Great Smokies Diagnostic Laboratory March 2001 Volume 10, No. 1

Smokies Digest

Effects over time of the body's decreasing ability to metabolize sugar...

Special Metabolic Dysglycemia Issue

Insulin

Blood Sugar Level

TIME

A Progressive Assault on Human Health

Smokies Digest

CONTENTS

FEATURES

8-9 **Treatment Options**
by Russel Sher, D.C.

10-11 **Obesity**
by T. Michael Culp, N.D.

12-13 **Case Study**
by Hunter Yost, M.D.

14-15 **Dyslipidemia**
by Myron B. Lezak, M.D.

16-17 **Syndrome X: CVD, Hypertension**
by John Furlong, N.D.

18-19 **Hormones/PCOS**
by Mary James, N.D.

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DEPARTMENTS

3 **From the Founder's Desk**

4-5 **The Functional Perspective**

6-7 **Quality Assurance**

20-21 **Practice Management**

22 **Developments: Compliance/International**

23 **Book Reviews**

24 **Profiles**

"It is not how old you are, but how you are old"
Marie Dressler (1869-1934)

COMING IN OUR NEXT ISSUE:

Healthy Aging Medicine: *Focusing on the eight modifiable risk factors in aging, this issue will feature assessment and preventive strategies for promoting optimal health and influencing genetic expression of disease.*

Great Smokies Diagnostic Laboratory

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Reaching out with our field-based consultant network

part of GSDL's educational mission to help practitioners meet the challenges of preventive medicine

By Stephen Barrie, N.D.
Founder

It's been a busy year so far for everyone at Great Smokies Diagnostic Laboratory. In addition to our ongoing efforts to refine methods and materials, we have also worked to expand our test portfolio and support network. Several of our plans to improve service and quality have already reaped benefits for you:

- We have added key personnel, including Crystal McLaughlin, N.D., as a Staff Physician in Medical Science and Kelly McClellan, M.S., as Special Studies Department Coordinator

- Our Functional Medicine Consultants have helped hundreds of practices nationwide and continue to be proactive in offering ways to increase the usefulness of our assessments in your practice

- Our On-line Test Reporting is linking more and more healthcare providers all over the world with nearly immediate access to test results

- We continue to expand our presence on the worldwide web with easy loading pages with new resources and now offer an HTML version of our e-mail newsletter

Are you receiving the ***Great Smokies Connection****, our e-mail newsletter? To subscribe, visit http://www.gsdl.com/education/connection/index.html or call 800-522-4762.*

Great Smokies have also introduced major improvements for several assessments and developed new profiles to enhance your practice of functional medicine. See this issue's Back Page for more information about these innovative products. These new markers and methodologies will offer you valuable added insight into your patients' health and physiological function for enhancing treatment and outcome.

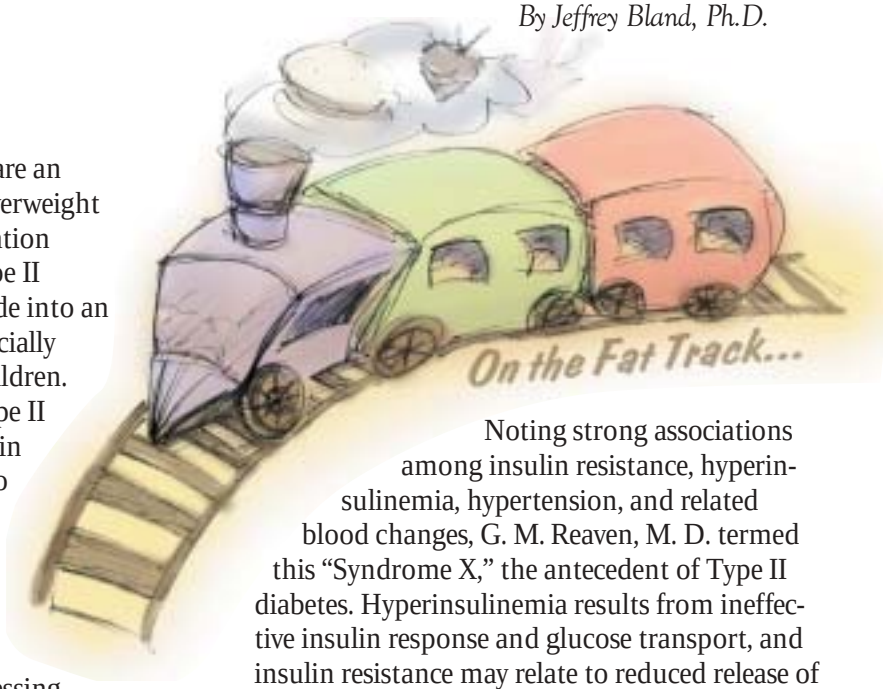
Thanks for allowing us to continue to be of service in assisting you achieve your goals with your patients. Our combined visions have allowed us to help over 2.4 million patients through GSDL testing and education.

Stephen Barrie, N.D.

Functional Medicine for Syndrome X

By Jeffrey Bland, Ph.D.

We are an overweight nation witnessing Type II diabetes explode into an epidemic, especially among our children. Since most Type II diabetics produce enough insulin but have developed resistance to normal insulin action in target tissues, this condition may more correctly be called "hyperinsulinemia/insulin resistance." Insulin resistance develops in stages before progressing into frank diabetes, and the condition may be identified in its early stages long before symptoms develop with appropriate functional assessment.



Over time, hyperinsulinemia alters genetic transcription factors that affect triglyceride and cholesterol metabolism, inflammatory cytokine release, and endocrine function.

The "Thrifty Genotype" and "Syndrome X"

Type II diabetes results from genetic, lifestyle, nutritional, and environmental factors. It is associated with abdominal fat and accelerated fat deposition, resulting from evolutionary adaptations to "feast or famine" conditions. Under continuous modern "feast" conditions, these individuals gain weight easily, and they metabolically preserve their fat stores while dieting. Neel has called this genetic condition the "thrifty genotype." As an example, within a century of adopting a refined American diet and sedentary lifestyle, sixty percent of adult Pima Indians in the Southwest United States are now Type II diabetics (see Figure 1). However, a related group of Pimas in northern Mexico has maintained its traditional unprocessed diet, active lifestyle, and low incidence of Type II diabetes.

Noting strong associations among insulin resistance, hyperinsulinemia, hypertension, and related blood changes, G. M. Reaven, M. D. termed this "Syndrome X," the antecedent of Type II diabetes. Hyperinsulinemia results from ineffective insulin response and glucose transport, and insulin resistance may relate to reduced release of nitric oxide from muscles. Over time, hyperinsulinemia alters genetic transcription factors that affect triglyceride and cholesterol metabolism, inflammatory cytokine release, and endocrine function. Cardiovascular disease, colon disease, and kidney, eye, and nerve damage are associated with Type II diabetes and hyperinsulinemia.

Pharmacological and Functional Medicine Approaches

Diabetes drugs aid insulin biodynamics, and starch and fat blockers can improve postprandial glycemic response, but their side effects are considerable. Exercise and dietary quality and balance greatly influence blood glucose levels. At the Functional Medicine Research Center in Gig Harbor, Washington, Daniel Lukaczer, N.D., and Robert Lerman, M.D., Ph.D., have developed a diet providing approximately 50% of calories from unrefined carbohydrate, 25% from omega-3 fatty acid-rich fats, and 25% from plant, poultry, and fish protein sources. This diet limits simple sugars and high-glycemic index foods, is high in fiber, and is low in saturated fats.

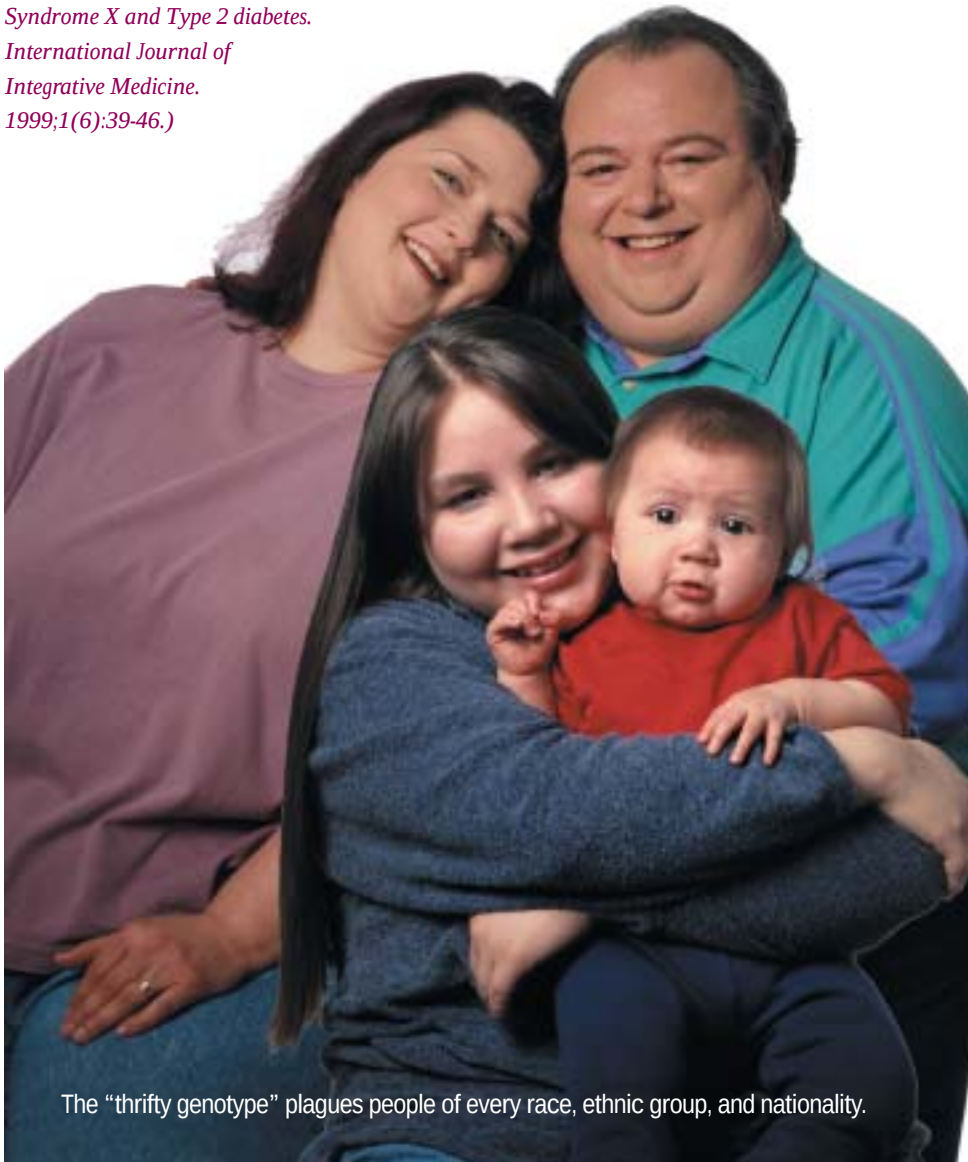
Figure 1
The effect of an American diet and sedentary lifestyle on an adult Pima Indian - one consequence of America's westward expansion.

Source: Jeffrey Bland, Ph.D.

Understanding a food's glycemic index (GI) is crucial in controlling insulin resistance. Generally, the less refined the food, the lower its GI and the flatter the glycemic response. However, GIs of individual foods do not predict GIs of meals, so they should be viewed as guidelines, not "prescriptions." Undesirable foods include refined flours and sugars, saturated fats, and combinations of these. Desirable foods include high-amylose rice (e.g. basmati), legumes (especially mung beans), mustard family vegetables, green leafy vegetables, bitter gourd (*Momardica charantia*), ivy gourd (*Coccinia indica*), maitake mushroom, soy foods, and omega-3-rich foods (e.g. fish, flaxseed). These foods have hypoglycemic and antioxidant effects and may improve gene expression, insulin sensitivity, and glucose transport. Nutrients and phytonutrients like vitamin E, flavonoids, alpha-lipoic acid, l-arginine, chromium, vanadium, and d-chiro-inositol can substantially support insulin response and insulin sensitivity, reduce oxidative stress, support vascular and cell membrane function, and aid glucose regulation in Type II diabetes and Syndrome X.

The functional medicine approach nutritionally supports insulin and glucose control in those with hyperinsulinemia/insulin resistance - many experience a reduction in body fat as their insulin sensitivity improves. Trials evaluating long-term benefits of this functional medicine approach have not been conducted, but evidence indicates possible lower risks for heart disease, stroke, tissue damage, polycystic ovary syndrome, and perhaps colon disease, without many of the risks of pharmacological therapy.

(Jeffrey Bland, Ph.D., is the Chief Executive Officer of HealthComm International and President of the Institute for Functional Medicine in Gig Harbor, WA. He has written extensively on health and nutrition and is currently engaged in research and development of new approaches to diseases related to disturbances in cellular communication and genetic expression. Every year he delivers a series of seminars to disseminate the results of his work and organizes the annual International Symposium on Functional Medicine. This article was adapted and condensed from: Bland JS. Functional medicine approach to managing Syndrome X and Type 2 diabetes. International Journal of Integrative Medicine. 1999;1(6):39-46.)



The "thrifty genotype" plagues people of every race, ethnic group, and nationality.

Quality Assurance

Assuring Quality Results on the Metabolic Dysglycemia Profile

By Leslie Hart

Leslie Hart, M.T., B.S.
QA Coordinator

Like all of our testing, we subject tests performed in the Endocrinology and Chemistry Laboratories to careful Quality Assurance methodology. The laboratory undergoes annual, alternating on-site inspection by the College of American Pathologists (CAP) and New York State (NY). These physical evaluations of lab testing cover all aspects of lab operation (safety, specimen handling, controls, etc.) as well as the personnel qualifications and licensing of employees.

In between the on-site physical examinations, there are periodic proficiency test events scheduled by the regulatory agencies. In some cases, split sample test result comparisons with other laboratories (or kit manufacturers) are performed where available. In lieu of structured proficiencies from licensing bodies or other outside sources, we perform in-house split sample comparison two to four times each year. The in-house proficiencies are supervised by the Quality Assurance team, professionals who report directly to lab executives – Compliance Officer Earlene Clark and Laboratory Director Jian Ho, M.D., Ph.D. This organizational arrangement ensures that in most cases neither employees nor supervisors know which samples are undergoing proficiency tests.

QA in the Endocrinology Laboratory

By Sheila Nadkarni, Ph.D., and Jim Kelton, M.T.

Sheila Nadkarni, Ph.D.
Manager of Immunology and Endocrinology

Jim Kelton, M.T., B.S.
Supervisor of Endocrinology

The components of the Metabolic Dysglycemia Profile related to hormone function and balance are performed in the Endocrinology Laboratory. We have established QA measures appropriate for each of the tests performed.

Insulin – Both CAP and NY competencies are performed periodically for serum insulin. We have passed all of our proficiencies and achieved perfect 100% results on most of them. In June, we began using a chemiluminescent immunoassay Ultrasensitive Insulin test, one of the most sensitive methods now available for commercial use and an important tool for identifying signs of insulin resistance as early as possible.

IGF-1 – No competencies for this serum assessment are currently available from CAP or NY. However, we participate in split-sample competencies offered by the kit manufacturer, and our performance has been outstanding. Combined with in-house split sample comparisons, IGF-1 undergoes this kind of testing every six months.

Salivary Cortisol/DHEA – CAP does not offer proficiencies for these hormones. In developing the test (adapting a serum kit to saliva assessment), we compared four kits from different manufacturers before selecting the one we use. In addition to in-house split sample competencies, we have also compared our levels of sensitivity, recovery, and in-run and between-run variability to research procedures used in recent studies.

At the laboratory bench, our immunoassay methods are checked by establishing controls for every run (high and low) on each of the four analytes evaluated in Endocrinology. For insulin, there is an additional level of control to further ensure reliability.

QUALITY ASSURANCE

QA in the Chemistry Laboratory

By Uta Levinson, M.S

In the Chemistry Laboratory, the majority of the tests related to glucose and lipid metabolism are subjected to proficiencies judged by CAP and New York. The tests are performed on high throughput automated analyzers with two-level assay controls. Our correlations with other methods are high.

Glucose - We have consistently achieved 100% on CAP and NY proficiencies for glucose, and successfully completed the first CAP survey for **HbA1c** recently. Because there are no proficiencies available for **fructosamine**, we use the manufacturer's controls in-house and perform split samples with other labs and in-house.

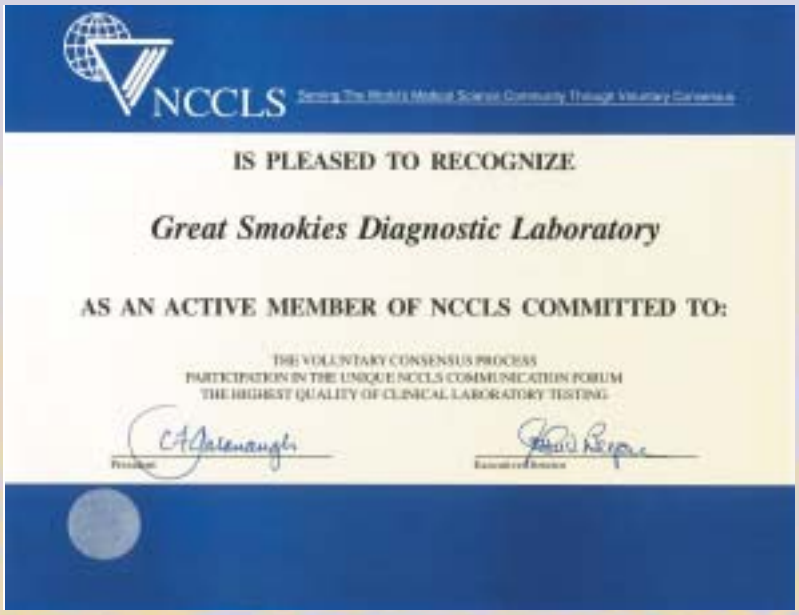
Lipids – We have received perfect scores on CAP and New York proficiencies for HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides. For uric acid, we have received 100% ratings on New York proficiencies and in split samples with other labs.

Our research and development efforts in the Chemistry Laboratory are focused on attaining higher throughput to increase efficiency and improve turnaround times.

Uta Levinson, M.S. Supervisor of Chemistry

Credentials

By participating in the National Committee for Clinical Laboratory Standards (NCCLS), Great Smokies Diagnostic Laboratory keeps abreast of the development of new standards and guidelines. NCCLS is based on the principle that voluntary consensus standards are essential for performing clinical laboratory testing at the high level necessary for quality patient care.


NCCLS

IS PLEASED TO RECOGNIZE

Great Smokies Diagnostic Laboratory

AS AN ACTIVE MEMBER OF NCCLS COMMITTED TO:

THE VOLUNTARY CONSENSUS PROCESS
PARTICIPATION IN THE UNIQUE NCCLS COMMUNICATION FORUM
THE HIGHEST QUALITY OF CLINICAL LABORATORY TESTING

On-site inspection every two years and quarterly proficiency testing by the College of American Patholgists are just two of the ways Great Smokies ensures that its testing meets the highest standards in the industry.

Therapeutic Approaches to the Management of Dysglycemia

By Russel Sher, D.C.

Consideration of natural treatment options for dysglycemia should include addressing the etiology of this condition – primarily the lifestyle choices of diet and exercise, and these are the most important factors to consider in treatment.

Initially, the first order of business would be to establish healthy lifestyle choices that promote healthy glucose and insulin levels. A healthy diet should be composed of unrefined wholesome foods in a balanced combination. Foods should provide about 50% low glycemic index complex carbohydrates, 25% protein derived from plant and animal protein and 25% high quality fats – with emphasis on omega-3 fatty acid fats.

Supplementation with soluble and insoluble fiber has been shown to help improve glycemic control and reduce hyperinsulinemia. The ADA (American Diabetic Association) recommends 24g of total fiber supplementation made up of 8g of soluble fiber and 16g of insoluble fiber. However, other studies have indicated that a higher fiber intake of a total of 50g made up of 25g of soluble fiber and 25g of insoluble fiber was significantly more effective.

A regular aerobic exercise program will go a long way toward improving insulin sensitivity and reducing insulin and glucose levels. A moderate intensity walking program for twenty minutes a day will provide great benefit.

Gymnema sylvestre

In addition to improving lifestyle choices, supplementation with vitamins, minerals, and herbs have shown great benefit in improving insulin receptor function and balancing glucose levels. The herbs *Gymnema sylvestre*, Fenugreek (*Trigonella foenumgraecum*), and Bitter Melon (*mormordica charantia*) assist in improving blood sugar control. Bilberry (*Vaccinium*

Fenugreek (Trigonella foenumgraecum)

Bitter Melon (momordica charantia)

Both omega-6 and omega-3 fatty acids provide benefit. Metabolism of omega-6 fatty acids is disturbed in hyperinsulemic states, so supplementation with gamma linolenic acid offers protection against developing diabetic neuropathy as well as being a precursor to anti-inflammatory eicosanoids. In addition to being precursors to anti-inflammatory eicosanoids, eicosapentaenoic acid and docosahexaenoic acid improve fluidity of cell and organelle membranes thereby improving insulin sensitivity. These fatty acids also lower cholesterol and triglyceride levels. Some studies have implied that supplementation with fish oils elevates plasma glucose levels; however high amounts of these fatty acids were used (4-10g). Supplementation of around 2.5g of fish oil has shown beneficial results.

When supplementing with fatty acids it is always wise to include vitamin E to reduce the lipid peroxide production. The **Essential and Metabolic Fatty Acids Analysis** can uncover imbalances and ratios among fatty acids, as well as determine the state of the metabolic pathways by which important fatty acids are utilized in the body.


Bitter Melon
(Momordica Charantia)

myrtillus) has a history of folk use as a therapy for diabetes. Not only does it normalize high levels of glucose, but the flavonoids (anthocyanosides) assist in improving blood vessel integrity and circulation, particularly in the retina and macula.

(Consulting Staff Physician Russel Sher, D.C., practiced integrative chiropractic and nutritional medicine for 12 years in the United States and South Africa. His primary interest is the application of Functional Medicine in clinical practice utilizing primarily natural approaches.)


Bilberry (Vaccinium myrtillus)

Vitamins and Minerals

Vitamin B6 appears to provide protection against diabetic neuropathy. Magnesium is important for proper vitamin B6 utilization. Zinc is required for gluconeogenesis and glycogenolysis, as well as being involved in synthesis, secretion, and utilization of insulin. Zinc is also protective against beta cell destruction. Organic trivalent chromium such as chromium picolinate and chromium polynicotinate also has a beneficial influence on insulin receptor sensitivity for patients who are depleted in chromium.

Elemental Analysis of hair, blood, and urine can pinpoint deficiencies of these important minerals and elements, while **Amino Acids Analysis** is useful in understanding vitamin and protein metabolism.

*The latest **Clinical Insights** discusses Alzheimer's. It is available exclusively on-line at www.gsdl.com/news/publications/index.html We are in the process of making all past issues of **Clinical Insights** available at www.gsdl.com*

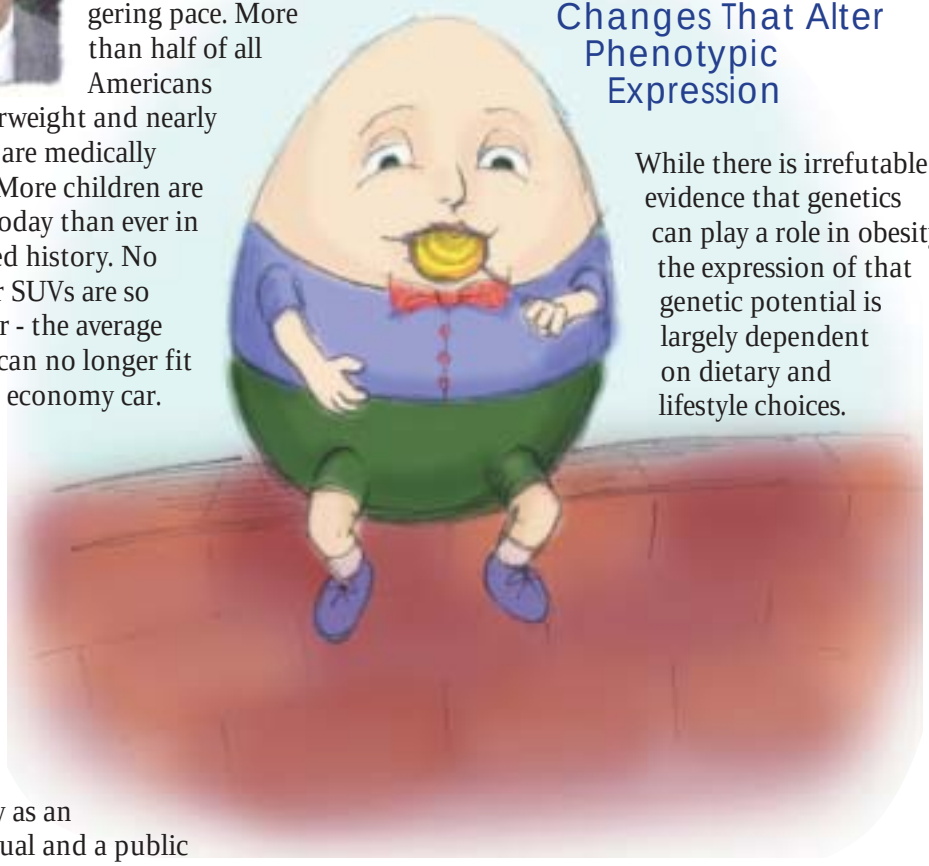
NEW APPROACHES

The Bigger They Are, The Harder They Fall

by T. Michael Culp, N.D.

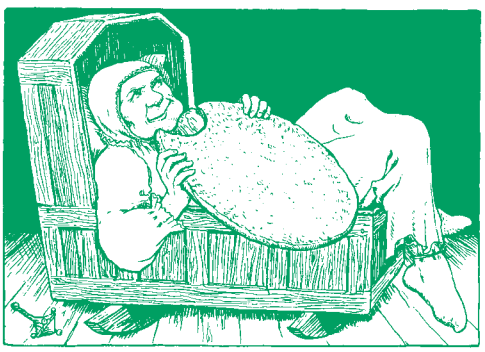
The number and percentage of obese Americans continues to climb at a staggering pace. More than half of all Americans are overweight and nearly a third are medically obese. More children are obese today than ever in recorded history. No wonder SUVs are so popular - the average family can no longer fit into an economy car.

"... this association [between obesity in early adulthood and later development of diabetes] appeared to be independent of parental diabetes history."
Brancati FL et al. Arch Intern Med 1999;159:957-63.



Changes That Alter Phenotypic Expression

While there is irrefutable evidence that genetics can play a role in obesity, the expression of that genetic potential is largely dependent on dietary and lifestyle choices.



Obesity as an individual and a public health issue has enormous implications for the development of chronic diseases like diabetes and heart disease. Central obesity is a key clinical sign of insulin resistance and an increased risk for diabetes and for cardiovascular disease. Take this simple test. Measure your waist at the level of the navel and your hips at their widest point. Divide the waist measure by the hip measure. If the ratio is >1 (in men), or >0.8 (in women), then you are centrally obese.

There is a big (fat) elephant sitting in the middle of our collective living rooms which no one wants to talk about, namely, Americans eat too much, they eat the wrong things, and they move too little. Adding injury to injury, most of us work sitting down, drive everywhere, and even take our recreation sitting down (television comes to mind).

Contributing Metabolic Imbalances

While diet and exercise remain the cornerstone of weight management, functional medicine can identify metabolic imbalances that contribute to the complex problem of obesity. Two major functional imbalances frequently play a significant role: endocrine dysfunction and food allergies.

The standard American diet (high calorie, high carbohydrate, deficient mineral and omega-3 fat intake) contributes to insulin receptor dysfunction and insulin resistance. Excess calories, whether carbohydrate, protein or fat, are converted by the body and stored as fat. Insulin resistance causes serum hyperglycemia and intracellular hypoglycemia (since serum glucose cannot get into the cells), and the cells perceive this as a state of starvation. In response, the body releases glucagon, cortisol, and catecholamines which further raise blood sugar levels. In addition, the hormone-stimulated increase of an enzyme known as hormone-sensitive lipase leads to the release of triglycerides into the blood stream (dyslipidemia). A good portion of these fats are taken up by the abdominal fat cells under the influence of the excess insulin resulting in the central obesity typical of Syndrome X and diabetes.

The high carbohydrate, high calorie intake also suppresses anabolic hormone production, especially growth hormone and IGF-1, which further exacerbates the intra-cellular starvation state. The **Metabolic Dysglycemia Profile** is designed to reveal not only glucose and insulin fluctuations but also to measure the hormone counter-regulators that play an enormous role in the pathophysiology of obesity.

Interestingly, food sensitivities can also play an important role in obesity, quite independent of insulin resistance. Nature's solution to pollution is dilution. And the "pollution" of food antigens in the blood stream causes intra-vascular and interstitial water retention. Food sensitivities have also been postulated to cause serotonin depletion resulting in intense carbohydrate cravings. A number of studies have demonstrated more efficient weight loss in patients who identified and removed sensitive foods from the diet. A **Food Antibody Assessment** should be considered in all weight loss patients, but especially in those who cannot lose weight with dietary and lifestyle changes alone.

(Consulting Staff Physician T. Michael Culp, N.D., worked as a family doctor in Seattle and taught nutritional biochemistry and other courses at Bastyr University prior to joining Great Smokies in 1998. His special interests are nutritional interventions and Essential and Metabolic Fatty Acids Analysis.)

Obesity and the American Diet

- **The average American adult eats 3600 calories of food a day when half of that would meet our energy needs.**
- **20% of those calories come from simple sugars, and nearly 40% come from fat.**
- **White sugar, white flour, vegetable oil and animal fat make up more than half of our diet.**
- **Less than 10% of Americans meet the RDA for vitamins and minerals in the diet (some studies have shown 0%). Omega-3 fats found in grass-fed animals and fish are essentially absent from our diet.**

Drawings by Paula Bishop

Using the Metabolic Dysglycemia Profile: Lessons From A Sunbelt Practice

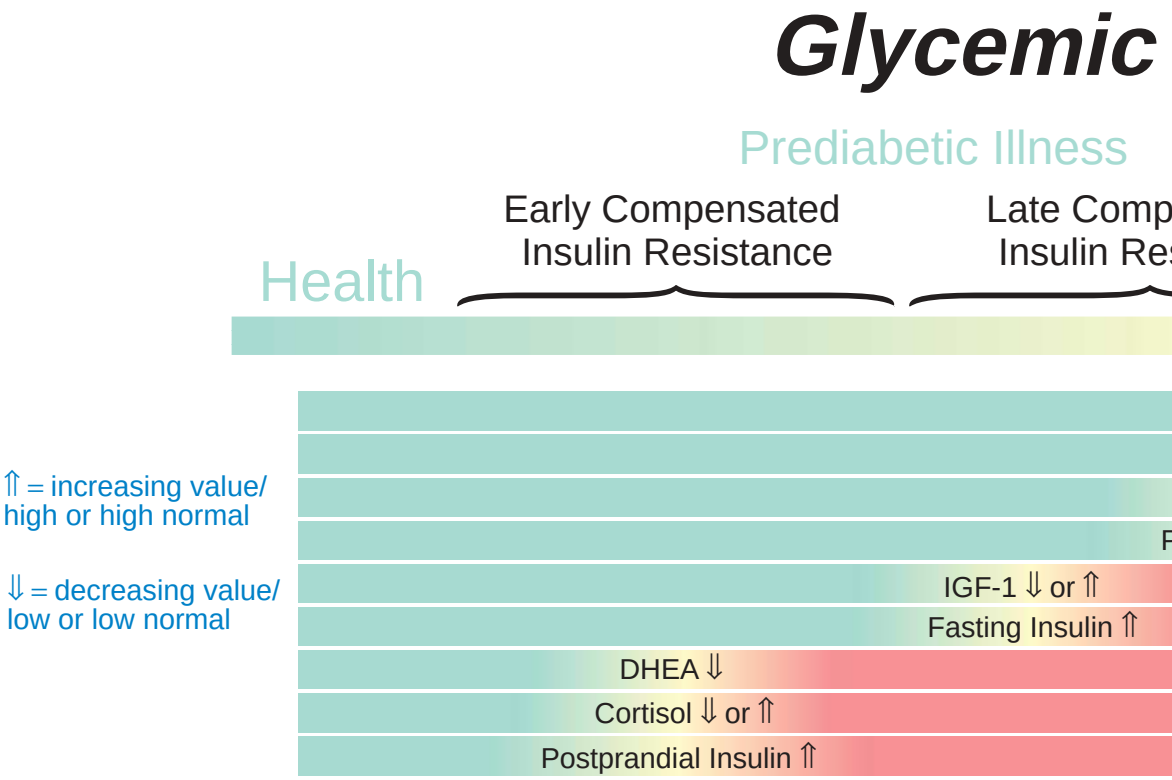
By Hunter Yost, M.D.

According to molecular gerontologists, the single most important process of aging is the optimal management of glucose. The development of insulin resistance and subsequent protein glycation or AGE's (advanced glycosylated end products) may begin as early as the third decade of life. By the fourth, fifth, and sixth decades, hypertension, Type II diabetes, and cardiovascular disease may become manifest.

The development of insulin resistance and subsequent protein glycation or AGE's (advanced glycosylated end products) may begin as early as the third decade of life.

A substantial portion of my practice involves a "senior age" population (55 years and older), who are mostly retired. They are very concerned about their health and want to stay as active as possible. They comprise a population as likely as any to comply with my treatment plans, especially with effective educational materials to help them continue even after many of them return north for the summer.

On initial exam, many have an elevated waist to hip ratio (WHR) >.88 and Body Mass Index (BMI) >27. Some may have a history of "borderline blood sugar levels" in the past but have not been diagnosed as diabetic. They may be taking anti-hypertensives, have gained 10 or more pounds since age 20, have sweet cravings, and hypoglycemic episodes. If they have scores of greater than 7 on the insulin resistance screening questionnaire, I will automatically order a **Metabolic Dysglycemia Profile**.



One lady, age 64 years with a BMI of 32, and WHR of .91, who had coarsening of her skin and acne symptoms, was found to have an elevated testosterone level by her primary care physician. Her **Metabolic Dysglycemia Profile** indicated elevated 2-hour post-prandial insulin and depressed DHEA. I explained to her that because of the elevated insulin, her body was now producing more male hormones and that by decreasing her insulin through a nutritional program, we could correct this hormonal imbalance and her DHEA would most likely come up on its own.

Another lady, also in her sixties, with elevated BMI and WHR, had elevated cortisol and high normal insulin on her profile. She admitted that she was a "hot reactor" to stress and found it difficult to stay calm during stressful periods. She had carbohydrate cravings, hypoglycemic episodes, and difficulty losing weight. I explained to her the relationship of sustained elevations in cortisol levels and abdominal adiposity. For her, stress was a trigger for the mediators of cortisol and insulin with subsequent symptomatology.

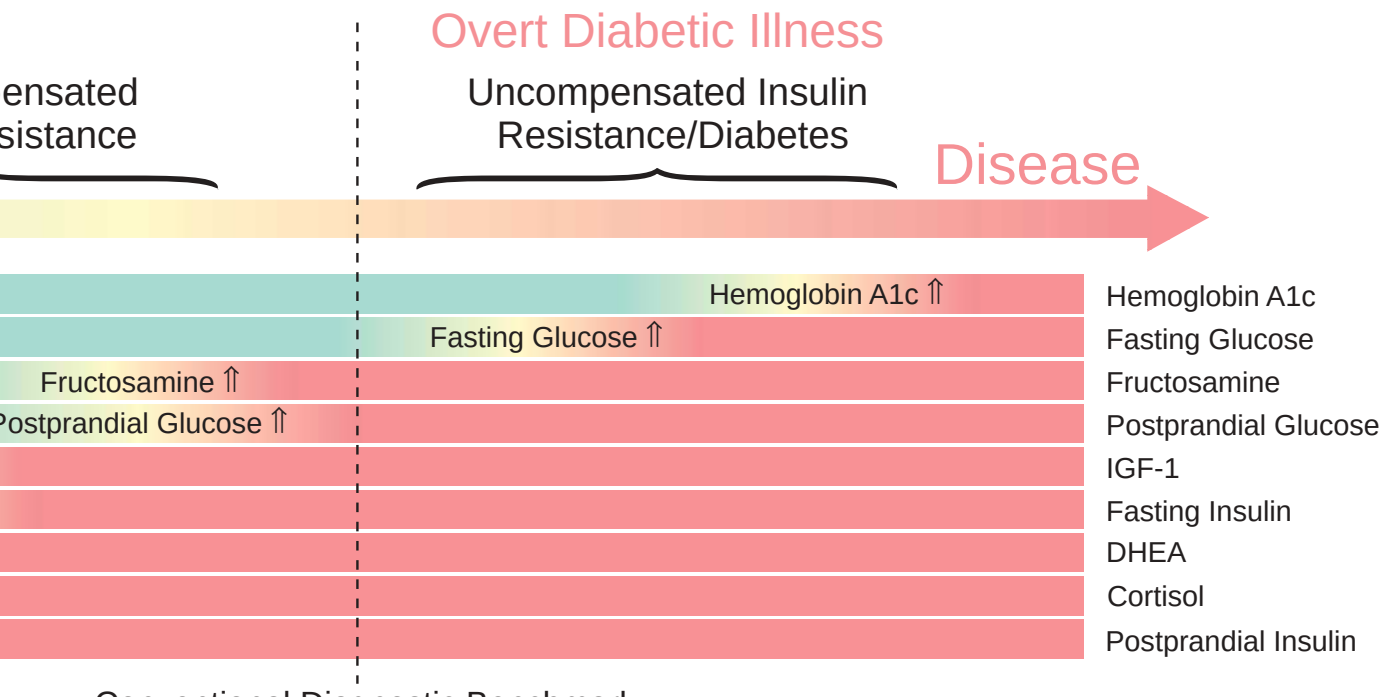
She also had the antecedent factor of a family history of heart disease, and her father had died at age 54 of a heart attack.

For these patients, the test report format of **Metabolic Dysglycemia Profile** serves as an excellent teaching tool by which patients can see the relationships of the test components as they are explained. In my practice, this graphic demonstration of test results and commentary, which reinforces my own explanation, leads to greater patient motivation to make the necessary lifestyle and dietary changes. Patients gain a greater understanding of what is happening in their bodies and how important stabilizing and improving their condition is to healthier aging.

(Hunter Yost, M.D., practices Functional and Nutritional Medicine in Tucson, Arizona. He acts as a consultant to many primary care physicians for their chronically ill patients. In March 2000, he gave a presentation at the Tucson Heart Hospital on "Syndrome X and the Metabolically Obese Normal Weight Individual." He has given Grand Rounds presentations on Functional Medicine at several Tucson hospitals. He can be reached at Cazadoryos568@cs.com or his website: http://doctor.medscape.com/HunterYostMD)

Call 800-522-4762 or send an e-mail to cs@gsdl.com to order test kits or find out more about the ways functional assessments can work in your practice.

Dynamics



The Role of Lipid Abnormalities in Metabolic Dysglycemia

By Myron B. Lezak, M.D.

In "developed" nations worldwide, the increasing incidence of insulin resistance poses important challenges for healthcare providers. This mismatch of our evolving modern environment (and the choices in diet and activity that we make as a result of that environment) with our much less rapidly evolving DNA has produced a variety of consequences. In subtle and insidious ways, insulin resistance increases risk for a growing list of health conditions associated with premature aging, reduced quality of life, and mortality.

Insulin resistance leads to increased lipogenesis and cholesterol synthesis. With central obesity, adrenal function alters, resulting in increased cortisol and adrenaline production. Levels of glucagon increase, and the resultant change in lipoprotein lipase activity contributes to dyslipidemia. Altered lipid metabolism is certainly a major problem that is significantly correlated with generalized vascular disease, as well as with various cancers - particularly those related to the breast, ovary, uterine endometrium, prostate, colon, and, possibly, pancreas.

The assessment of these alterations is of prime importance in identifying and thereby modifying and reducing the risks to these disorders. Hypertriglyceridemia, elevated apolipoprotein B (apo B), and reduced high density-lipoprotein (HDL) cholesterol are all part of the complex of metabolic dysglycemia and insulin resistance. In addition, the genetically determined elevation of lipoprotein (a) - a smaller, denser low-density lipoprotein - can be seen with some individuals with insulin insensitivity. Not all of these abnormalities manifest in every individual with this problem, so it is important to assess each patient for a comprehensive determination of risks and potential synergistic effects of interaction.

Moreover, there is a definite familial pattern to these abnormalities so that screening of family members would also be appropriate. The continuing (and disturbing) increase in childhood obesity suggests that the genetic expression of the disorders of metabolic dysglycemia is appearing earlier and earlier among young people. Timely assessment and early intervention can help impact the fate of the next generation by pointing to interventions for influencing genetic expression.

Hypertriglyceridemia is caused by an elevated synthesis and secretion of VLDL (very low-density lipoprotein) in the liver and by reduced metabolism of lipids mediated by lipoprotein lipase. These alterations are associated with a reduced concentration of HDL cholesterol. In addition, the composition of the lipoprotein particles can be altered, interfering with their normal metabolism. Abnormalities in lipid metabolism are often clustered with the other abnormalities of Syndrome X (central adiposity, hypertension, impaired glucose tolerance, and hyperinsulinemia).

Lipid abnormalities can also be initial features of a gradually progressive problem and may therefore serve as markers

"Aggressive therapy of diabetic dyslipidemia will probably reduce the risk of CHD [Coronary Heart Disease] in patients with diabetes."
American Diabetes Association. Diabetes Care 2000:23(Suppl 1):S57-60.

for significant disease risks. Consequently, the evaluation of these lipids periodically during therapy can help practitioners determine therapy effectiveness and identify shifts in the patient's metabolic profile. The importance of monitoring dyslipidemia has been recognized in recent American Diabetes Association treatment guidelines calling for ongoing (in most cases, at least annual) assessment.

It is not presently well understood how all of these factors interrelate to manifest as the several disease processes that correlate to abnormal levels. Lipoprotein (a) is probably the most atherogenic of all the lipoproteins. The apo A-1 protein component of lipoprotein (a) binds to endothelial and macrophage cells, promoting the deposition of atherogenic material into blood vessels. Research points to these lipids, especially in the setting of oxidative stress, as the cause of arterial wall damage and, perhaps, damage to other cellular membrane components as well. Insulin resistance is a factor in increasing oxidative stress.

Metabolic dysglycemia is a complicated, multi-factorial condition that can vary in significant ways from individual to individual, depending on a patient's unique biochemical profile. Along with assessment of insulin and glucose metabolism, an optional component of the **Metabolic Dysglycemia Profile** provides this information for lipids (total cholesterol, triglycerides, HDL, LDL). For added insight into cardiovascular risk, the **Comprehensive Cardiovascular Assessment** evaluates apo B, lipoprotein (a), and additional independent markers, as well as the extent to which these factors interact with one another to affect cardiac health.

(Myron B. Lezak, M.D., is board certified in Internal Medicine and Gastroenterology. He has been in private practice for over 25 years and serves as a consultant for GSDL.)

Call 800-522-4762 or e-mail cs@gsdl.com for more information

Finding Connections with the Metabolic Dysglycemia Profile

Hormones, Carbohydrates, and Cardiovascular Disease

By John Furlong, N.D.

"... our population-based prospective study on elderly subjects demonstrates that cardiovascular risk factors typical of the insulin resistance syndrome cluster and that this clustering predicts CHD [Coronary Heart Disease] events, at least in men."
Lempiäinen P et al. Circulation 1999;100:123-28.

It has been estimated that as many as half of the people experiencing a heart attack have normal cholesterol and other markers of blood lipids and do not fall into traditional risk categories. Over the past 5-6 years as researchers have examined independent markers of cardiovascular disease (CVD), it's become evident that we must look to other areas to more fully assess risk for cardiovascular disease. Increasingly, CVD is being seen as a multi-factorial condition, with some of the markers for risk exercising a synergistic effect that can significantly increase patient risk.

One particularly fruitful area of investigation relates to the effect that persistent high blood sugar and the hormonal aberrations stemming from hyperglycemia have on the vascular system. Fasting glucose and insulin levels, HbA1c, fructosamine, DHEA, cortisol, and IGF-1 all undergo changes in response to age and/or blood sugar stressors. The physical signs of Syndrome X (hypertension, abdominal obesity, etc.) can provide early warning of increased risk for diabetes and CVD, pointing to the need for comprehensive assessment and focused interventions. Glucose and insulin levels are becoming recognized as important gauges of cardiovascular risk and have been specified as such by the American Diabetes Association and the World Health Organization. While traditionally used for the diagnosis of diabetes, elevated levels of these markers, even if within the "normal" ranges, have been linked with CVD risk. Additionally, HbA1c levels are directly correlated with advanced glycosylated end products (AGE's) - key initiators of the damaging tissue changes inherent in diabetes.

A preventive approach to CVD risk should include assessment of insulin and glucose. For their part, HbA1c and fructosamine give predictive information and are useful monitors of treatment efficacy. In order to minimize cardiovascular risk, clinicians may use a target of fasting insulin levels below 13 microUnits and fasting glucose levels of 90 mg/dl or below as optimal laboratory goals.

Levels of DHEA are associated with metabolic capacity for repair and recovery of an individual. Thus, assessment of DHEA levels can provide insight into hormonal response to stressors and a person's resilience under stress. While studies linking DHEA levels and cardiovascular disease are varied in their conclusions, there are many reasons to pay close attention to this steroid. For example, hypertension and overall cardiovascular risk appear to be negatively correlated with DHEA levels.

In premenopausal women, hyperinsulinemia and low levels of DHEA were associated with increased risk for coronary heart disease.

In healthy men, levels of DHEA drop steadily from the age-range of 20-29, until by the seventh and eighth decades of life they may be less than 20% what they were in early adulthood. Along with this drop in DHEA, there is a strong tendency for lower levels of IGF-1. It is postulated that

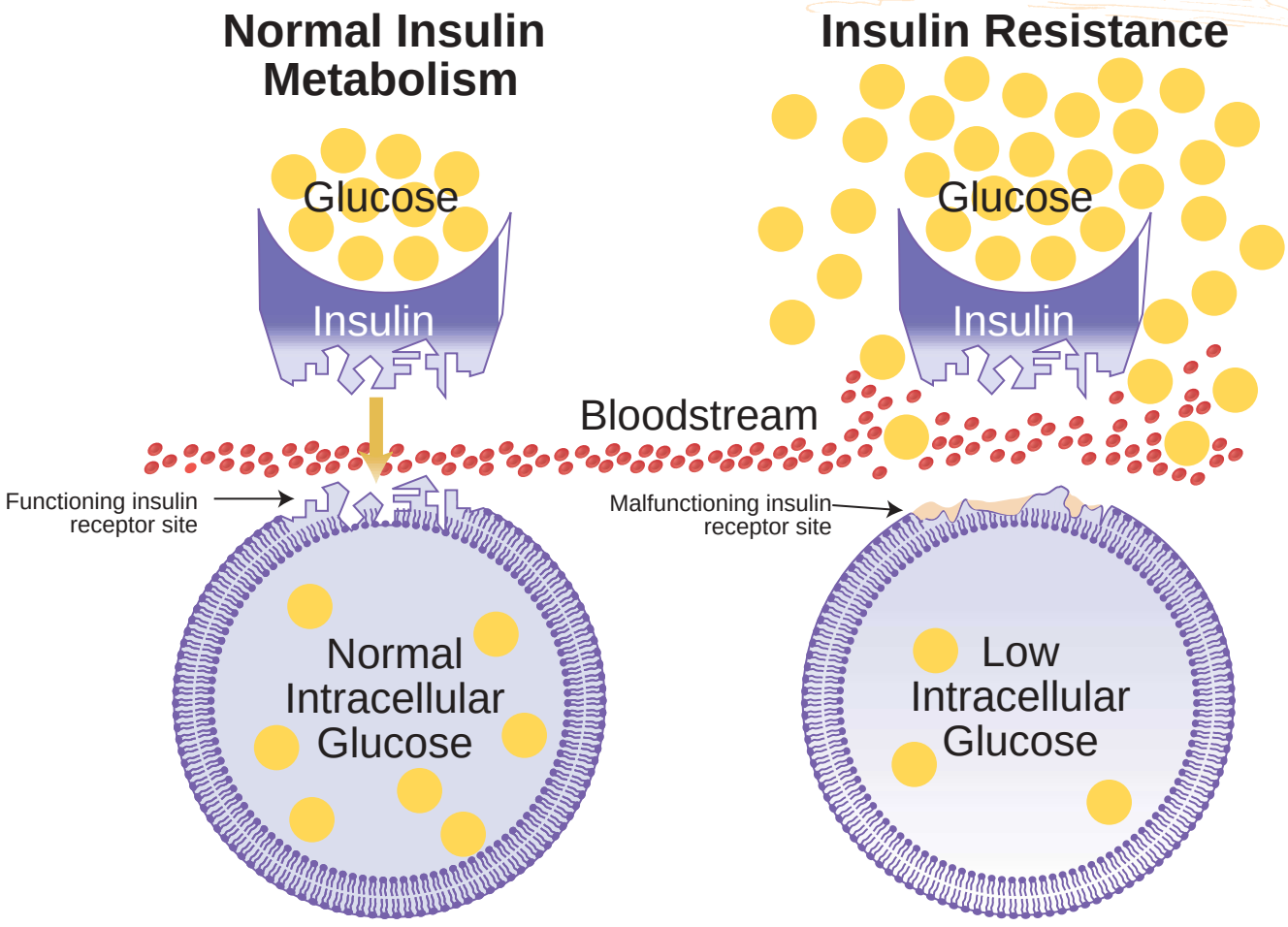
these two systems (DHEA-derived hormones including testosterone, and the IGF-1 axis) represent distinct factors in physical and cognitive aging.

The level of growth hormone, as reflected by IGF-1 levels, also declines with age, bringing difficulties with retention of lean muscle mass, among other changes. The cardiac muscle appears to be similarly affected and the serum level of IGF-1 serves as yet another window on the functional health of the cardiovascular system. Assessment of cortisol levels also provides additional therapeutic direction for the clinician. Recent studies show that the combination of obesity and high cortisol levels to be particularly troublesome in regard to cardiovascular risk.

By considering the markers contained in this one combination test, the **Metabolic Dysglycemia Profile**, practitioners can gain critical clinical direction (which they would miss with blood lipid testing alone) enabling them to prevent the #1 cause of death in developed countries. The panel offers healthcare providers an opportunity for early detection and careful monitoring of important CVD risk factors.

(Staff Physician John Furlong, N.D., spent ten years in private practice prior to joining the educational staff of Great Smokies in 1996. Dr. Furlong divides his time between consulting laboratory clients and his private practice.)

For more information about assessments related to obesity and metabolic dysglycemia, call 800-522-4762

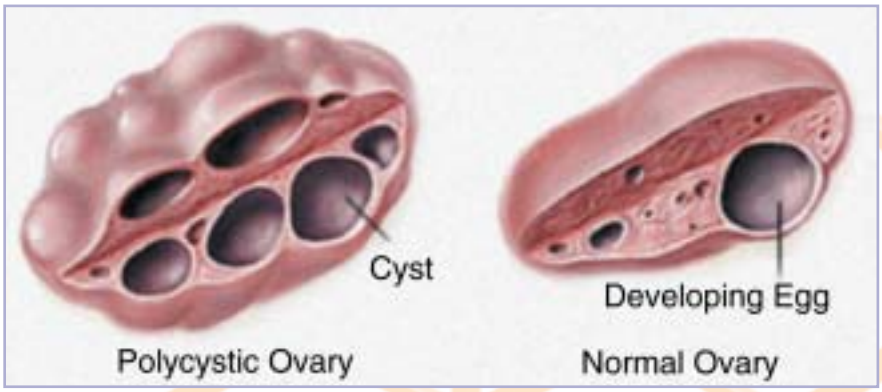


PCOS: Syndrome X in the Ovaries?

By Mary James, N.D.

Organ systems never function in isolation, but are rather interconnected in a complex system of regulatory feedback. Nowhere is this complexity more apparent than the endocrine system, with its network of feedback loops. One of the chemical messengers traveling this system is insulin, and as we learn more about hyperinsulinism, we see that insulin influences far more than glucose entry into the cell. In the area of sex hormones, insulin exerts a powerful influence, most notably in polycystic ovary syndrome (PCOS), the most common endocrinopathy affecting premenopausal women.

Women with PCOS are at higher risk of diabetes, cardiovascular disease, and endometrial cancer.



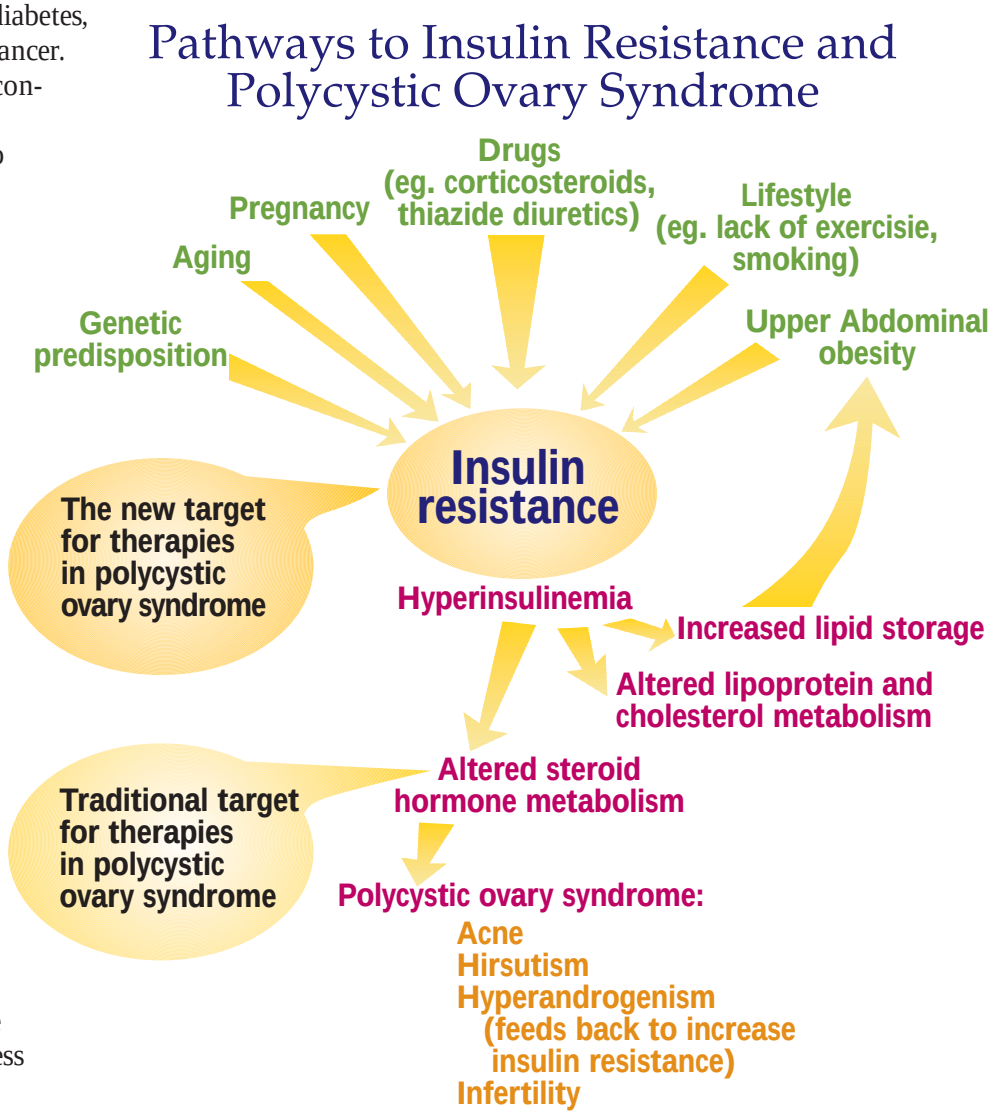
The vast majority of women with PCOS experience insulin resistance, particularly if obese. Fasting and post-prandial insulin tends to be elevated. Insulin resistance, regardless of its cause, is closely associated with hyperandrogenism. Insulin increases the output of luteinizing hormone (LH) from the hypothalamus. Excess LH, in turn, leads to elevated levels of testosterone relative to follicle-stimulating hormone (FSH) and estradiol. Elevated insulin also reduces sex hormone-binding globulin (SHBG), resulting in increased levels of free (bioavailable) testosterone and estradiol.

Two other situations besides PCOS known to exhibit both hyperandrogenism and insulin resistance include acromegaly and normal puberty, suggesting that insulin may exert most of its effects by activating the IGF-1 receptor on ovarian cells. Both insulin and IGF-1 (the main mediator of growth hormone activity) stimulate production of androgens in the ovaries, inhibit hepatic production of SHBG, and have the ability to bind to the other's receptor. Furthermore, excessive insulin lowers IGF-1 binding protein, resulting in a higher free IGF-1. Interestingly, this binding protein is low in PCOS and inversely correlates with serum insulin.

Although there is some thought that androgens instigate insulin resistance, mounting evidence supports hyperinsulinemia as the major physiologic link between nutrition, obesity, and the development of a hyperandrogenic profile. For example, studies of insulin-resistant women with PCOS have demonstrated a return to ovulatory cycles with the administration of insulin-lowering drugs. Pharmaceutical ovarian suppression, and even ovariectomy, don't appear to eliminate the insulin resistance. Interestingly, although not all women with Type II diabetes (NIDDM) develop PCOS, as many as 82% of women with NIDDM have polycystic ovaries. In contrast, Type I diabetes (associated with deficient insulin) is linked with ovarian hypofunction, featuring primary amenorrhea, late menarche, anovulation, infertility, and early menopause. It's intriguing that these young women assume normal reproductive function only after insulin administration.

Take advantage of our 24 hours a day, 7 days a week on-line resources at www.gsdl.com

Women with PCOS are at higher risk of diabetes, cardiovascular disease, and endometrial cancer. Breast cancer might be added to the list, considering the fact that insulin promotes growth of breast tumors and women who develop breast cancer tend to have higher levels of free testosterone and estradiol and lower levels of SHBG. Does this mean that a woman with polycystic ovaries will go on to develop these disorders? We need to remember that genetic predisposition is but one factor influencing the expression of chronic illness, including PCOS, and that modifying other contributing factors may make all the difference. Weight loss and improved insulin sensitivity, for example, have been seen to restore hormone balance in PCOS women. We also know that insulin sensitivity, as well as endocrine feedback loops, are influenced by many other factors, such as dietary fats, stress, exercise, and nutrient status. Assessing function with the **Metabolic Dysglycemia Profile** and **Comprehensive Female Hormone Profile** can help target areas for intervention in PCOS that help to restore normal function and prevent serious illness down the road.



(Consulting Staff Physician Mary James, N.D., was in private practice for four years before becoming a nutritional consultant for a supplement manufacturer. With five years experience at Great Smokies, she is our senior laboratory physician and a popular speaker at conferences and special training sessions.)

Hormone Metabolism and PCOS

While the term "PCOS" makes many of us think of an obese, anovulatory woman with facial hair, obesity is actually only found in 50% of women with PCOS, and not all are anovulatory or hirsute. The full expression of the syndrome depends upon multiple ovarian cysts, signs of androgen excess, a sustained production of luteinizing hormone (LH), and a relative deficiency of follicle stimulating hormone (FSH). Adrenocortical excess is common, with elevated cortisol and DHEA. Familial clustering of PCOS suggests a genetic component; however, as in any "functional" disorder, the development or persistence of it is also strongly influenced by environmental factors. This is partly what makes PCOS such an interesting study—the mechanisms, although exaggerated in a woman with the genetic predisposition—may occur in any woman.

Preventive Medicine Vs. Early Detection

By Brad Rachman, D.C.

One of the advances of modern medicine of which we can be most proud is the emergence of the field of preventive medicine. The concept of preventing the expression of a disease process is a fundamental tenet of functional medicine. While we all may agree in principle with the value of this approach, fully integrating preventive medicine protocols into a busy practice can sometimes be a major challenge.

One of the difficulties often encountered in the successful implementation of preventive strategies may originate from a primary conceptual misunderstanding. We as clinicians often include in our "preventive medicine" repertoire many strategies that would be better classified as "early detection." Early detection strategies seek to identify the existence of pathology (cancer, degeneration) in its earliest stages. While preferable to the strategy of "late detection," early detection of pathology and disease is not "prevention"; you cannot prevent that which you have already diagnosed. Mammography, PAP smears, and colonoscopy are all screening procedures belonging to the practice of early detection - not prevention. In order for any of these procedures to be meaningful, the pathology (in these examples, cancer) must already be present.

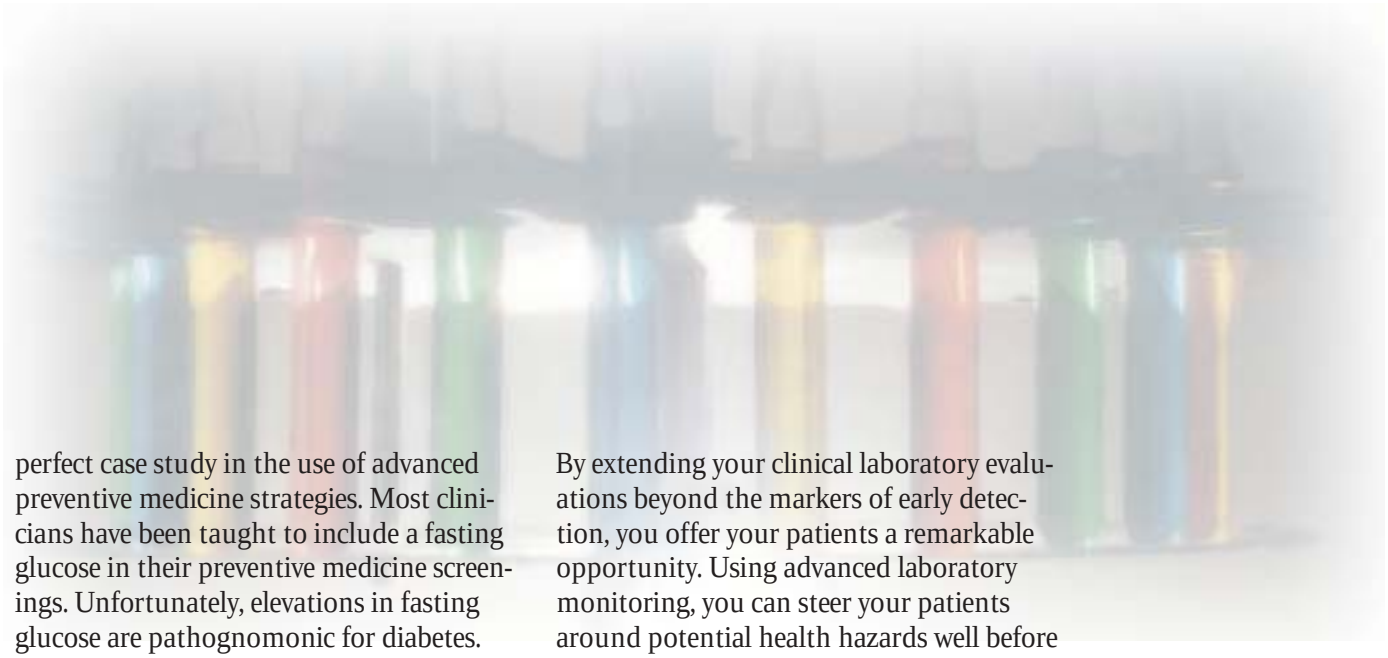
Instead, preventive medicine includes medical strategies which identify the antecedents and pathophysiologic processes which precede the expression of true pathology and frank disease. Identifying the risk factors and aberrant intercellular communicators that promote specific disease states affords clinicians the opportunity to employ interventions which promote positive health outcomes.

Key preventive medicine strategies include the use of functional laboratory profiles. These profiles monitor the specific physiologic aberrations that lead to overt illness. Observing subtle shifts in physiology provides significant indications of the risk of developing chronic and disabling illness.

In this issue we have been exploring the pathophysiologic process known as dysglycemia. A modern day "scourge," few health conditions have escalated so significantly in the last 50 years. Dysglycemia is a

Examining the patient during a doctor's visit

"... nondiabetics appear to have an elevated risk of colorectal cancer as their fasting insulin and glucose rise, even if glucose levels do not reach levels defined as consistent with diabetes."
Schoen RE et al. J Nat Cancer Inst 1999;91:1147-54



perfect case study in the use of advanced preventive medicine strategies. Most clinicians have been taught to include a fasting glucose in their preventive medicine screenings. Unfortunately, elevations in fasting glucose are pathognomonic for diabetes. The overt illness of diabetes must already exist for this marker to be elevated.

We are now aware that the frank illness of diabetes is preceded by months, years, or decades of aberrant glucose/insulin response. Detecting this imbalance affords the opportunity to interrupt the process before the expression of diabetes.

By extending your clinical laboratory evaluations beyond the markers of early detection, you offer your patients a remarkable opportunity. Using advanced laboratory monitoring, you can steer your patients around potential health hazards well before they produce any physical manifestation or limitation.

Brad Rachman, D.C, D.A.B.P.M.,. is the Director of Medical Science for Great Smokies Diagnostic Laboratory. The Medical Science staff is a multidisciplinary team with substantial collective experience in the field of functional medicine. While in private practice, Dr. Rachman was the founder and director of one of the most progressive and successful Functional Medicine centers in the US.

Our laboratory physicians help you get the most benefit from functional testing. Call 800-522-4762.

Analyzing samples in the laboratory

The GSDL *Metabolic Dysglycemia Profile* utilizes several unique approaches to advanced preventive screening.

Functional challenge - observing the effect of a 75-gram, 2-hour glucose load on both insulin and serum glucose levels offers assessment of sugar metabolism across a broad range of physiologic function.

Glycation markers - by measuring the binding of glucose and lysine residues, potential health complications associated with dysglycemia can be assessed.

Endocrine Sequellae - assessing cortisol, DHEA and IGF-1 offers valuable indication of the progress of dysglycemia toward frank diabetes. Also, serial sampling both pre- and post- intervention can be utilized to assess efficacy of the therapeutic approach.

Earlene Clark
Corporate Compliance and Quality Officer

Getting It Right Up Front

If you need more copies of these resources or if you have questions about a requisition that you or your staff is filling out for a patient, please contact us at 800-522-4762.

Two new client- and staff-friendly documents are now available from Great Smokies Diagnostic Laboratory to help boost compliance and reduce the time you and your employees spend re-submitting samples, correcting requisitions/invoices, and learning about the network of services we offer. Since our goal is to help you treat your patients as efficiently as possible, based on clinically useful test results, we want all of the procedures involved in sampling, ordering, and testing to go smoothly… the first time.

New resources include:

• Getting Started… A simple step-by-step guide to using Great Smokies' Functional Laboratory Assessments is a colorful, twelve-page booklet designed to be easily read initially and serve as a quick-glance guide for all of your staff.

• The latest New York State Test Availability chart indicates which tests (and test components) are not approved by New York state for NY residents or for testing sent from physician offices in New York state.

Please call our Clinical Support Specialists at 800-522-4762 to get your copies of these valuable resources.

Sincerely,

Earlene Clark

Earlene Clark

International Update...

...Reporting From the Four Corners of the World

By David Matheson

Great Smokies' international presence continues to grow in the new millennium, as new distributors join our team, technology enhances communication, and training opportunities spread the word about functional medicine worldwide. Recent developments include:

- The lab signs up new distributors in Israel, Canada, and New Zealand
- On-line Test Reporting proves its value globally by improving access and reducing turnaround times for test results – what once took days at best now transpires in hours
- Consutling Staff Physician T. Michael Culp, N.D., delivers ten presentations about using functional assessments to distributors and clients in Europe
- The lab develops an International Requisition Form tailored to the needs of foreign clients

Meanwhile our efforts to increase the range of materials available in several languages continue as healthcare practitioners overseas expand the range of functional testing in their practices.

David Matheson joined Great Smokies as International Sales Coordinator in 1999. He has been involved in sales and customer service for over fifteen years.

Doctor's Bookshelf

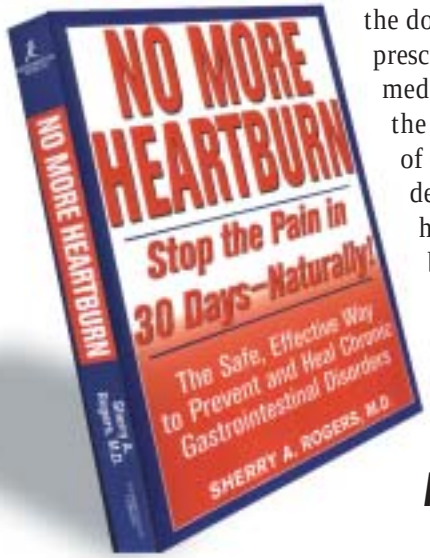
No More Heartburn

by Sherry A. Rogers, M.D.
Reviewed by Alison Levitt, M.D.

Book Review

To order *No More Heartburn: Stop the Pain in 30 Days – Naturally!* (ISBN 1-57566-510-7) by Sherry A. Rogers, M.D., call Kensington Books at 1- 888-345-BOOK (2665), shop at their web site www.kensingtonbooks.com or your favorite internet bookseller, or visit your local bookstore.

Sherry Rogers, M.D., is definitely on a mission to educate people about the myriad of gastrointestinal disorders - anything from ulcers, gas, inflammatory bowel disease to cancer - helping patients work with their practitioners to treat them safely, effectively and naturally. She is adamant about getting the message across to consumers about the downfalls of prescription medicine for the treatment of GI disorders, not holding back any of her well thought-out and usually critical opinions about the pharmaceuticals generally used for these ailments. On the other hand, however, she also does not leave the reader hanging with any questions about what the options are. She offers well informed and researched diagnostic advice about testing for some of the underlying pathology and dysfunction in these ailments, as well as offering full treatment protocols.



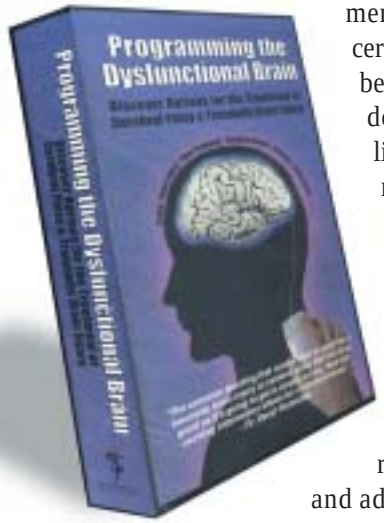
For the practitioner who believes in the concept of "empowering" patients, Rogers offers a valuable tool for reinforcing the importance of partnership to your patients. There are many gems in this book that can greatly impact the health of your patients and the success of your interventions. Plus, it is written in a style that can be understood by all, and it is definitely worth recommending.

Video Review

To order "Programming the Dysfunctional Brain" (ISBN 0-9668350-2-6), featuring David Perlmutter, M.D., et al., call the distributor, Successful Images, Inc. at 954-467-7200, extension 18, contact your favorite on-line bookseller, or visit www.successfulimages.com to print their order form.

Programming the Dysfunctional Brain

featuring David Perlmutter, M.D., et al.
Reviewed by Alison Levitt, M.D.



Neurological disorders have always been a challenge for most physicians and patients. This is not surprising since many neurological disorders have no known effective treatment. If your child is born with cerebral palsy, or a family member has a stroke, common wisdom is that you just have to live with whatever functions remain intact. Luckily, however, this is not always the case. As Dr. Perlmutter and his team of specialists explain on this video tape, there are integrative therapies that can offer a significant amount of recoverability for children and adults alike.

"Programming the Dysfunctional Brain" is a wonderful educational video focusing on brain-injured patients and the different therapeutic options available. The beauty of this video lies in the fact that it offers a more holistic, comprehensive look at treating a patient with a brain injury, examining such innovative and effective treatments as hyperbarics, focused nutritional interventions, and suggestions for physical and occupational therapy. In addition, it also offers complete demonstrations of the exercises that parents or other loved ones can do with the patients, at home or in the hospital.

Watching this video was inspiring and educational. For those individuals who are coping with brain disorders, this video may help them find the beginning of the path towards recovery.

Innovations in Functional Assessment

Great Smokies is introducing improved methodologies for several of our major profiles. We have also developed a new ***Cellular Energy Profile***, ***Comprehensive Thyroid Assessment***, and 20-analyte ***Toxic Element Exposure Profile***.

New Profiles:

- ***Cellular Energy Profile*** – evaluates energy metabolism at the cellular level for assessment of physiological factors involved in chronic fatigue and related conditions

- ***Comprehensive Thyroid Assessment*** – evaluates central and peripheral thyroid function by assaying hypersensitive TSH, free T4, free T3, and reverse T3, as well as Anti-thyroglobulin and Anti-thyroid peroxidase antibodies

- ***Toxic Element Exposure Profile*** – evaluates hair for "classic" toxics, such as mercury and lead, and less well known toxics used in modern manufacturing, such as palladium and tungsten

Women's Health Assessments:

- ***Menopause Profile*** – now reports estriol and estrone, in addition to estradiol, testosterone, and progesterone for a more comprehensive assessment of hormone balance

- ***Vaginosis Profile*** – now uses a DNA probe to identify definitively the most common organisms responsible for vaginosis

Metabolic Assessments:

- ***Comprehensive Cardiovascular Assessment*** – new high sensitivity C-reactive protein test (hs CRP) is highly reproducible and ten times more sensitive than conventional CRP assessment.

- ***Metabolic Dysglycemia Profile*** – now utilizes Ultrasensitive Insulin which is capable of detecting levels as low as .03 microinternational units/milliliter (µIU/ml) for additional insight into a patient's insulin metabolism.

Gastrointestinal Assessments:

- ***Comprehensive Parasitology*** – now features Optimized Parasite Recovery to enhance detection rates

- ***Comprehensive Digestive Stool Analysis*** – now includes a new latex agglutination test for lactoferrin and a new occult blood test that identifies monoclonal antibodies to intact human hemoglobin

Contact Clinical Support at 800-522-4762 to or der kits for these innovative assessments.

Great Smokies Diagnostic Laboratory℠
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