# IS THE CURE FOR BRAIN DISORDERS OUTSIDE THE BRAIN?

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Attention deficit hyperactivity disorder (ADHD) is a label we now give 8.7% of children between the ages of 8 and 15 years.[1] Over 8 million, or 1 in 10, children now take stimulant medications like methylphenidate (Ritalin).[2] From 1987 to 1996 the use of these medications increased 400%. Autism now affects 1 in 166 children and has increased 11-fold over the last decade.[3] Learning disabilities affect between 5% and 10% of school-age children.[4]

Major depression has a lifetime prevalence of 1 in 10.[5] Alzheimer's disease will affect 30% of people over 85 years old, which is the fastest growing segment of the population. The prevalence of Alzheimer's is expected to increase 3-fold by 2050, at an annual cost of $83.9 billion.[6]

Psychiatric or psychotropic medications are the number 2–selling class of prescription drugs.[7] This includes medication for depression, bipolar disease, anxiety, panic disorder, posttraumatic stress disorder, psychoses, attention deficit disorder, autism, Alzheimer's, and more. Taken as a whole, these conditions pose a significant burden to society in terms of individual suffering, loss of optimal social functioning, and economic costs.

Could it be that we are looking in the wrong place for the answers to our epidemic of neurological and psychiatric disorders? Could it be that our psychotropic medications attempt to control the smoke while ignoring the fire?

Could it be that these are, in fact, not primary brain disorders at all, but systemic disorders that affect the brain?[8] And could it be that therapies primarily aimed at altering brain function through antidepressants, stimulants, anti-psychotics, and seizure medications may miss the primary mechanisms or disturbances that manifest as behavioral, mood, or neurologic symptoms?

I suggest that the communication between the brain and the body is bi-directional and that although mind-body medicine has been studied and accepted as legitimate,[9] it provides only a one-dimensional view of the interaction between brain and body.

The conclusion from the science is irrefutable and must be heeded to effectively address the epidemic of "brain" diseases—mood disorders, attention deficit disorder, autism, psychoses, Alzheimer's, Parkinson's, and other neurodegenerative disorders. Unless we focus on the metabolic, nutritional, and environmental influences that exert their effects on the brain through the body, we will not succeed in our efforts to promote mental and cognitive well-being.

The next frontier is the delineation and analysis, as a whole, of all the aspects of "body" dysfunction or imbalance that lead to abnormal neurochemical signaling, altered behavior and mood, and neurodegeneration. Scientists have been skirting the edges of this frontier, discovering relationships and patterns that connect the pieces of the puzzle, but the larger picture formed by those puzzle pieces has remained unclear. Synthesizing the patterns in the research and forming and testing clinical hypotheses based on these patterns are essential for the next step in the evolution of psychiatry and neurology that can illuminate the false dichotomy between the brain and the body.

What is emerging is a model that incorporates understanding of the role of nutritional deficiencies, hormonal imbalances, inflammation, altered immunity, toxins, oxidative stress, mitochondrial dysfunction, altered cell bioenergetics, and digestive dysfunction in altered behavior, mood, and brain function.

It is only by teasing apart how each of these fundamental physiological processes alters brain function and studying how correcting them can restore normal function that a new model of psychiatry, neurology, and clinical neuroscience can emerge that provides more satisfactory answers than only partially effective pharmacologic treatments.

The paradox is that the answer will not be found in the detail of any one pattern or system of physiologic disturbance. It is only in the putting together of all the pieces of the puzzle, in the assessment and treatment of all disordered systems (nutritional, hormonal, inflammatory, immune, toxic, metabolic, digestive, oxidative) simultaneously that true advances can occur. Single agent or modality interventions are destined to fail. The nature of biology is that of a system, one whole, interdependent, interconnected system. And that, by nature, is complex and resists the linear analysis common to most research methodologies.[10] New methodologies must be developed to research the clinical application of systems biology.[11]

We must understand the role of altered gene expression

patterns and the resulting disturbances in systemic molecular signaling and physiologic and biochemical function that are responsible for much of the accelerating prevalence of psychiatric and neurologic morbidity today.

**CASE REPORT: HOW THE BODY INFLUENCES THE BRAIN**

A clinical vignette will serve to illustrate how this model might take form in the treatment of real patients. The wonder of the body continues to delight and amaze me, as I understand more clearly how the entire body is one interacting, interlocking, networked system. Nowhere is this truer than in how the brain is connected to the rest of the body.

This is a story about one boy, but his story is repeated millions of times over in America. Each story has its personal flavor, and each child may have different imbalances in physiology. But the overarching principle remains the same: that brain dysfunction resulting in altered mood, memory, and attention is a result of systemic disorders that affect that brain. This one story will clarify more than a detailed exploration of the neurotransmitters and biochemical pathways involved in the bi-directional communication between the brain and the body, many of which have not yet been delineated.

This story is about a 12-year-old boy, "Jayson," who was brought to my office by his mother. He had ADHD, behavioral problems, and severe dysgraphia, though he excelled in math. He also suffered many physical problems for which his doctors had treated him. These included asthma, "environmental" allergies, sinus congestion, postnasal drip, sore throats, eczema, pale skin, nausea, stomach pain, diarrhea, frequent headaches, anal itching, canker sores, myalgias, muscle cramps, hypersensitivity to noises and smells, poor sleep, and trouble breathing at night. He complained of frequent sneezing, hives a few times a week, and itchy skin. He also suffered from anxiety, fearfulness, and carbohydrate cravings. In most realms of psychiatry, these "physical" problems are irrelevant, marginal, and unhelpful in guiding diagnosis and therapy of his "brain" disorder or ADHD. Yet, I suggest, they are the most relevant findings in his history and provide the clues to navigating his disordered brain function.

He was born at 7 lbs, 10 oz at term via a difficult vaginal birth and was treated for hyperbilirubinemia. He was breastfed for 10 months. He had a "sensitive stomach" as an infant and needed soy formula. He was introduced to gluten before he was 1 year old.[12] He was prone to diaper rash, had sensitive skin, and received frequent antibiotics for otitis media as a toddler. He received the full complement of childhood immunizations and annual influenza vaccines.

As a child he developed asthma, eczema, and hyperkeratosis pilaris and suffered a concussion at age 5. He repeated kindergarten because of attention and behavioral difficulties and was put on methylphenidate from first to fourth grade. Off the medication, he gained weight but increased his intake of junk food, sugar, and deli meats. He always had severe dysgraphia. He stopped the stimulant after fourth grade because of growth retardation. He continued to have trouble focusing in school, "zoned out," was disruptive, and had never had a positive teacher report. And his handwriting, as is common in children with ADHD or on the autistic spectrum disorder, was nearly illegible.

All of these symptoms were being treated with medication, but he didn't experience relief from his physical or behavioral symptoms.

His father is in good health, and his mother suffers from chronic migraines, sinusitis, and food allergies. His sister has mild allergies.

His house had severe mold infestation, which was aggressively addressed during his treatment. His diet consisted of eggs and bacon for breakfast; deli meats, cookies, peanut butter crackers, carrots, and lemonade for lunch; and his dinner was pizza, pork, or chicken, broccoli, green beans, and rice. He also frequently ate candy, cookies, and ice cream.

His conventional medical therapy included an optimal, well-designed cocktail of medications—cetirizine (Zyrtec), an antihistamine; an albuterol and levalbuterol inhaler (Xopanex) for his asthma; flunisolide (Nasarel), a steroid nasal inhaler for allergies which inhibits growth in children[13]; cimetidine (Tagamet), a stomach drug used as an antihistamine, which inhibits B-vitamin and magnesium absorption; and acetaminophen (which depletes glutathione)[14] and ibuprofen (which increases intestinal permeability)[15] for his myalgias and headaches.

This was quite a pharmacopoeia for a 12-year-old boy, and his physical, mental, and behavioral symptoms still were not under control. Even his prior treatment with methylphenidate did not significantly help his school performance or behavior or "cure" his ADHD (or the label or ICD-9 code we give children who can't pay attention, are impulsive and distractible, and can't function well at home, in school, or with friends).

The desire to treat is understandable given the suffering, but our conventional tools are limited. They include stimulants, antidepressants, anti-psychotics, and anti-seizure medication, many given as untested cocktails for "off-label" indications. As physicians we feel we must do something to help these children, so we do the best we can. As parents we take them to the doctor, who also wants to help and gives the child the only thing he or she knows how—medications.

And now the list of medications and cocktails and combinations has grown to frightening proportions. These children now get anti-psychotic medications like risperidone (Ripserdal); antiseizure medications like oxycarbazepine (Trileptal); and antidepressants like fluoxetine (Prozac)—all on top of their stimulant medications like methylphenidate (Ritalin, Concerta); dexmethylphenidate (Focalin); and Adderall (dextroamphetamine/amphetamine composite). And the drugs pile on and on.

Is this the right approach? Is there another way to help children deal with the social, behavioral, and academic challenges that arise from this problem? And why are we seeing such an epidemic in our society?

Is it possible that our nutrient-poor, trans fat– and sugar-rich diets, high in food additives[16] could lead to the epidemic of behavioral, mood, attention, and neurodegenerative disorders?

Could the increasing load of environmental toxins influence mood, attention, behavior, and memory?[17]

Is there a different way to approach diagnosing and treating these children that recognizes that the brain is affected by the body? Is there a way to use clues from the whole body to figure out what to do?

I suggest there is a new, more effective approach available now, but it is not widely understood or applied. It is an effective, scientifically founded, systematic way of thinking about health and behavioral problems that directs us to the causes of the problem and helps us use tools and treatments to not just cover over the symptoms with cocktails of pharmaceuticals but to correct the root of the problems.

The details of Jayson's story are so important because hidden in the story are the clues to the origins of his illness and the seeds of his recovery. His "psychiatric" history included every one of his symptoms, all of which formed pieces of the puzzle, from rectal itching to eczema and headaches to dysgraphia as well as his behavioral symptoms. We can no longer assume the brain functions independently of the body. Yet this is the fundamental paradigm that governs current psychiatric assessment and treatment. It is reminiscent of previous and erroneous assumptions that autism and schizophrenia were the result of poor parenting.

Within medicine there is a pejorative nod to the theory that the mind can influence the body through psychosomatic influences. But "somato-psychic" medicine is hardly on the radar. The notions that the body can influence the brain; that mood, behavior, and attitude are primarily influenced by nutritional status, food allergies, toxins, or digestive or immune imbalances; and that psychiatric or neurologic diseases can be treated, not by psychotropic medication, but by altering the internal milieu in which the brain functions, are resisted by conventional psychiatry and neurology. Perhaps the greatest myth of neurology is the impenetrability of the blood-brain barrier. It is permeable and communicates with the rest of our physiology and biochemistry through newly mapped mechanisms.[18]

## A NEW ROAD MAP: THINKING AND LINKING RATHER THAN NAMING AND BLAMING

Our typical conventional methodology focuses on the differential diagnosis: naming the condition or conditions that result in signs and symptoms and then treating each ICD-9 diagnosis with distinct and separate medications. In effect, once the diagnosis is made, analysis ceases, and the drug is matched to the disease. Stimulants for ADHD, inhalers for asthma, antihistamines for hives, analgesics for headaches, steroid inhalers for "environmental allergies" or postnasal drip. Stomachaches, sensitivity to loud noises, muscle aches, and insomnia are all attributed to "stress," and a sedative or psychotherapy is prescribed.

But taken as a whole, thinking systemically, associations and patterns can be discerned, and therapeutic strategies based on this hypothesis can be generated that attempt to address primary causes.

Jayson's symptoms could be assembled into new categories that are the root of clinical symptoms. Here is how we might invite all elements of his condition, not solely the behavioral or psychiatric symptoms, into his assessment and treatment. Here is how we might reorganize our thinking.

He manifested multiple immune and inflammatory imbalances (asthma, allergies, hives, sinusitis, itchy skin, a history of intolerance to formula, diaper rash, frequent otitis media as a toddler, a family history of allergies). These would not be seen as separate conditions but rather as an activated immune response to some trigger—food or environmental allergy, infection or toxin, or a combination. Aphthous stomatis may be indicative of celiac disease or gluten intolerance.[19] Seeking and treating those triggers might be expected to relieve his symptoms. Perhaps even his neurologic and behavioral symptoms could be influenced by what might be termed a "brain allergy."[20,21]

Nutritional deficiencies or imbalances can explain some symptoms. Headaches, insomnia, muscle spasms, cramps, and hypersensitivity to noise suggest magnesium deficiency.[22] Hyperkeratosis pilaris may indicate deficiencies in vitamin A or omega 3 fatty acid.[23] His poor diet that included trans fats, food additives, and abundant sugar and refined carbohydrates has been associated with ADHD.[24] His dietary history indicated the risk for essential fatty acid deficiency—also associated with eczema and immune deficiency, as well as ADHD.[25] Zinc deficiency could explain frequent infections, eczema, and allergies.[26] Mood disturbances, sleep disruption, and ADHD may suggest pyridoxine or $B_6$ deficiency, which can occur as the result of medication side effects.[27]

Frequent nausea, diarrhea, and stomachaches suggest digestive imbalances. His history of a "sensitive stomach," frequent antibiotics, and anal itching suggests yeast overgrowth and altered gut flora leading to increased intestinal permeability and systemic allergy, inflammation, and food allergy.[28]

And his severe dysgraphia and behavioral symptoms suggest neurotransmitter and neurohormonal imbalances. The imbalances may be reflective of birth trauma as indicated by his "difficult birth" or head trauma (his concussion) or through systemic influences modulated through inflammatory, immune, toxic, nutritional, and digestive imbalances. Heavy metal toxicity also can affect cognitive and immune function.[29] His full complement of immunizations and influenza vaccines containing thimerosol increase his risk for mercury toxicity.

He also had mild lead toxicity, an indication of toxicity and impaired detoxification. Lead toxicity has been associated with cognitive and behavioral problems in children.[30] Lead toxicity and environmental toxins also have been linked to ADHD in a recent study.[31]

Thus a new road map emerges, one not based on ICD-9 disease classification but on underlying core interlocking physiological systems that, in fact, underlie all disease.[32] No one element can explain Jayson's constellation of symptoms, but his particular puzzle tells a unique story when taken as a whole. And while there may be similar patterns in children with ADHD, his pattern

is unique. Another child with ADHD might have different imbalances and require different diagnostics and therapies.

His diagnostic assessment supported these hypotheses and imbalances. His IgG antigliadin antibodies were 17 units (normal <19 U), though his tissue transglutaminase antibodies were low. His complete blood count was normal, with a white blood cell count of 6.4 (1000/mL), but his lymphocyte count was higher than his neutrophils count, which often is indicative of yeast or viral infection. He had mild thrombocytosis. His vitamin D was low, at 30 ng/mL. His homocysteine was normal, at 6.2 µmol/L. His red blood cell magnesium and zinc were low, at 35 and 4.9 parts per million packed cells, respectively. His vitamin E was low, at 8.3 mg/L and his beta-carotene nearly undetectable, at <0.2 mg/L. Amino acid analysis revealed low tryptophan, which is important for mood stability as well as sleep. His fatty analysis showed high levels of linoleic and arachidonic acid and all saturated and trans fats, with deficiencies of the omega 3 fats eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA). Urinary organic acids showed elevated kyurenate, reflective of $B_6$ deficiency. IgG food sensitivity revealed 18 reactive foods, including dairy, peanuts, yeast, and citrus. A post 2,3-Dimercapto-1-propanesulfonic acid (DMPS) provocation challenge showed elevated lead of 17 mg/g creatinine.

These findings confirmed suspicion of nutrient deficiencies (zinc, magnesium, $B_6$, vitamin D, vitamin E, beta-carotene, tryptophan, essential fatty acids) with elevated omega 6, saturated, and trans fats. He also had IgG food sensitivities, borderline elevation of anti-gliadin antibodies, and altered lymphocyte:neutrophils ratio, indicative of yeast overgrowth. Low tryptophan may relate to irritability, anxiety, and sleep disturbances. Tryptophan is a precursor to serotonin and melatonin, whose conversion is facilitated by $B_6$ (pyridoxine). He also had mild lead toxicity.

These are not "incidental" findings but critical and essential indications of disordered immune, nutritional, digestive, toxic, and neurochemical status. Not only are they relevant, they are also the real reasons we are seeing an epidemic of psychiatric and neurologic disease. Noxious influences such as a diet poor in nutrients but rich in additives and sugar, overuse of antibiotics, early introduction of gluten and dairy proteins in infancy, environmental toxins, and others all interact with a susceptible genome to collectively alter the landscape of the mind.

The problem is clearly not a Ritalin deficiency or bad parenting!

Jayson's treatment was disarmingly simple. Eliminate noxious influences and allergens and treat microbial imbalances through recommending a whole-foods diet free of additives, sugar, trans fats, processed foods, and his particular reactive foods—gluten, dairy, citrus, peanuts, and yeast—as well as treating yeast overgrowth (supported by his history of antibiotics, anal itching, and relative lymphocytosis) with fluconozole. His lead toxicity was not initially addressed.

He was then given the raw materials for normal cellular, enzymatic, and biochemical functioning: a multivitamin, additional zinc, magnesium glycinate, pyridoxal-5-phosphate, omega 3 fatty acids, vitamin D3, 5-hydroxytryptophan, and a broad-spectrum probiotic. He was later treated with DMSA for his lead toxicity.

At his follow-up visit 2 months later, he had stopped all his medications, including his antihistamines (cetritizine and cimetidine), bronchodilators, steroid inhaler, acetaminophen, and ibuprofen. His mood and behavior were back to normal, including his attention; his disruptiveness, irritability, and anxiety were gone. His hives, asthma, rhinorrhea, anal itching, stomachaches, nausea, diarrhea, headaches, muscle cramps, and sensitivity to loud noises all completely resolved. He was sleeping at night. He found himself for the first time in his life free from all his chronic symptoms and, more importantly, succeeding in school, socially and academically.

Jayson did not have a neurologic or psychiatric disease but rather nutritional imbalances, toxicity, and altered immune and digestive function. Treating those root causes and correcting the imbalances led to the resolution of his symptoms.

These findings, though impressive, could be dismissed or explained away by skeptics. One irrefutable finding, however, underscores the effectiveness of this approach. His dysgraphia completely resolved within 2 months of therapy (Figures 1 and 2).

His mother's e-mail report on her meeting with his school underscored his transformation:

> *We had a 504 meeting at Jayson's school this morning (where the teachers, school counselor, parents, and principal all get together to review "the plan" for kids with special educational needs—in Jayson's case prompted by the ADHD diagnosis). This was the first time in his entire schooling history that everything seems to be going well. The input from his teachers was that he is "a different kid" than they saw in the first half of the year and that they're amazed by the difference. The school nurse hasn't seen him since March (and he used to be in her office several times a week). The school psychologist said his social skills are very good, age appropriate, and that she sees no problems at all. She also noted that Jayson seems very proud of himself and his new health and that he's taking good ownership of all the changes in his diet. He even seems to be shrugging it off when the other kids at school tell him he's an "alien" because he doesn't drink soda.*
>
> *This was just such a fantastic meeting and I wanted to pass along the good news and say Thank You!*

This is not an isolated anecdote but a story repeated over and over in medical practices focused on systems or functional medicine. This case suggests that priority be given to research that teases out the subtleties of the clinical application of systems biology and the environmental influences and genetic influences that are at the root of our epidemic of psychiatric and neurologic diseases rising at alarming rates and whose morbidity is second only to obesity in children.

An unpublished review of the effectiveness of pharmaceutical

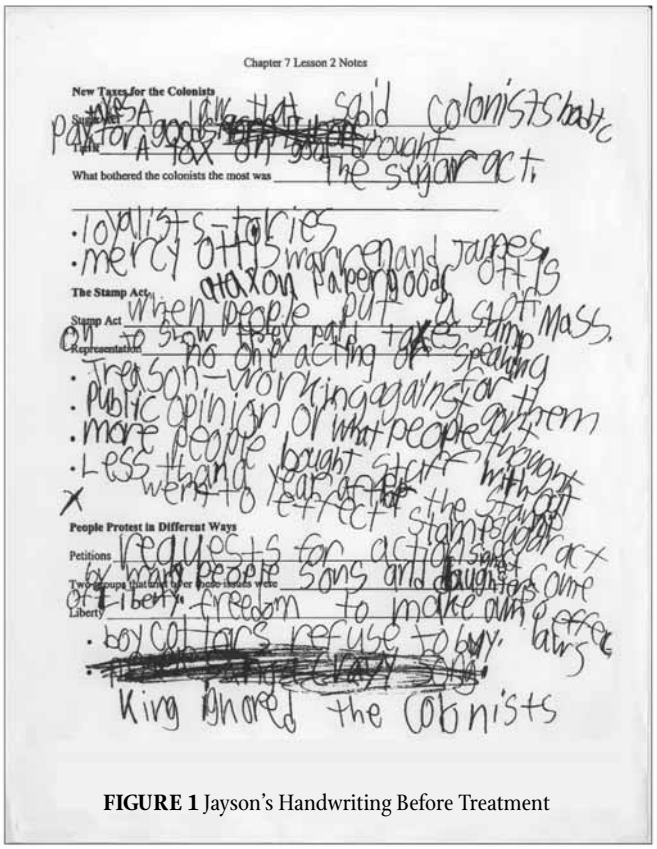



**FIGURE 1** Jayson's Handwriting Before Treatment

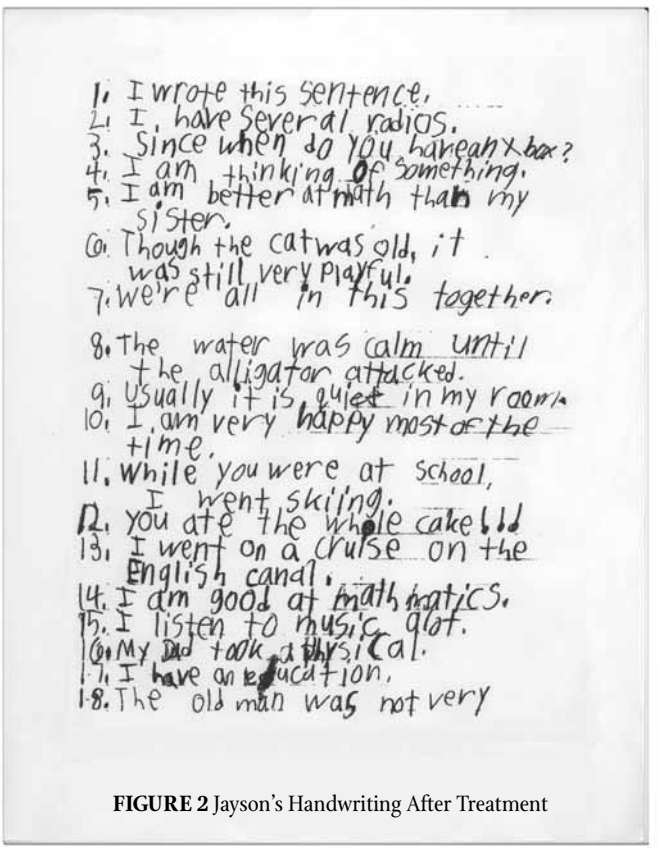
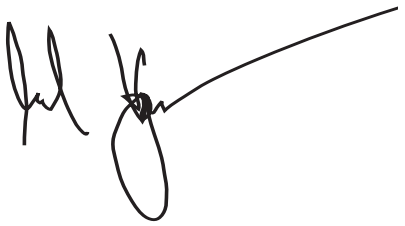



**FIGURE 2** Jayson's Handwriting After Treatment

therapy compared to nutritional interventions by Dr Bernard Rimland in 191 children found a nutritional approach 18 times more effective and without side effects.[33] If in fact this is true, which this case and others suggest, and because of the risks and limited efficacy inherent in psychotropic medication, then it is incumbent upon the scientific and medical community, as well as policy makers and educators, to aggressively pursue a systems medicine approach to neurobehavioral disorders.

Clearly the time has come that the body's influence on the brain must come to the forefront of research and treatment of psychiatric and neurologic disorders.



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**ERRATUM**

On pages 46 and 47 of the article by Innes and colleagues, "Chronic Stress and Insulin Resistance-related Indices of Cardiovascular Disease Risk, Part 2: A Potential Role for Mind-Body Therapies" published in our Sep/Oct 2007 issue, the figures that appear are incorrect. The article should have included only one figure, as follows.

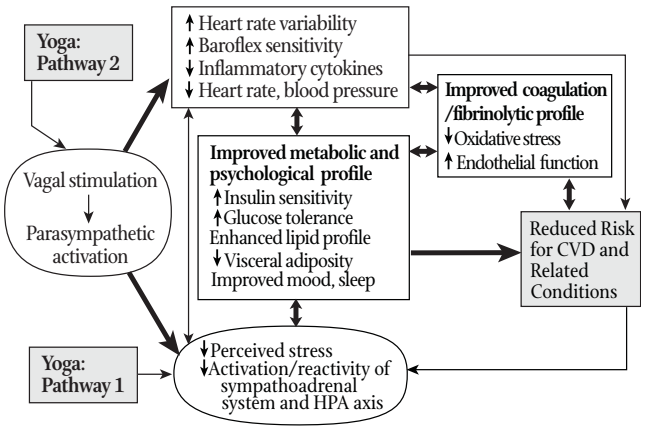


**FIGURE 1** Hypothesized Pathways by Which Yoga May Reduce Cardiovascular Disease Risk

(Adapted with permission from the American Board of Family Medicine from: Innes KE, Bourguignon C, Taylor AG. Risk indices associated with the insulin resistance syndrome, cardiovascular disease, and possible protection with yoga: a systematic review. *J Am Board Fam Pract*. 2005;18(6):491-519.)