

# Beyond Insulin Resistance and Syndrome X: The Oxidative-Dysoxygenative Insulin Dysfunction (ODID) Model – Part II

by Majid Ali, MD

## Nitric Oxide Dynamics and ODID

Reactive oxygen species (ROS) induce production of reactive nitrogen species (RNS). RNS, in turn, stimulate the generation of reactive oxygen species. The feedback loops provided by ROS-RNS dynamics feed the oxidative fires and inflict oxidative cellular injury. Under physiologic conditions, superoxide dismutase, catalase, glutathione peroxidase, and a host of enzymes support the reduction arm of redox equilibrium. In hyperinsulinemic and hyperglycemic states, the ROS/RNS loops significantly add to cumulative oxidosis.<sup>158-160</sup>

Endothelium-derived nitric oxide exerts several homeostatic effects in the vascular ecology, including regulation of vasomotor tone, inhibition of platelet aggregation, and prevention of adhesion of leukocytes to the endothelial surface (Vane 1990). In animal models as well as in both type 1 and type 2 diabetes, nitric oxide-dependent vasodilation is impaired.<sup>158</sup> Ascorbic acid improved the vasodilatory response in both types of diabetes.<sup>29,30</sup> Endothelium-dependent vasodilation is impaired in healthy subjects after six hours of hyperglycemic clamp.<sup>159</sup> Studies with incremental brachial artery administration of methacholine chloride during euglycemia and hyperglycemia support one of the core tenets of oxidative insulin dysfunction in that hyperglycemia contributes to abnormal endothelial function through production of superoxide anion.<sup>37</sup>

Higher concentrations of insulin in the blood increase blood flow to the skeletal muscle.<sup>164-170</sup> Some of the increase in the cellular glucose uptake has been attributed to that effect of insulin on the blood flow. The precise mechanism of action of insulin in blood vessel musculature has not been elucidated, but the role of nitric oxide in it has been postulated.<sup>167</sup> Other data suggest that the vasodilatory effect in the skeletal muscle is dependent on hyperinsulinemia and not consequent upon changes in carbohydrate metabolism. There is also evidence there is a reduction in insulin-induced vasodilation in insulin resistance associated with obesity.<sup>165,169,170</sup> In other words, *insulin facilitates its own delivery to the cell membrane and degradation.*

Activation of endothelial NO-synthase in higher concentration is deemed necessary for initiation of the oxidative cascade in endothelial cells that leads to production of excess reactive oxygen species and induction of NF- $\kappa$ B.

## Tumor Necrosis Factor (TNF- $\alpha$ ) and ODID

The secretion of TNF- $\alpha$  by adipocytes is of special interest to me in the context of the proposed oxidative insulin dysfunction model of insulin resistance and type 2 diabetes. This cytokine plays many well-established and crucial roles in the inflammatory and immune responses.<sup>94,171-176</sup> It is expressed in excess in adipocytes of obese patients and is known to

cause insulin resistance through its effects on insulin-mediated cellular signaling pathways.

Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) is a potent inhibitor of insulin signaling in myocytes and adipocytes.<sup>174</sup> Since serum concentrations of TNF- $\alpha$  are very low in lean as well as obese subjects, this cytokine produced in the muscle and fat cells appears to function in a paracrine fashion. TNF- $\alpha$  expression is high in the muscle and fat cells of obese and diabetic subjects. Furthermore, the administration of antibodies that neutralize TNF- $\alpha$  to genetically obese Zucker (*fa/fa*) rats reverses insulin resistance.<sup>171</sup> That creates another mechanism of insulin resistance in mice. Interestingly, administration of the same antibodies to diabetic patients did not reverse insulin resistance.<sup>175</sup>

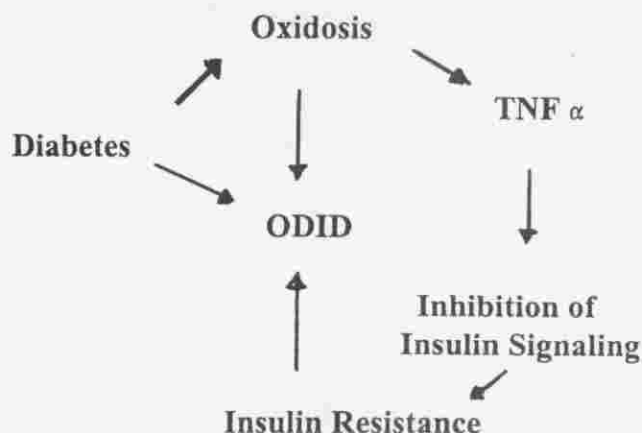
All known inflammatory and immunologic responses are initially triggered as well as regulated by oxidative and oxygenative phenomena.<sup>173-175</sup> Blockade of TNF- $\alpha$  can ameliorate, albeit for limited periods of time, both experimental and clinical forms of autoimmune disorders, such as Crohn's colitis and rheumatoid arthritis.<sup>177-180</sup> Hypersecretory TNF- $\alpha$  responses induced by oxidative stresses are likely to play a role in insulin homeostasis in states of oxidosis associated with hyperinsulinism.

## NF- $\kappa$ B, Endothelial Cells, and ODID

NF- $\kappa$ B is a potent proinflammatory molecule.<sup>181-183</sup> Blockade of NF- $\kappa$ B decreases inflammatory responses in experimental and clinical forms of autoimmune disorders, such as Crohn's colitis and rheumatoid arthritis.<sup>184-186</sup> All inflammatory responses create regional oxidosis and most also lead to systemic oxidosis. Such theoretical considerations strongly suggest that NF- $\kappa$ B might play some roles in the pathogenesis of oxidative-dysoxygenative insulin dysfunction.

Thus, it comes as no surprise that high concentrations of glucose (10-30 mM) result in excess generation of reactive oxygen species which, in turn, activate NF- $\kappa$ B and induce endothelial cell apoptosis.<sup>187</sup> Studies with 3-O-methyl-D-glucose (a glucose derivative which is taken up but not metabolized by cells) and L-glucose have shown that endothelial reactivity is mediated by glucose-specific pathways. This finding is of direct relevance to the pathogenesis of oxidative coagulopathy

Figure 1 – TNF- $\alpha$  I and the ODID Wheel





in uncontrolled diabetics. Endothelial apoptosis results in denudation of the nonthrombogenic inner lining of the vessel wall, resulting in the exposition of highly thrombogenic subendothelial matrix.

#### IGF-1, IGF-2, and ODID

Both insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2) have insulin-like effects on glucose transport in the myocyte and adipocyte.<sup>188-190</sup> That is not unexpected in light of close sequence homologies between insulin and both IGF-1 and IGF-2. In addition, there is also a high degree of sequence homology between the insulin receptor and the IGF-1 receptor. Again, not surprisingly, intracellular signaling pathways activated by both receptors are similar. Like insulin, IGF-1 affects translocation of GLUT-4 to the myocyte surface *in vitro*<sup>188</sup> and exerts a potent hypoglycemic effect.<sup>191</sup>

In health, the glucoregulatory roles of IGF-1 and IGF-2 have been thought not to be significant since these factors are sequestered by specific binding proteins and their serum concentrations in a free state are low. IGF-1 bypasses the insulin receptor and, under those conditions, exerts a significant glucoregulatory role by facilitating glucose uptake in the myocyte and adipocyte.<sup>192</sup> This has been shown in persons with type 1 and type 2 diabetes as well as in instances of mutations in the insulin receptor.

In the oxidative insulin dysfunction states, however, oxidatively induced alterations in the structure and function of those binding proteins are likely to occur. Indeed, there is some evidence that is so in patients with severe insulin resistance, hyperinsulinemia, and poorly controlled diabetes.

#### PPAR $\gamma$ and ODID

Adipocytes are rich in nuclear factor called peroxisome proliferation activator receptor- $\gamma$  (PPAR $\gamma$ ). This receptor is an important determinant of adipogenesis and stimulates adipogenesis in fibroblasts.<sup>193</sup> Persons heterozygous for a dominant-negative PPAR $\gamma$  allele suffer from severe insulin resistance.<sup>194</sup> Mice heterozygous for a null PPAR $\gamma$  allele on a high-fat diet have increased insulin sensitivity and develop adipocyte hypertrophy.<sup>195</sup>

Ligands for PPAR $\gamma$  include thiazolidinediones (TZDs), a class of drugs for diabetes (discussed later). PPAR $\gamma$  binding *in vitro* correlates well with *in vivo* lowering of blood glucose levels. Non-TZD PPAR $\gamma$  ligands also increase insulin sensitivity. Furthermore, activators of the PPAR $\gamma$  heterodimer partner, retinoid X receptor, also increase insulin sensitivity and exert antidiabetic effects.<sup>196</sup>

The antidiabetic effects of some drugs, such as those in the thiazolidinedione class, are due to their ability to decrease insulin resistance. This effect is mediated by a nuclear receptor protein called peroxisome proliferator activated receptor- $\gamma$  (PPAR $\gamma$ ). This protein is involved in the differentiation of adipocytes and is found in large quantities in those cells. PPAR $\gamma$  also affects insulin sensitivity by mechanisms that are presumed to involve altered gene dynamics in adipocytes. Specifically, it was thought that some factor like PPAR $\gamma$  might switch on and off some adipocyte-specific gene involved in insulin-mediated signaling pathways.<sup>197</sup>

Mutations in PPAR- $\gamma$  may be associated with decreased, increased, or variable effects on insulin sensitivity and body weight.<sup>198</sup> Subjects affected by loss-of-function PPAR $\gamma$  mutations show several but not all characteristics of insulin resistance syndrome (including hyperinsulinemia, diabetes, hypertension, and dyslipidemia) as well as acanthosis nigricans not seen in the common type of that syndrome. However, such persons are not obese.<sup>199</sup> Furthermore, in subjects with gain of function, by contrast, obesity is associated with relatively low levels of insulin, pointing to the existence of increased sensitivity to insulin. On the surface, those findings raise the theoretical possibility of prevention of insulin resistance by genetic engineering. However, the situation here is also far more complex than it may seem. A third type of PPAR $\gamma$  mutation results in variable effects on obesity and insulin sensitivity.

Some free fatty acids appear to serve as ligands for PPAR $\gamma$ . Obesity by altering the availability – or possibly qualitative characteristics – of free fatty acids may directly and adversely affect PPAR $\gamma$  signaling and lead to insulin resistance. The increased free fatty acid metabolism, of course, also increases the generation of reactive oxygen species.

## Insulin Dysfunction

The reported incidence of mutations in PPAR $\gamma$  associated with disease to date has been low. However, it is not clear what role impaired PPAR $\gamma$  signaling might play in the common insulin resistance syndrome. The incidence and degree of insulin resistance increase with increasing amounts of abdominal adipose tissue, which enhance insulin sensitivity of not only adipocytes but also of myocytes. That has been attributed to increased release of free fatty acids from triglyceride-laden adipocytes, thus providing a nonglucose metabolic substrate for energy and diminished cellular dependence on glucose. That can be expected to reduce insulin-stimulated glucose clearance – an effect manifested in insulin resistance.

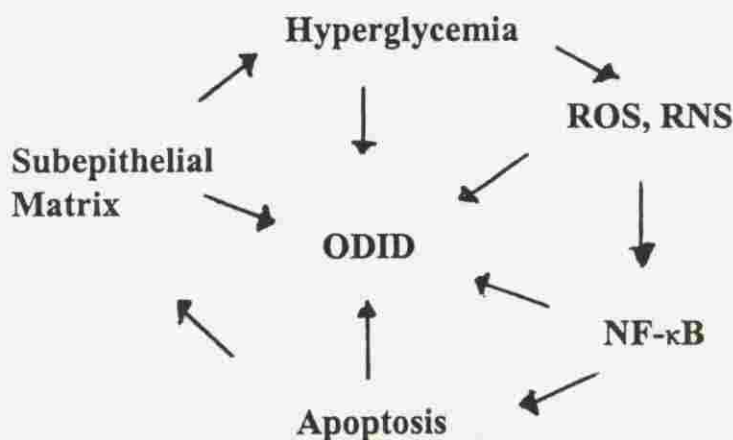
There are yet other molecular facets of adipocyte-insulin-PPAR $\gamma$  dynamics. Phosphorylation of PPAR $\gamma$  on serine residues adversely affects its functionality, even in the presence of thiazolidinediones. That provides another possible mechanism by which expanding fat stores of the body may contribute to insulin resistance.

#### Resistin and ODID

Recently, a new messenger RNA expressed only in adipocytes was recognized by treating differentiated adipocytes with thiazolidinediones.<sup>200</sup> This mRNA is suppressed by that class of drugs. Furthermore, the protein coded by this mRNA, dubbed resistin, suppresses glucose uptake by fat cells mediated by insulin. Finally, several lines of evidence point to that protein being an important link between type 2 diabetes and obesity.

Those observations suggest that PPAR $\gamma$  is a biologic target for thiazolidinedione (TZD) drugs. Recent search for genes that are activated during adipocyte differentiation but

Figure 2 – NF- $\kappa$ B and the ODID Wheel





## Insulin Dysfunction

are downregulated in mature fat cells exposed to TZDs led to the discovery of resistin, a polypeptide specifically expressed and released by adipocytes and named for its ability to produce insulin resistance. Serum levels of resistin are elevated markedly in genetic and diet-induced obesity. Immunoneutralization in that animal model of type 2 diabetes enhanced insulin action and exerted a glucoregulatory role. Resistin messenger RNA is induced during adipocyte differentiation of 3T3-L1 cells, as is the case with other adipocyte-specific genes, such as PPAR $\gamma$  gene. Treatment with TZDs (rosiglitazone, pioglitazone, troglitazone) leads to downregulation of the resistin gene. Interestingly, in such states resistin expression was greater in white fat than in brown fat, in which resistin mRNA was barely detectable.

Administration of resistin led to insulin resistance and hyperglycemia. Those observations point to resistin as one of the important culprits in linking obesity to diabetes as well as being involved in glucoregulatory effects of TZD drugs.

### Leptin: An Integrative Model of Dual Actions

Leptin is an adipocyte hormone with insulin-like activity. It facilitates insulin-stimulated glucose uptake. It functions as an adipostat, signaling the brain in response to changes in availability of energy.<sup>201</sup> The blood levels of leptin correlate well with body fat. It suppresses hunger and thus leads to weight loss. (The term leptin is derived from the Greek word for thin.) However, in the obese subjects and in animals, sensitivity of target tissues to leptin is reduced and leptin resistance (like

insulin resistance) is associated with excess weight gain. Women have higher serum concentrations of leptin than men.<sup>202,203</sup>

The absence and deficiency of leptin leads to obesity and severe insulin resistance in rodents.<sup>202,203</sup> An inherited deficiency of this hormone, for instance, results in both insulin dysfunction and obesity. Administration of leptin to such animals results in reversal of insulin resistance. That effect is independent of weight and food intake and appears to be exerted both within the brain and peripheral tissues. Interestingly, blood leptin levels are higher in obese humans than in persons with normal weight.<sup>204</sup>

The hypothalamus is leptin's primary site of action, but it also affects peripheral tissues. It is not clear how much of the leptin's glucoregulatory effects are mediated through the sympathetic nervous system. In the normal, genetically obese, and diabetic rodents, leptin diminishes the degree of hyperinsulinemia and increases sensitivity to insulin, thus decreasing insulin resistance.<sup>205,207</sup> This action is independent of changes in the diet or weight.

Leptin does not directly increase glucose transport in adipocyte or muscle cells. However, it increases oxidation of fatty acids and so indirectly affects glucose transport and metabolism.<sup>208</sup> Leptin also influences physical activity, thermogenesis, serum concentrations of fatty acids, and glucose flux in the liver.<sup>209</sup> There are yet other effects of this hormone. The brain centers involved with appetite are rich in leptin receptors. Leptin suppresses the production of two recently discovered hormones, orexin-A and orexin-B, that increase appetite. (*Orexis* is the Greek word for hunger.) Since orexins regulate diverse autonomic functions in the bowel, bladder, and other tissues, leptin indirectly affects glucose and insulin metabolism in myriad other ways.

In addition to its roles in the long-term energy balance, leptin has dual and seemingly paradoxical effects on neurons in the hypothalamus. Proopiomelanocortin (POMC) and neuropeptide-Y (NPY) types of neurons in the arcuate nucleus produce potent neuropeptide modulators, melanocortins and neuropeptide-Y, that exert opposing effects on feeding, metabolism, and weight. Those neurons are also principal sites of leptin receptor expression. Leptin increases the frequency of action potentials in the anorexigenic POMC neurons both by depolarization through a nonspecific cation channel and by decreased inhibition by local orexigenic neuropeptide- $\gamma$ /GABA neurons. Thus, leptin directly depolarizes the POMC neurons while simultaneously hyperpolarizing the somata of NPY/GABA, diminishing the release of their peptides. The diminished GABA release disinhibits the POMC neurons. POMC and NPY neurons express autoreceptors for some of their own neuropeptide products ( $\beta$ -endorphins or  $\alpha$ -MSH and NPY respectively). Melanocortin peptides exert an autoinhibitory effect on that circuit.

In essence, this model recognizes two classes of neurons accounting for leptin sensitivity: those depolarized (activated) to release anorexigenic peptides and those hyperpolarized (inhibited) to decrease the output of orexigenic peptides. Based on those findings, an integrative model of regulation of the leptin-related circuit has been proposed.

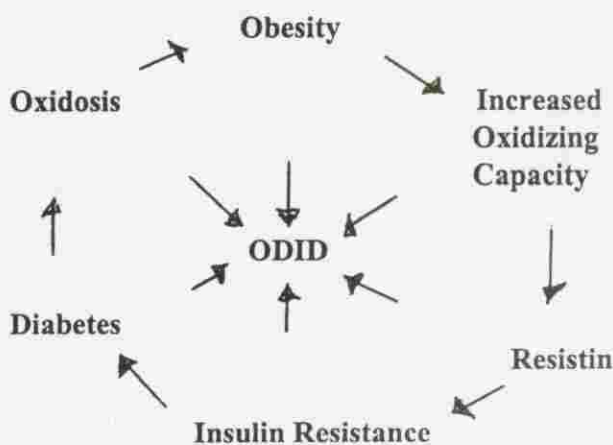
### Thyroid, Adrenals and ODID

In animal studies, basal and insulin-stimulated uptake of glucose by myocytes and adipocytes is increased after administration of thyroid hormone in normal animals.<sup>210-212</sup> That effect of thyroid hormone appears to be mediated, at least partially, by increased GLUT-4 expression. Furthermore, in obese Zucker rats, hyperinsulinemia is reversed with thyroid hormone replacement.<sup>213</sup> Those thyroid/insulin interactions provide a possible explanation of several clinical observations and biochemical abnormalities encountered in patients with fibromyalgia, chronic fatigue syndrome, chemical sensitivity syndrome, and a host of indolent autoimmune disorders.<sup>214</sup>

Patients with fibromyalgia (FM) and chronic fatigue syndrome (CFS) often complain of undue cold sensitivity. Most such patients show circulating antithyroid antibodies and abnormal thyroid function tests, i.e., low serum values of T4 coexisting with low serum concentrations of thyroid stimulating hormone. Nearly all such patients respond well to low-dose thyroid hormone supplementation.<sup>215</sup>

Corticosteroid therapy is known to lead to the development of frank diabetes in many subjects with a family history of diabetes and/

Figure 3 – Resistin and the ODID Wheel





or hyperinsulinemia. A more commonly observed pattern is that of abnormal urinary excretion of adrenal metabolites in patients with ODID. Many patients with FM/CFS complex suffer from episodes of weakness, lightheadedness, rapid heart rate, palpitations, and sweating. Those symptom-complexes may be attributed to rapid hyperglycemic-hypoglycemic shifts and brisk glucose-insulin-adrenaline responses. Dietary plans that prevent rapid hyperglycemic/hypoglycemic shifts commonly afford symptom relief. Similarly, nutrient supplements that exert glucoregulatory influence (such as chromium) and herbal preparations with empirical salutary effects on glucose metabolism (such as *Gymnema sylvestre*) are of considerable clinical benefit. However, symptoms often persist with lesser intensity in many such cases until adrenal support is provided in the form of dehydroepiandrosterone (10 to 50 mg daily) and/or hydrocortisone (5 to 10mg in am and 2.5 to 5 mg in the afternoon).<sup>216</sup>

My clinical and biochemical observations led me to put forth the oxidative-dysoxygenative model of FM/CFS complex in *The Canary and Fibromyalgia*.<sup>217</sup> In that model, both autoimmune and non-autoimmune forms of thyroid and adrenal dysfunctions encountered in FM/CFS complex are caused by the same oxidative-dysoxygenative elements that cause all other patterns of injury to cellular microecologic and tissue/organ macroecologic systems of the body.

### Sex Hormone Dynamics and ODID

Nearly six percent of women of reproductive age in the United States develop polycystic ovary syndrome.<sup>218</sup> It is characterized by multiple small-sized stromal ovarian cysts, prolonged periods of anovulation, hyperandrogenism, insulin resistance, compensatory hyperinsulinemia, and increased risk of syndrome X and type 2 diabetes. Production of ovarian testosterone is stimulated by insulin surfeit in this syndrome,<sup>219-221</sup> whereas ovulation is inhibited.<sup>222</sup>

I have on some occasions observed the development of type 2 diabetes mellitus after antiandrogenic therapy for prostate cancer. In some cases, such diabetes was controlled with dietary and exercise programs, obviating the need for oral hypoglycemic agents or insulin.

### D-Chiro-Inositol and Gonadal Dysfunction

The case of inositol phosphoglycan, an insulin-like mediator, provides yet further windows to the workings of insulin.<sup>185-190</sup>

Among the mediators involved in the actions of insulin are low-molecular-weight inositol phosphoglycan. Mediators of this class

are generated by hydrolysis of glycerophosphatidylinositol lipids located at the outer leaflet of the cell membrane. Such mediators are then internalized, where they exert their intracellular metabolic effects. Notable among these mediators is an inositol phosphoglycan molecule containing D-chiro-inositol, which activates enzymes that catalyze both oxidative and nonoxidative metabolism of glucose.<sup>223</sup> Deficiency of D-chiro-inositol phosphoglycan has been linked to impaired glucose tolerance, insulin resistance, compensatory hyperinsulinemia, syndrome X, and diabetes mellitus in humans<sup>224-226</sup> and primates.<sup>227</sup> The concentration of D-chiro-inositol in the muscle tissue is lower in type 2 diabetics than in healthy subjects.<sup>228</sup> In limited studies, administration of D-chiro-inositol to rats and monkeys resulted in decreased insulin resistance and accelerated glucose disposal.<sup>227</sup> Presumably, D-chiro-inositol so administered is used to synthesize active D-chiro-inositol phosphoglycerate mediator which, in turn, facilitates the actions of insulin, so decreasing insulin resistance.<sup>229</sup>

In women with polycystic ovary syndrome, insulin resistance is accompanied by gonadal dysfunction, including anovulatory status and excessive ovarian production of androgens. The potential benefits of orally administered D-chiro-inositol for normalizing such gonadal abnormalities has been explored. In one recent study, oral administration of a daily dose of 1200 mg of D-chiro-inositol to women with polycystic ovary syndrome resulted in improved ovulatory function, lower serum concentrations of free testosterone and triglycerides, and improved insulin sensitivity.<sup>230</sup>

D-chiro-inositol/insulin dynamics is not unidirectional. Insulin both influences and is influenced by D-chiro-inositol. Specifically, insulin stimulates biosynthesis of chiro-inositol-containing phospholipids in a rat fibroblastic cell line expressing the human insulin receptor.<sup>231</sup>

Two possible pathophysiologic derangements have been postulated to explain the pathogenesis of D-chiro-inositol deficiency. Conversion of intracellular myo-inositol into chiro-inositol is catalyzed by an epimerase-type enzyme.<sup>232-233</sup> It has been suggested that inactivation of this enzyme results in deficiency of D-chiro-inositol.<sup>228</sup> Alternatively, it has been proposed that D-chiro-inositol deficiency is caused by excessive breakdown prior to renal clearance. It seems safe to predict that the impairment or inactivation of this enzyme will be proven to be due to oxidative injury, just as has been the case of enzymatic failures involving other enzyme systems in chronic states of oxidosis and acidosis.

## Insulin Dysfunction

### Genetic Syndromes of Insulin Dysfunction

The number of disorders accompanied by insulin dysfunction considered to be genetic in origin is growing rapidly.<sup>234-243</sup> The well-characterized entities in this category include the classical Type A syndrome of insulin resistance, the Rabson-Mendenhall syndrome, pseudoacromegaly, leprechaunism, and variants of lipodystrophy (total congenital lipodystrophy and partial congenital lipodystrophy).<sup>231</sup> Advances in the exploding fields of genomics and proteomics will undoubtedly further differentiate those entities into a far more heterogeneous group. In some entities among the group, the role of oxidative phenomena is direct and readily discerned. In others, the genetically determined deficits seem to be amplified by their sensitivities to oxidative stress. I include below brief comments about those syndromes to provide a framework for presenting an integrated view of genes, environment, nutrition, and insulin dysfunction later in this article.

The best known among genetic insulin dysfunction is the Type A syndrome of insulin resistance. It classically occurs in adolescent girls and is characterized by pronounced endogenous hyperinsulinemia, ovarian hyperandrogenism, acanthosis, and varying degrees of glucose intolerance.<sup>235</sup> Clinical features of hyperandrogenism include amenorrhea, hirsutism, and virilization. The ovaries exhibit hyperthecosis and stromal hyperplasia of the type commonly seen in women with polycystic ovary syndrome.<sup>236,237</sup> The Rabson-Mendenhall syndrome is a variant of Type A syndrome with features of pineal hyperplasia, dental hyperplasia, and dysmorphic features.<sup>238</sup> Some patients also exhibit features of acromegaly, coarsened features, widened spaces between teeth, and normal or low circulating levels of growth hormone and IGF-1.<sup>238</sup> Mutations recognized in many subjects with Type A syndrome include those that cause defects in insulin receptors,<sup>239-240</sup> the signaling capacity of the receptor,<sup>241,242</sup> insulin-receptor binding (affinity as well as number), and insulin-stimulated receptor autophosphorylation and kinase activity. In a single case of Type A syndrome, complementary DNA was found to be normal, raising the likelihood that defects in receptor-gene promoter or other involved proteins may be the molecular lesion involved.<sup>239</sup>

Leprechaunism is an uncommon disorder characterized by intrauterine growth retardation, lipodystrophy, acanthosis nigricans, dysmorphic facial features, and severe insulin resistance.<sup>243</sup> Affected girls usually have cystic



# Insulin Dysfunction

ovaries and exhibit hirsutism and clitoromegaly. In some instances of leprechaunism, abnormalities of receptors of epidermal growth factor and IGF-1 are also seen.<sup>244</sup> Those and several other observations alluded to in other parts of this article strongly suggest the existence of extensive links between insulin pathways and those of myriad other receptors.<sup>245</sup>

Lipodystrophy may be total with complete absence of adipose tissue (Berardinelli-Seip syndrome) or partial with variable regional fat hypertrophy or lipoatrophy.<sup>246</sup> Absence or paucity of fatty tissue leads to severe hypertriglyceridemia and consequent fatty infiltration in the liver and spleen and hepatosplenomegaly. Dysmorphic and acromegalic features are often present. Predictably, a plethora of defects in insulin receptor expression, insulin binding with receptor, signaling pathways, receptor kinase function, and post-receptor pathways are present and provide the underlying mechanisms of insulin resistance.<sup>247</sup>

Type B insulin resistance syndrome is essentially characterized by the presence of anti-insulin-receptor autoantibodies.<sup>248-249</sup> Not surprisingly from the perspective of nature's

preoccupation with complementarity and contrariety, antireceptor antibodies can function both as agonists and antagonists.<sup>250</sup> Thus, patients with this syndrome often show a diverse and changing clinical picture, with fasting hypoglycemia, postprandial hyperglycemia, insulin resistance, overt diabetes, and hyperandrogenism appearing and disappearing at various stages during the course of the illness. Eventually most patients develop severe diabetes, acanthosis nigricans, and hyperandrogenism in young women. Variable degrees of clinical success with glucocorticoids, plasmapheresis, and immunosuppressant drugs have been reported.<sup>250-252</sup>

To add to diversity, insulin-receptor autoantibodies of unknown functionality have been documented in patients with typical NIDDM.<sup>253</sup> It is noteworthy in this context that the ability of insulin to stimulate autophosphorylation and tyrosine kinase activity is decreased in insulin receptors derived from not only myocytes, adipocytes, and hepatocytes but also those taken from circulating monocytes of patients with NIDDM.<sup>254</sup> Furthermore, weight reduction in obese patients with NIDDM results in improved blood glucose levels and corrects the defect in kinase activity of insulin receptors.<sup>255</sup>

## Hypoglycemia and ODID

The hypoglycemia controversy is spurious. It arises from a failure to consider some elementary aspects of the glucose tolerance study. Doctors without any interest in nutrition rarely diagnose hypoglycemia whereas physician-nutritionists consider it a common clinical entity. The former often accuse the latter of succumbing to patients' persuasions and diagnosing and treating an imaginary disorder (the old "all in the head" story). Nutritionists dismiss that opinion as ignorant.

There is something peculiar about this so-called hypoglycemia controversy. There is an enormous body of literature about insulin-induced hypoglycemia and other forms of cellular glucopenia associated with defects in glucose counterregulation in diabetes as well as certain other metabolic disorders. Those were the subjects of a recent book.<sup>256</sup> Table 3 shows how broadly and profoundly hypoglycemia affects the entire endocrine system. And yet, hypoglycemia in nondiabetic subjects with brisk symptomatic hyperglycemic-

hypoglycemic shifts rarely, if ever, evokes interest among endocrinologists.

So profound are the effects of hypoglycemia in glucose counterregulation that a single episode may lead to lowering of neuroendocrine responses. In diabetes, the glucagon response to hypoglycemia is attenuated and the impairment of growth hormone and cortisol responses to glucopenia may be reduced by as much as 25%. There are other important metabolic shifts in hypoglycemia. For instance, under physiologic conditions, glucose is the primary source of energy in the brain. During hypoglycemia associated with starvation, ketones may be the substrate for up to 60% of the energy requirement of the brain.

The medical texts usually state that the diagnosis of hypoglycemia should be made only when the blood sugar level of 50 mg/dl or lower is associated with symptoms of hypoglycemia (weakness, sweating of acute onset, tremors, nausea, cramps, vomiting, lightheadedness, headache, and tachycardia). The frequency of hypoglycemia, as defined by the above classic criteria, is considered very low. The nutritionists, by contrast, use clinical criteria of the above symptom-complexes when the symptoms can be relieved with appropriate dietary measures. They also pay attention to subtle consequences of hypoglycemia, such as unexplained moodswings and a vague sense of ill-being, that respond well to nutritional glucoregulatory therapies. I explored those issues with a large study of 1,000 glucose tolerance tests performed for outpatients in a hospital laboratory. The staff was asked to diligently explain to the patients the nature of the test and ask them to make entries on a symptom sheet for all symptoms (including subtle effects mentioned above) experienced throughout the duration of the test. The phlebotomists were required to ask specific questions about symptoms each time a blood sample was obtained. Thus, the records of symptoms were far more accurate than if the staff had inquired about symptoms after finishing the test or, worse, the physicians had tried to elicit the history of symptoms during their visits with the patients some days later.

In the above study, two important observations were made: First, a far greater number (22%) of subjects reported one or more symptoms (among those listed above) during the test period than that generally given in textbooks. Second, nearly nine times as many subjects reported symptoms during the early part of the test when the blood glucose values were rising than during the late stages of the test when the glucose values were falling. Those findings strongly suggest that symptoms associated with glucose tolerance

**Table 3**

### Effects of Hypoglycemia on the Endocrine System

Organ	Hormone	Effect
Hypothalamus	Growth hormone releasing hormone	Increased
	Corticotrophin releasing hormone	Increased
Anterior Pituitary	Growth hormone	Increased
	ACTH	Increased
	Prolactin	Increased
	Beta endorphin	Increased
	Thyroid stimulating hormone	Decreased*
Posterior Pituitary	Vasopressin	Increased
	Oxytocin	Increased
Adrenals	Cortisol	Increased
	Adrenaline	Increased
	Aldosterone	Increased
Pancreas	Insulin	Decreased
	Glucagon	Increased
	Pancreatic polypeptide	Increased
	Somatostatin	Increased
		Increased
Thyroid	Thyroxine, T3	None established
Misc.	Gastrin	Increased
	Parathyroid hormone	Increased

\*In states associated with dysoxygenosis, such as chronic fatigue/fibromyalgia, the thyroid stimulating hormone is often low while blood thyroxine level is increased.



that are usually associated with hypoglycemia are, in reality, associated with rapid rises in blood glucose levels.

Brisk insulin responses triggered by rapid hyperglycemic shifts lead to catecholamine release. Since the symptoms associated with glucose tolerance studies are also classically seen in hyperadrenergic states, it is likely that such symptoms are caused by hyperglycemic-insulin-adrenergic responses. In all symptomatic subjects in this study, symptoms were relieved within several minutes by reassuring the patient as well as with the use of self-regulatory methods, further supporting the role of adrenergic response in this setting.

The clinical problems of hypoglycemia are complicated by the fact that lay people misunderstand the disorder, and patients may attempt to impose their views on the physicians. (*Postgraduate Medicine*, July 1990)

This is an illuminating statement. The first part of this statement concerns the nature of this problem. As a hospital pathologist, I examined over a thousand glucose tolerance test results. As clinicians, my colleagues at the Institute and I have managed over 5,000 patients with chronic fatigue/fibromyalgia complex and nutritional disorders. A majority of such patients suffered from symptoms of rapid hyperglycemic-hypoglycemic shifts and brisk insulin and adrenergic responses. It is my sense that hypoglycemia is misunderstood by endocrinologists much more frequently than by the patients. Patients know something about this problem because they suffer from it. Doctors who limit their practice to use of drugs are restricted to the textbook descriptions of hypoglycemia. They neither vigorously study the subject nor put to test the corrective nutritional approaches recommended by physician-nutritionists.

The second part of this statement is equally interesting. The author laments the fact that patients who suffer from this problem may attempt to impose their views on the physician. This fascinates me. In classical medicine, we physicians are brought up to be on guard against patients imposing their views on us. The unstated operant principle here is that patients' descriptions of their suffering should be dismissed if the laboratory criteria (set arbitrarily) are not met. In integrative medicine, a clinician wants to be guided by the patient's views. After all, one thing a practitioner can never do is to get under the patient's skin. That brings me to an important question: Who is a better judge of what works and what does not, the patient or his physician? In matters of clinical observation in an acute illness, clearly the experienced physician is a better judge. When it comes to long-term management of chronic symptoms such as

those caused by blood sugar rollercoasters, my unequivocal answer is: the patient.

I estimated that the diet of a child, at the turn of the last century, included five to ten pounds of sugar per year. Recently collaborating with the cook of a boys' summer camp and extrapolating from the amount of sugar consumed in two months at the camp, I calculated that 143 pounds of sugar were ingested by each boy that year. Such massive overload of sugar with consequent unrelenting oxidosis is rarely, if ever, mentioned in discussions of insulin resistance and type 2 diabetes. As I indicated earlier in this article, sugar and insulin are potent oxidizers. A hyperadrenergic state created by those two factors is also a powerful oxidizing influence.

Figure 4 shows what I call the "glucose rollercoaster" pattern of abnormal glucose tolerance curve indicating rapid insulin and counterregulatory responses.

#### Noninsulin Glucoregulatory Dynamics of the Human Ecosystems

In the Western deterministic-reductionistic model of insulin resistance, the dynamics of the bowel, blood, and liver ecosystems are completely ignored. Indeed, except in a handful of reports concerning the nutritional and herbal therapies for management, none of the papers cited in this article make even a passing reference to dynamic events in the bowel and blood ecosystems that profoundly affect glucose and insulin pathophysiology in health and disease. Specifically, the dynamics of digestive-absorptive phenomena occurring in the gastrointestinal tract as well as issues of bowel motility, altered bowel flora, and long-term consequences of xenobiotic overload were singularly avoided in those articles.

Myriad symptom complexes are associated with rapid hyperglycemic-hypoglycemic shifts and abnormal glucose-insulin-adrenaline responses in non-diabetic subjects in a host of nutritional, ecologic, and immune disorders.<sup>257</sup> Glucose regulation is markedly impaired in such subjects. Indeed,

## Insulin Dysfunction

the non-glucoregulatory events that occur in the bowel, blood, liver, and other major ecosystems of the body and lead to clinically significant disruptions of carbohydrate metabolism are generally completely ignored. This is all the more puzzling since rapid and symptomatic hyperglycemic/hypoglycemic shifts and glucose-insulin-adrenaline responses in those nondiabetic subjects are generally easily controlled with appropriate therapies that restore the involved ecosystems. This may strain the credibility of doctors that limit their work to pharmacologic interventions but will be readily confirmed by physician-nutritionists and nutritionists well-versed with those therapies. Below, I present some morphologic, biochemical, clinical, and historical aspects of the non-insulin-glucoregulatory aspects of the bowel, blood, and liver ecosystems.

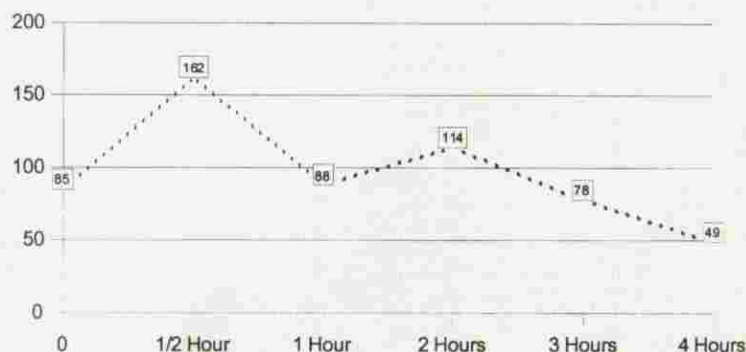
#### A. Morphologic Aspects

In my view, the most direct, cost-effective, and timely method to assess the integrity of the bowel and blood ecosystem is examination of peripheral blood smears with high-resolution, phase-contrast microscopy. I have published a large number of photomicrographs to support this conclusion.<sup>258</sup> Specifically, the frequency and degree of oxidative coagulopathy correlates well with symptom-complexes associated with altered states of bowel ecology.<sup>259</sup> Salient features of oxidative coagulopathy are illustrated in Figures 5-10.

#### B. Biochemical Aspects

I have commonly observed a "double-camel-hump" pattern of fluctuations in the blood glucose and insulin levels tolerance test and timed insulin studies in patients with a host of nutritional, digestive-absorptive, and ecologic disorders who were not receiving insulin or oral hypoglycemic agents. An

Figure 4 - A "Glucose RollerCoaster" Pattern of Blood Glucose Levels Produced by Rapid Hyperglycemic-Hypoglycemic Shifts





## Insulin Dysfunction

example of such a roller coaster effect is given in Figure 4. Voluminous literature on glucose and insulin pathophysiology is peculiarly silent on this subject. Perhaps that is so because the rates of rises and falls in insulin and glucose levels are rarely, if ever, critically looked at by insulin researchers and diabetologists when the absolute numerical highs and lows do not reach their expected levels.

The factors related to the bowel permeability, transit time, abnormal flora, and digestive-absorptive dysfunctions that lead to altered states of bowel ecology profoundly affect blood glucose levels and the type of hyperglycemic-hypoglycemic shifts illustrated in Figure 4. Similarly, the role of the liver in the pathogenesis of rapid hyperglycemic-

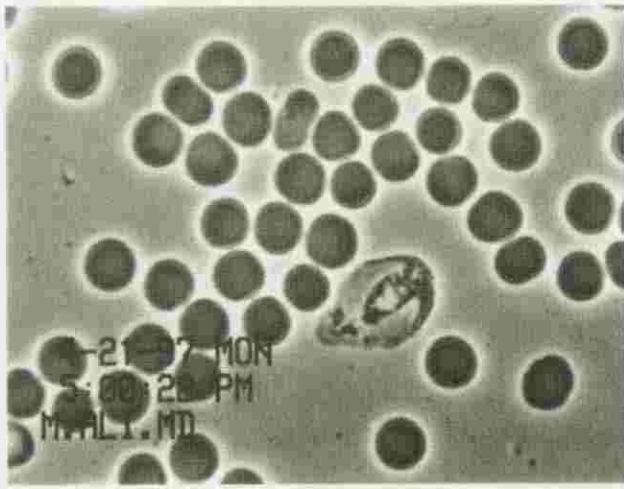
hypoglycemic shifts is often not given due consideration. It is well-established that the liver responds directly to ambient blood glucose concentrations, independent of insulin dynamics. Specifically, *in vitro* experiments with perfusion of the liver with glucose solution in the absence of insulin have demonstrated inhibition of glycogenolysis and stimulation of glycogenesis. Those effects are attributed to allosteric inhibition of phosphorylase by glucose and secondary stimulation of protein phosphatase activity. Those essential aspects of hepatic reactions are considered important by nutritionists since the concept of "liver toxicity" is greatly emphasized in their schools of thought. Furthermore, therapies for "liver detoxification" are vigorously employed by them in the management of disorders of carbohydrate metabolism. Endocrinologists and internists, with rare exceptions, neither

believe in liver toxicity (in the absence of abnormal liver function tests) nor test naturopathic therapies directed to normalization of liver function. That viewpoint may seem untenable to the latter group, but that is strongly supported by both the empirical clinical and laboratory observations of the former.<sup>261-263</sup>

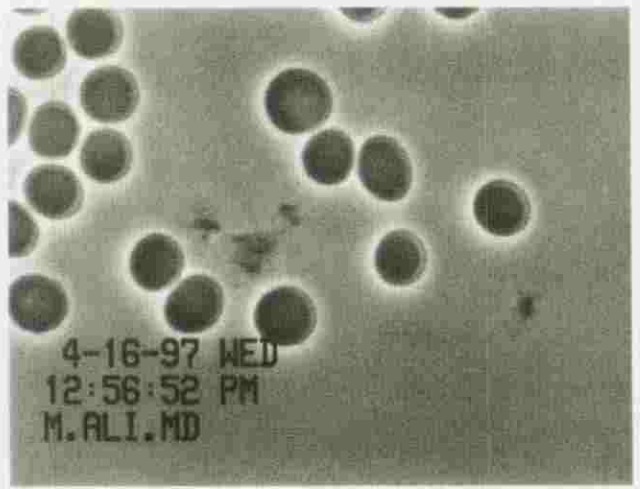
### C. Clinical Aspects

Reports by integrative physicians that focus heavily on issues of diet, nutrition, bowel flora, and hepatic detoxification, on the other hand, nearly always show improvements in glucose homeostasis as well as clinical symptom-complexes attributable to brisk hyperglycemic-hypoglycemic shifts and rapid glucose-insulin-adrenergic responses.<sup>260</sup> I have commonly observed amelioration of those symptoms in patients with fatigue/fibromyalgia complex when I incorporated in

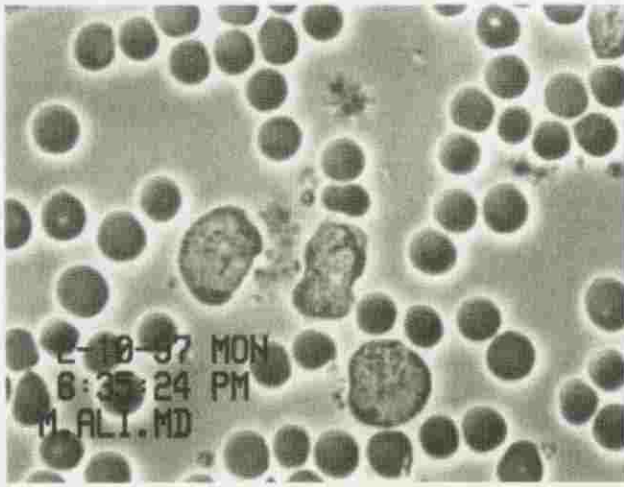
**Figure 5. Peripheral Blood Morphology in a Healthy Control Subject (x10,000). Note Clear Background and a Leukocyte**



**Figure 6. Early Changes of Oxidative Coagulopathy. Note a Microclot Formed by Congealed Plasma in the Center Field.**



**Figure 7. Early Changes of Oxidative Coagulopathy. Note Three Microclots (Center Field, and at 12 and 2 O'Clock)**



**Figure 8. An Intermediate Stage of Oxidative Coagulopathy. Note Multiple Microclots**





my management plan (in small doses) thyroid replacement and adrenal support in the form of DHEA, pregnenolone, or androstenedione (unpublished data).

#### D. Historical Aspects

In the Indian Ayurvedic, traditional Chinese, African indigenous, and medieval European naturopathic traditions, there was a sharp focus on the "health of the bowel and liver" for normalizing sugar and insulin derangements.<sup>261-263</sup> The practitioners of those healing arts continue to subscribe to the clinical notions of their predecessors and consider issues of the bowel and liver fundamental to their management of carbohydrate disorders. That is so because their empirical and laboratory observations concerning carbohydrate metabolism and insulin dysfunctions fully validate the purely clinical concepts of the earlier practitioners. Furthermore, they observe that carbohydrate metabolism in those cases can be restored to normal with resolution of the bowel and liver factors that caused the abnormalities in sugar and insulin metabolism. This is readily evident from their literature<sup>261-263</sup> and can be validated by brief visits to their clinics.

Below, I include a simple schema of the relative importance of the human ecosystems which I use for patient education.

#### Oxidative-Dysoxygenative Cell Membrane Dysfunction

In 1987, in a monograph entitled *Leaky Cell Membrane Dysfunction*,<sup>2</sup> I introduced the term "oxidative cell membrane dysfunction" to draw attention to diverse cellular dysfunction that seemed to result from unrelenting oxidative injury to the cell membrane.<sup>2</sup> That simple concept originally arose in my mind when I reflected on the

diverse clinical observations of mainstream doctors about the clinical efficacy of calcium channel blockers<sup>264-266</sup> and of nutritionists concerning the value of magnesium supplementation.<sup>267-269</sup> Subsequently, I recognized the strong explanatory power of this model in a host of nutritional, ecologic, immune, and degenerative disorders.

The cell membrane separates internal order of a cell from external disorder. I introduced the term oxidative cell membrane dysfunction for a state in which accelerated oxidative injury to cell membrane lipids, proteins, sugars, and antioxidant enzyme systems leads to membrane-related functional deficits in cellular homeostasis. That simple conclusion seemed inescapable to me in light of my: (1) clinical observations in patients who experienced symptomatic rapid hyperglycemic-hypoglycemic shifts and abnormal glucose-insulin-adrenaline responses associated with hyperinsulinemia; (2) studies of oral glucose tolerance test and timed serum insulin concentrations; and (3) high-resolution phase-contrast microscopic evidence of accelerated oxidative molecular injury.<sup>2-5</sup> Subsequently, I conducted extensive surveys of oxidative phenomena in human biology and marshaled extensive evidence for my view.<sup>6-10</sup>

#### Insulin resistance, in essence, is an oxidative cell membrane dysfunction.<sup>2</sup>

In that monograph, I included the above words to express my view of insulin resistance.<sup>1</sup> It seemed self-evident to me that global oxidative cell membrane can be expected to interfere with any or all cell receptor-ligand systems as well as the signaling pathways triggered by them. I could see no reason why insulin-insulin receptors dynamics and the signaling pathways activated by that complex could be a singular exception to that. There is

## Insulin Dysfunction

some evidence to support that theoretical consideration. For example, insulin stabilizes cell membrane function in cases of calcium channel blocker drug toxicity.<sup>270</sup> Such toxicity is characterized by conduction delay, bradycardia, peripheral vasodilation, hypoinsulinemia, hyperglycemia, metabolic acidosis, and shock.<sup>271</sup> The interactions between insulin and calcium channels have not been elaborated. Hypoinsulinemia in such toxicity appears to be causally related to the clinical features of the syndrome, most likely because it impairs glucose entry into myocytes and leads to loss of inotropy, decreased peripheral vascular resistance, and shock.<sup>272</sup> It is noteworthy in this context that myocytes oxidize free fatty acids in an unstressed state for energy needs, but only glucose in states of shock.<sup>273</sup> Furthermore, hyperinsulinemia-euglycemia therapy is usually effective in

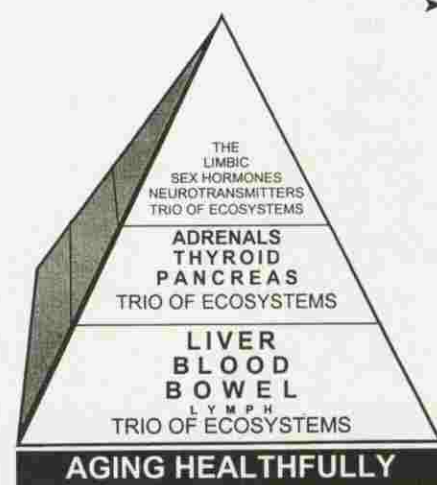


Figure 11  
The Pyramid of Human Ecosystems

Figure 9. An Advanced Oxidative Coagulopathy. Two Well-Formed Microplaque Are Present in the Center Field

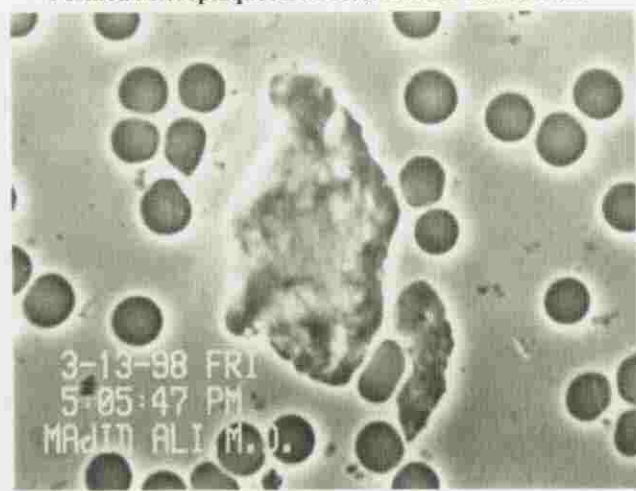
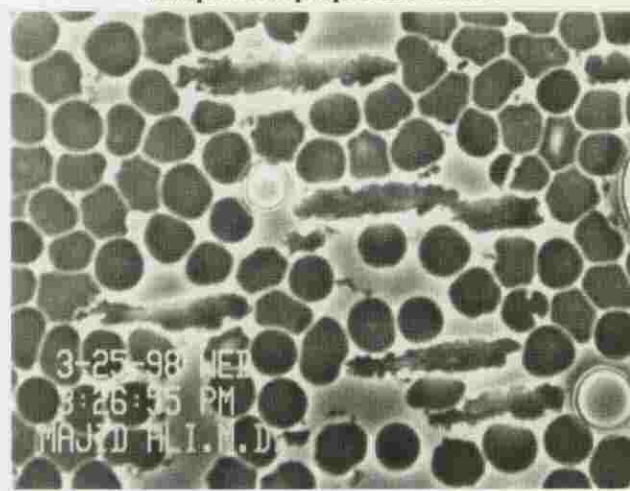


Figure 10. Advanced Oxidative Coagulopathy. Multiple Microplaques Are Present





## Insulin Dysfunction

controlling shock associated with toxic calcium channel blockade.<sup>270</sup>

### The Plasticized Cell Membrane Dysfunction

For patient education, I also use the term "plasticized cell membrane dysfunction." This term allows me to create an image of cell membranes coated with synthetic chemicals and other toxins that make it difficult for them to "breathe" and perform their myriad regulatory functions – including those involving the receptor and signaling pathways of insulin as well as those of glucose counterregulatory factors. Beyond my attempt to create a readily understandable image for my patients without biochemistry background, I believe this term effectively explains the larger concept of ODID model. Specifically, insulin pathophysiology, in my view, results from the cumulative "plasticizing" effects of all oxidative and dysoxygenative factors that impede or block the above-mentioned pathways as well as those that involve induction, silencing, and mutations of related genes.

### Ecogenomics and Econeutrogenomics

In these times of buzz words, sooner or later someone will come up with the terms "ecogenomics" and "econeutrogenomics." So I propose those terms, only half in jest. On a serious note, I now address what I believe to be one of the foremost challenges in the pathophysiology of insulin today: How to integrate explosive advances in the knowledge of genomics and proteomics into clinical management strategies for those with obesity, oxidative insulin dysfunction, diabetes, and a

host of related metabolic disorders. In the past decades, great strides have been made in defining individual steps in biologic pathways with molecular dissections under experimental conditions. That knowledge was used to develop a rich repertoire of blocker drugs that suppress (usually) or promote (uncommonly) molecular events to seek glucose homeostasis. With advances in genomics and proteomics, undoubtedly newer and novel agents will be forthcoming that will allow yet further improvement in glucoregulatory efforts.

My purpose in proposing those terms is to underscore the need for "integrative thinking" and focusing on interrelationships between environment, nutritional, and genetic factors.

Explosive and sustained advances in the fields of genomics and proteomics are rapidly changing the landscape of experimental medicine. It is now abundantly clear that individual steps in molecular pathways that were once considered discrete in the past are in reality components of vast and ever-changing kaleidoscopes of human biology. None of those steps may be blocked with impunity for long. And the pathways of insulin pathophysiology are no exception.

In the earlier section of this article, I have described many dynamics of insulin that influence, and are influenced by, molecular pathways of exercise, nitric oxide, IGF-1, NF- $\kappa$ B, TNF $\alpha$ , leptin, peroxisome proliferator activated receptor- $\gamma$  (PPAR $\gamma$ ), resistin, glutamic acid decarboxylase (GAD), and derangements of the thyroid and adrenal glands. Of special interest in the context of oxidative insulin dysfunction is the ability of insulin to induce expression of plasminogen-activator inhibitor type 1 (a prothrombotic molecule) that provides one of the several direct and indirect links between insulin pathways, inflammatory responses, and oxidative coagulopathy.<sup>69</sup>

Insulin affects human life span in many well-established ways. It may be noted here that an insulin-like signaling system has been linked to development, metabolism, and aging in *Caenorhabditis elegans*.<sup>274</sup> Mutations in the *daf-2* insulin receptor-like gene (as well as downstream *age-1* phosphoinositide 3-kinase gene) extend the life span of the adult worm two- to three-fold. Interestingly, in such studies, insulin-like signaling in neurons alone was sufficient to prolong the life span, thus decoupling regulation of life span from energetic metabolism. It is highly likely that with time many more genes affecting the metabolism of insulin and additional insulin-like signaling systems will be discovered.

I believe the future studies in ecogenomics and econeutralgenomics will be properly conducted only by clinicians with a broader view of those relationships. Specifically, the prevailing model of blinded studies with single drugs will not be acceptable. Nor will it be tenable to study individual molecular steps in mutant mice and with impunity extrapolate the animal data for designing long-term therapies for humans.

For patient education, I use the following schema to explain the relationships between genes, environment, and nutrition in the pathogenesis of ODID and diabetes mellitus.

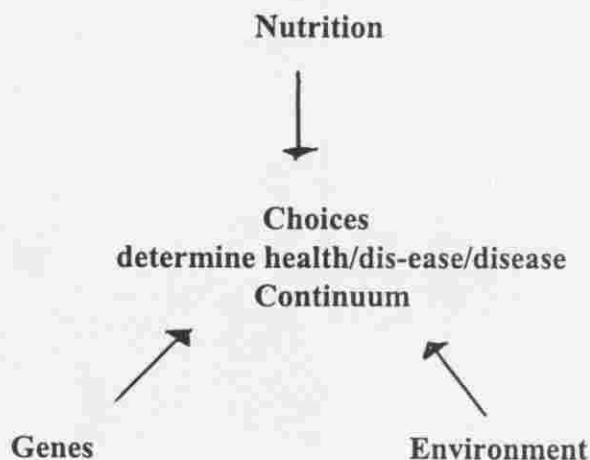
Control of clinical symptom-complexes of oxidative insulin dysfunction with integrative nutritional, ecologic, and self-regulatory measures has been reported by nutritionist-physicians and nutritionists for decades.<sup>275-276</sup>

At present there is intense interest in defining the genetic basis of insulin resistance, syndrome X, and diabetes. The critical questions in that regard are the following: (1) What comes first, gene mutations or ecologic changes? (2) What factors cause the gene mutations? and (3) What elements lead to ecologic changes? I believe the available evidence overwhelmingly points to incremental oxidizing stress on the human biology.

### Genetic Roulette: The Cancer-Diabetes Trade-Off

There is another aspect of genetic consideration in the pathophysiology of insulin dysfunction. A good case study: the PPAR $\gamma$  receptor, which plays an important role in insulin activity. It controls both the entry of glucose in cells and its metabolism there. Recent research has identified three different groups of mutations involving that receptor in a small number of type 2 diabetics: (1) a group of loss-of-function mutations; (2) a group of gain-of-function mutations; and (3) a group of other mutations that are associated with variable effects on insulin sensitivity. It can be safely predicted that many more mutations in each of those and other categories will be

Figure 12 – Neuroecogenomics and ODID





found in the future. The gene therapies involving this receptor will carry the risk of ending up with a *gainer* gene when the intended gene was the *loser* gene. Or the unintended result might involve the variable loss-gain genes. To date, mutations of only PPAR $\gamma$  receptors have been identified in a small number of type 2 diabetics. How many other receptors are there which affect insulin activity?

How many other groups of mutations involving those receptors lurk behind the visible tip of the iceberg? The enthusiasm about curing diabetes by replacing the faulty genes must be tempered with the sobering thoughts concerning those questions.

The PPAR $\gamma$  receptor is an important determinant of adipogenesis. This receptor is also involved in phagocytic and endothelial cell function. Mutations in those functions are thought to increase the risk of carcinogenesis and lead to obesity. If we learn to genetically manipulate this receptor for controlling insulin dysfunction and diabetes, will there be a diabetes-cancer trade-off? How will we assure that while we try to cure diabetes by altering this gene, we do not induce neoplasia?

#### Mechanisms of Action of Drugs for Diabetes

For the general interest of the reader, I include below brief comments about the recognized mechanisms of action of pharmacologic agents commonly prescribed for controlling diabetes.

Sulfonylureas work by increasing insulin secretion from pancreatic beta cells by augmenting potassium-channel activity.<sup>277-278</sup> The secondary effects of this group of hypoglycemic agents include improving glucose transport in insulin-resistant adipocytes by drugs facilitating translocation of GLUT-4 and GLUT-1.<sup>261</sup> Both mechanisms ameliorate the baneful effects of direct glucose toxicity in peripheral tissues. Thus, the mechanism of action of sulfonylureas point to the existence of functional deficits involving beta cells, glucose transporters, and glycolytic pathways in peripheral cells. As surveyed in this article, the essential nature of all of the above molecular lesions is oxidative.

Biguanides (metformin and others) lower the blood glucose level by the primary action in the liver. These agents also increase glucose uptake in tissues,<sup>279,280</sup> and exert insulin-like effects on glucose transport and GLUT-4 translocation.<sup>281</sup> However, the latter effects seem to be achieved in *in vitro* studies with doses that are far larger than those in clinical use at present.

Thiazolidinediones (TZDs) are insulin-sensitizing agents that increase glucose disposal in peripheral tissues by facilitating the actions of insulin. TZDs normalize impaired

glucose tolerance and so have the potential to delay the onset as well as to prevent the progression of diabetes. The administration of TZDs to insulin-resistant rodents with hyperglycemia and hyperinsulinemia restores expression and translocation of GLUT-4 in fat cells and so reduces insulin resistance.<sup>281-282</sup> In nondiabetic animals, TZDs do not cause hypoglycemia.<sup>283</sup> This effect was also documented in human subjects. This class of drugs is especially valuable in diabetics who respond poorly to exercise, changes in diet, sulfonylureas, metformin and acarbose.<sup>284</sup>

## Insulin Dysfunction

Part III Next Month:  
Darwin, Dysoxygenosis and ODID

#### Correspondence:

Majid Ali, MD  
95 East Main Street, Suite 101  
Denville, New Jersey 07834 USA  
973-586-4111  
Fax 973-586-8466

## KNOW YOUR SOURCE

### Whole World Botanicals Sources its Maca Roots Directly from Growers in Their Fields.



Dr. Viana Muller, co-founder of Whole World Botanicals receives freshly harvested organic maca roots from a grower in the high Andes of Peru. To support organic production, the soil must undergo a long fallow period. Only the choicest (fleshy) roots are selected for extract preparation.

## Certified Organic ROYAL MACA™ Root Extract



Royal Maca™ (*Lepidium peruvianum*)

Powder and Capsules

Certified Organic



- No additives, excipients, colors, flavors.
- No irradiation, gas or autoclave used.

Works through the hypothalamus and pituitary to support endocrine gland function for people of all ages.

#### Supports:

- Erectile Function\*
- Libido\*
- Healthy Menopause (relieves hot flashes, vaginal dryness, mood swings)\*
- Ovarian, Uterine, and Breast Health\*

Provides nutritional, herbal support for people with:

- Parkinson's disease\*
- Multiple Sclerosis\*
- Chronic Fatigue\*

Hormonal balancing effects help improve immune function mental focus and physical energy.\*

WHOLE WORLD BOTANICALS™

\*This product is not intended to diagnose, prevent or treat any disease.

FOR PROFESSIONAL PRICES and TO ORDER: 1-888-757-6026  
INTERNATIONAL ORDERS ACCEPTED by FAX: (212) 781-0440

We accept Master Card and Visa.

Visit our web site: [www.wholeworldbotanicals.com](http://www.wholeworldbotanicals.com)



Copyright of Townsend Letter for Doctors & Patients is the property of Townsend Letter Group and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.