalize function?"

These questions are not new to medicine, or antithetical to conventional training. In fact, they are the basis of pre-clinical training in medicine and were relegated to the recesses of awareness when biochemistry and genetics found little intersection with clinical training during the transition from the classroom to the hospital. Yet for the first time, the practice of medicine can embrace the concept that abnormal biochemistry (often a product of the environment influencing gene expression, proteins, and metabolic functions) is *always* the antecedent to observed pathology. In the first chapter of the revered medical canon of pathology, *Pathologic Basis of Disease*, Robbins and Cotran counsel the neophyte physician on the origins of pathology and the key pathologic processes that must be considered in any disease.[1]

Four intracellular systems are vulnerable to biochemical injury: a) adenosine triphosphate (ATP) production, b) maintenance of cell membrane integrity, c) synthesis of enzymatic and structural proteins, d) preservation of integrity of genetic apparatus of the cell. The structural and biochemical elements of the cell are so closely related that whatever the precise point

of initial attack by the damaging agent, injury at one locus leads to wide ranging secondary effects ... . The morphologic changes of cell injury become apparent only after some critical biochemical system within the cell has been deranged."[1]

The message is simple: form always follows function, disease follows disturbed biochemistry, and phenomenology follows physiology. What we can see with a microscope, an x-ray, or conventional blood tests are late smoke signals along the trajectory from dysfunction to disease. They are the noises our body makes when something is already out of balance. Treating the noises will not prevent the problem, nor correct the cause of the noises. A tumor or atypical cells are late manifestations of alterations in biochemistry and gene expression. Waiting for observed pathology is no longer necessary. Searching for, identifying, and correcting the deviations from ideal function through identification of biomarkers and genomic variations will make our current approaches to the treatment of existing pathology seem medieval. The tools to understand biochemistry, physiology, and function, though still rudimentary, have evolved beyond the theoretical to the practical.

We must understand the common roots to all pathology described by Robins and Cotran—altered mitochondrial bioenergetics, alterations in form and function of the complex phospholipid interface or membrane that surrounds all cells, the expression and performance of enzymatic proteins, the proper assembly, maintenance, repair, and regeneration of structural proteins, and lastly and perhaps most importantly, the variations in expression, function, and integrity of genes. How can this framework for thinking about disease and health be relevant to daily clinical practice? If we rely on the diagnostic and therapeutic tools at the disposal of conventional medicine—pathology, pharmacology, or surgery—then navigation is difficult, and the outcomes, although they may prevent cervical cancer as LEEP may have done in Sarah's case, they do not address the underlying biochemical or genetic factors that lead to the observed pathology. How, then, can a functional approach be a navigational instrument for restoring balance and enhancing or facilitating the activities of energy production, membrane integrity, cell communication, protein function, and gene expression and repair?

The human genome project provides a lens to view function in a new light. Collins et al lamented that despite our extensive knowledge of pathology and disease, our understanding of normal function and how to facilitate healing and repair are inadequate. "An understanding of the major pathways involved in normal homeostasis must be developed along with how those pathways are deranged in illness ... . Many of those will come as a surprise, since the current molecular understanding of most common diseases is rather limited."[2]

THE CAUSE OF THE NOISES: LOOKING UNDER THE HOOD

After asking Sarah different questions and after exploring hormone metabolism, nutritional status, and genetic polymorphisms, a picture emerged of the antecedents to her dysplasia—the altered biochemical and hormonal pathways that led to the pathology and the interventions that could restore normal homeostasis, improve hormone metabolism, reduce inflammation, and enhance gene expression. The outcome, a reversal of dysplasia and improvement of the biochemical and molecular markers of altered function, can all be clinically monitored.

In Sarah's "conventional" laboratory evaluation, which often reflects end stage pathology, homocysteine, C-reactive protein, methylmalonic acid, serum chemistry, complete blood count, and urine analysis were all normal.

Her "alternative evaluation" was designed to identify predisposing factors (genomics) and function. Nutritional assessment revealed a deficiency of vitamin D[3] and pyridoxine (important in methylation and DNA repair).[4] Assessment of her genome revealed a number of single nucleotide polymorphisms (SNPs) that are antecedents of abnormal methylation, detoxification, and estrogen metabolism, all of which may contribute to dysplasia.[5] Cytochrome (CYP) 1B1 variations alter estrogen metabolism and hormonal cancer risk, as do polymorphisms of catechol-o-methyltransferase (COMT).[6] These influence the hydroxylation and methylation of estrogen. Sarah carried polymorphisms in both CYP 1B1 and COMT, which increase cancer risk. In addition, she carried polymorphisms that impair glutathione function (GSTM1),[7] methylation (MTHFR),[8] and regulation of oxidative stress (superoxide dismutase 2 [SOD2] and CYBA*8. Sarah's lipid peroxides (oxidized lipids) were significantly elevated and represented the phenotypic expression of SNPs' regulating redox balance.[9,10] Peripheral markers of oxidative stress, including circulating lipid peroxides, are associated with increased risk of dysplasia and cervical cancer.

A 24-hour urinary estrogen metabolism analysis revealed a low 2-hydroxyestrone:16-hydroxyestrone ratio, which is correlated with increased breast and cervical cancer risk. She also had significantly elevated levels of catechol estrogens, which promote cervical and hormonal cancers. Urinary organic acids revealed an elevated dihydroxyphenylproprionate (DHPPA), a clostridial metabolite that reflects intestinal clostridial overgrowth. Clostridial bacteria produce the estrogen deconjugating enzyme β glucuronidase. This deconjugates the excreted estrogens, making them available for enterohepatic recirculation and increased toxicity.

Sarah's treatment was based on a rational, functional approach to improve gene expression, optimize methylation and DNA repair enzymes, enhance glutathione reserves and detoxification, reduce oxidative stress and normalize intestinal microecology, and up-regulate anti-cancer 2-hydroxylation of estrogens. The tools were modification of the environment, diet, and supplementation based on current scientific evidence, and based on 2 ancient Hippocratic principles: "first do no harm," and "leave your potions in the chemist's crucible if you can heal your patients with food."

Specific recommendations included elimination of alcohol to reduce abnormal estrogen metabolism; increased intake of cruciferous vegetables to facilitate 2-hydroxylation of estrogen, and

up-regulation of GSTM1 because glutathione conjugation is a key step in the detoxification of estrogens; garlic, onions to improve sulfation; increased fiber to reduce entero-hepatic circulation of estrogens;[11] ground flax seeds to promote the intestinal production of enterolactones that reduce hormone-dependent cancer risk; and to drink filtered water and eat organic food when possible to reduce xenoestrogen exposure. Exercise and a reduction in refined sugars help promote improved hormonal metabolism through central and peripheral effects on insulin activity.

Supplementation was designed to improve methylation through high-dose folate (5 mg) and B_{12} (2,000 mcg sublingual);[12] optimize detoxification of estrogen to 2 hydroxyestrone with indole-3 carbinol[13] (a phytonutrient from the cruciferous vegetable family); and enhance the production of glutathione[14] and the activity of glutathione-recycling enzymes through n-acetylcysteine, a lipoic acid, silymarin, and selenium.[15] To optimize vitamin D status 2,000 U a day of vitamin D_3 was prescribed.[16] A multivitamin and mineral supplement were also prescribed. Fluconazole was used to reduce vaginal yeast overgrowth. Probiotics were used to improve intestinal micro-ecology and reduce the entero-hepatic circulation of estrogens.[17]

After 2 months of treatment, Sarah's culposcopic examination returned to normal, and pathologic assessment no longer identified a "diagnosis."

The approach to the patient and to a particular clinical problem must allow clinicians to integrate the fundamental change from a disease-based model of diagnosis and treatment to a function-based model. The key features of the old and new models of inquiry and treatment help clarify the radical divergence in approaches. The old paradigm—what I consider the "real alternative medicine"—is based on the reductionistic framework of the differential diagnosis. This approach attempts to eliminate confounding variables in history taking and to discard symptoms or findings that are peripheral to or unexplained by a single diagnosis. The holy grail of the old model is identifying the unique name to fit a collection of symptoms. The name of the disease is the ultimate goal, followed by confirmatory laboratory or imaging studies, with treatment focused on symptom suppression or inhibition or the blocking of the physiologic processes or mediators involved in the disease.

The new model—and what should be "conventional medicine"—is based an etiologic and causative evaluation, inclusive of all variables attempting to identify hidden patterns and connections. A new organization and architecture of thinking is required based on genomics and function. Diagnosis is merely a waypoint in the process of inquiry. The new lenses for interpreting the same symptoms employ the emerging paradigm underlying the chemical, physical, biologic, and social worlds: systems, complexity, and chaos theory. New questions identify antecedents, triggers, mediators, and the influence of genetics, the environment, and mechanisms on illness. Testing is focused not on identifying pathology, but on seeking to uncover causes, mechanisms, and deviations from optimal function. These new navigational and diagnostic tools are used to evaluate toxins, allergens, infections, and biologic function (nutritional status, immune function, detoxification, oxidative stress, and hormonal function). Therapy is guided by 2 principles: removing underlying causes and restoring normal function. The new therapeutic tools include diet, movement, mind-body techniques, nutraceuticals, herbs, other complementary and alternative modalities, pharmaceuticals, and surgery designed to address causes and enhance function. The allopathic (the real alternative) approach uses substances that interfere with or block normal or abnormal physiologic function. A functional or integrative approach (what should be considered conventional medicine) employs methods or substances to remove impediments to health and to support and create health.

The question in Sarah's case is, "Which approach—surgical excision of abnormal cells or the removal of the impediments to healing and the optimization of the biochemical and metabolic conditions necessary for cell repair and function—is the best approach to her problem?"

Voltaire once said that "Doctors are men who prescribe medicines of which they know little to cure diseases of which they know less for human beings of which they know nothing." Perhaps we are entering a new era of medicine in which Voltaire's sentiments no longer reflect the knowledge or tools of physicians.

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