What Might APPNA Contribute for Stemming Global Tides of Hyperinsulinism and Type 2 Diabetes?

Shifting Focus From Glycemic Status to Insulin Homeostasis

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The author's work in molecular biology of oxygen[1-6]and molecular biology of insulin[7-12] led him to recognize a need for a shift of focus from glycemic status to insulin homeostasis (the "Shift").[13,14] Here he marshals strong basic science and epidemiological lines of evidence for the Shift (Tables 1-3), and presents robust reasons for suggesting that APPNA, a dedicated physician community, consider a long-term organizational initiative to contribute efforts to stem global tides of hyperinsulinism which predates Type 2 diabetes (T2D) by five, ten, or more years.

During the years of hyperinsulinism-to-T2D progression, cellular populations in nearly all body organs suffer diffuse and incremental damage inflicted by undetected and unmanaged non-metabolic toxicity of insulin dysregulation. Notable among them are disorders of neurodevelopment (autism and dysautonomia[15,16]), blindness from insulin-induced optic neuritis,[13] mitochondrial dysfunction,[1,13] immune-inflammatory entities,[13] endothelial dysfunction,[17] vagus nerve dysfunction,[18] persistent cellular repair response (after chemotherapy for cancer,[19] for instance), and hepatic lesions (such as steatosis). In his broader oxygen-insulin perspective of hyperinsulinism[8] the author recognizes hyperinsulinism as chronic energetic response to increased energy requirements of cellular repair processes.

It is noteworthy that all clinical and laboratory work done for the above-cited publications was completed without any private or government funding. The same held for author's related works in molecular and cellular pathology, as well as in therapeutics in the fields of environmental medicine, clinical nutrition, and immune-inflammatory disorders in the holistic-integrative models presented in the 10th, 11th, and 12th volumes of The Principles and Practice of Integrative Medicine.[20-22]

Insulin Homeostasis Protocol

The central goal of the proposed "Insulin Homeostasis Protocol" (the "Protocol") is for APPNA to develop and implement a long-term organizational plan for shifting focus from glycemic status to insulin homeostasis in order to: (1) improve clinical outcome of individual patients with integrative treatments: (2) simplify patient education for superior compliance; (3) build an organizational insulin database for ongoing studies of the non-metabolic and metabolic consequences of disrupted insulin homeostasis; (4) document the prevalence and patterns of progression of hyperinsulinism co-morbidities, including T2D; (5) gather clinical data for

examining the efficacy of indigenous therapies; and (6) foster the science and philosophy of holism in healing.

The Protocol is designed to be an all-voluntary distance-learning (internet-based) program. No need for significant outside funding is anticipated for APPNA participating clinicians; the initial time commitment of the APPNA administrative staff is expected to be modest.

Notable Strengths of the Protocol

The Protocol has some especial strength. Notable among them are: (1) enhanced clinical results for individual patients (extensively documented in the author's Darwin and Dysox Trilogy[20-22] and multiple case studies presented in this article); (2) no-cost internet-based distance learning for participating APPNA clinicians; (3) no clinical restrictions on the participants in the integrative model of the dietary, detox, and lifestyle Protocol guidelines; (4) no restrictions on concurrent use of pharmacologic regimens; (5) simplicity and uniformity of record keeping format for the insulin database for publications (illustrated in Tables used for presenting ; (6) no need for contractual obligations for APPNA, nor for APPNA clinicians; and (7) no additional uncovered cost of initial post-glucose challenge insulin and glucose profiles, and limited follow-up yearly insulin tests (as has been the case for the author and his colleagues).

Type 2 diabetes is a spreading pandemic. In 2013, China in a large national study reported a prevalence rate of prediabetes and Type 2 diabetes (T2D) (50.1% of adults).[1] In 2017, the author and his colleagues reported a prevalence rate of hyperinsulinism of 75.1% in a survey of post-glucose challenge insulin and glucose profiles in 684 subjects in New York metropolitan area.[13] This, to the authors' knowledge, was the first statistical documentation of hyperinsulinism-to-T2D progression with direct measurements of blood insulin and glucose concentrations with multiple timed blood samples following a 75-gram glucose challenge. The much higher rate of hyperinsulinism (75.1%) in New York population than the prevalence of prediabetes and T2D among the Chinese (50.1%) is not surprising since tests for the glycemic status provide only indirect information concerning the underlying insulin dysregulation.

In the 2017[13] and earlier reports,[7-12] the author and his colleagues explored the following questions: (1) How does insulin resistance begin; (2) What is optimal insulin homeostasis; (3) What is the prevalence of hyperinsulinism in a general population of New York metropolitan area; (4) What are the patterns of progression and/or arrest of hyperinsulinism-to-T2D continuum; (5) What are the non-metabolic developmental, differentiative, immune-inflammatory, degenerative, and metabolic effects of undetected incremental degrees of insulin dysfunction; (6) How do the diagnostic efficiencies for T2D of post-glucose challenge and insulin

responses compare with those of the standard glucose tolerance; (7) How does insulin-based hyperinsulinism modification and T2D reversal plan compare with those based on glycemic criteria, especially in the cases of gestational diabetes and large-sized babies; and (8) What might be the crucial clinical entities in which unmasked hyperinsulinism poses special hazards, i.e., autism, Asperger's syndrome, pediatric dysautonomia, childhood weight gain and obesity, pediatric fatty liver, peripheral neuropathy, drug-induced tissue repair responses (during chemotherapy for cancer, for instance), polycystic ovarian syndrome, pustular acne, and diverse allergic and chronic immune-inflammatory disorders.

Insulin Dysregulation in Chronic Cellular Repair Responses

All repair mechanisms in the body have expanded energy requirement demands. Insulin can be rightfully considered the master energy hormone of the body. From an evolutionary energetic perspective, the lowest blood insulin concentrations accompanied by unimpaired glucose tolerance have been designated optimal insulin homeostasis (Table 1). Table 2 showing the correlation of incremental glycemic changes sheds light on the hyperinsulinism-T2D continuum. Our article entitled "Shifting Focus From Glycemic Status to Insulin Homeostasis is posted in full at www.alidiabetes.org, and furnishes a large body of original observations, including many of the above-cited forms of toxicity of hyperinsulinism fully referenced.

Table 1. Insulin Homeostasis Categories in 506 Study Subjects Without Type 2 Diabetes

Insulin Category*	Percentage of Subgroup	Mean Peak Glucose mg/dL (mmol/mL)	Mean Peak Insulin (uIU/mL)
Exceptional Insulin Homeostasis N = 12**	1.7%	110.2 (6.12)	14.3
Optimal Insulin Homeostasis N = 126	24.9 %	121.2 (6.73)	26.7
Hyperinsulinism, Mild N = 197	38.9 %	136.5 (7.58)	58.5
Hyperinsulinism, Moderate N = 134	26.5 %	147.0 (8.16)	109.1
Hyperinsulinism, Severe N = 49	9.7 %	150.0 (8.33)	231.0
# Correlation coefficient, r value, for means of peak glucose and insulin levels in the five insulin categories is 0.84.			

*Criteria for classification: (1) Exceptional insulin homeostasis, a subgroup of optimal insulin homeostasis with fasting insulin concentration of <2 uIU/mL and mean peak insulin concentration of <20; (2) optimal insulin homeostasis, peak insulin <40 accompanied by unimpaired glucose tolerance; (3) mild

Table 2. Insulin Homeostasis Categories in 178 Study Subjects With Type 2 Diabetes

Insulin Category	Percentage of Subgroup	Mean Peak Glucose mg/dL	Mean Peak Insulin (uIU/mL)

		(mmol/mL)	
T2D With Hyperinsulinism, Mild N = 53	29.0%	252.0 (14.00)	55.4
T2D With Hyperinsulinism, Moderate N = 42	24.0%	242.1 (13.45)	112.4
T2D With Hyperinsulinism, Severe N = 24	13.9%	224.6 (12.47)	298.0
T2DF With Low Insulin Levels N = 59	33.1%	294.0 (16.33)	22.9

Reading Insulin/Glucose Profiles As Examining Surgical Pathology Slides

Within some months of beginning my study of insulin homeostasis with 3-hour post-glucose-challenge insulin and glucose profiles, I found myself reading the profiles as I read microscopic slides as a hospital surgical pathologist. One might expect that individual subjects will display wide variations in their insulin and glucose profiles in most instances. This, indeed, is the case . This point is amply demonstrated in case studies shown in Tables 3-7. Table 3 shows what is usually dismissed as an error of omitting the glucose challenge by the patient or the lab staff since the "flat" post-glucose-challenge tolerance pattern is not a generally recognized entity. It is caused by a brisk initial insulin spike which masks the expected initial glucose spike. This can be readily proved by taking measurements at 1/2-hour post-challenge blood sample. Tables 7 documents insulin dysregulation in autism and pediatric dysautonomia.

Table 3. Optimal Insulin Homeostasis With Very Low Blood Insulin Concentrations and Unimpaired "Flat" Glucose Tolerance Curve* of A 52-Yr-Old 5'1" Woman With Constipation and Osteoarthritis.

	Fasting	1-Hr	2-Hr	3-Hr
Insulin uIUi/mL	<2	17	15	6
Glucose mg/mL	75	61	72	71

Table 4. Insulin and Glucose Profiles of 75-Yr-Old 5'7" Woman Weighing 192 lbs. Who Presented Following A Coronary Bypass Procedure With Fatigue, Sinusitis, and Without Known Type 2 Diabetes (Not An Uncommon Case In the Author's Integrative Clinical Practice). A1c 5.6%.

6.3.2010	Fasting	1-Hr	2-Hr	3-Hr
Insulin uIUi/mL	9.8	25	92.4	2.2
Glucose mg/mL	112	170	241	273
7.23.2013. Insulin Tests Not Ordered By Her Primary Physician. A1c 5.8%				
Insulin uIUi/mL	-	-	-	-

Glucose mg/mL	97	159	219	247
5.11.2014. ”Mostly Good Compliance” By Patient’s Account. A1c 5.7				
Insulin uIUi/mL	6.43	58.2	33.87	6.4
Glucose mg/mL	99	182	139	81
2016 Hospitalized for Angina. A1c 5.7. No Diabetic Drugs Prescribed By the Attendning Cardiologist.				

Table 5. Reversal of Type 2 Diabetes in a 78-Yr-Old 5’2” Woman Weighing 162 Lbs. Achieved By Dramatic Hyperinsulinism Modification (Reduction of 3-Hr Insulin from 152 uIU/mL in 2013 to 75.2 in 2014 to 39.7 in 2015, indicating restoration of Insulin Homeostasis.				
4.30.2013	Fasting	1-Hr	2-Hr	3-Hr
Insulin uIUi/mL	16	59	113	152
Glucose mg/mL	112	214	241	155
10.17.2014, A1c 6.3%				
Insulin uIUi/mL	23.8	36.9	114.7	75.2
Glucose mg/mL	116	253	297	172
4.14.2015, A1c 5.9%				
Insulin uIUi/mL	6.2	42.9	51.2	39.7
Glucose mg/mL	96	193	112	105

Table 6. Severe Hyperinsulinism In A Previously Health 13-Yr-Old Girl With Multiple Hospitalizations for Recurrent Pneumonia, Thrombocytopenia, Polyarthralgia, Polymyalgia , and Severe Optic Neuritis With Complete Loss of Vision in Right Eye. Her Final Diagnosis in the Hospital was Systemic Lupus Erythematosus*				
	Fasting	1Hr	2Hr	3Hr
Insulin uIU/mL	27.9	424.0	718.2	571.7
Glucose mg/mL	70	157	150	111
Insulin and Glucose Profiles Obtained After Four Months of Robust Integrative Parenteral Nutritional and Detox Therapies With Focus on Restoration of Gut Flora.				
Insulin uIU/mL	7.2	238.5	208.0	132.0
Glucose mg/mL	81	181	130	97

*The patient showed dramatic improvement in all areas except in right eye blindness. Follow-up questioning revealed a history of massive exposure to mold overgrowth while playing in an abandoned building.

Information Sources

I consider the journal Nature to be the supreme source of information in the world of science. Since 2015, Nature frequently e-published my comments expressing holistic-integrative perspective on health and healing concerning major articles published by the journal. Below are excerpts from five of those pieces on the subject of this proposal for APPNA (citations within the text are originals from e-publications):

1. Shifting Focus From Glycemic Status to Insulin Homeostasis[14]

Type 2 Diabetes (T2D) is rapidly eclipsing other chronic diseases in becoming the preeminent threat to human health worldwide…. The work of Yamaguchi and colleagues must be celebrated in this larger context. Their previous work involved generation of whole organs from donor pluripotent stem cells using their chimaera-forming ability to complement organogenesis-disabled host animals *in vivo*. They now report generation of autologous functional islets with interspecies organogenesis through interspecies blastocyst complementation. This stellar work advances the goal of treating diabetes with islet transplantation. Here, Yamaguchi et al. also put forth a serious challenge to physician community: How to protect transplanted islet cells from the host elements that caused hyperinsulinism leading to Type 2 diabetes in the first place?

2. Obesity, Energetics, Environment, and Hyperinsulinism[23]

Just how error-prone and self-correcting is science? Allison and colleagues raise a question that physicians often raise – in hospitals, clinics, and laboratories. A more compelling question for those interested in obesity, energetics, and inflammation, and insulin homeostasis is: How can the subjects of obesity and energetics be

investigated and/or discussed without considering the tedious and disconcerting matter of environmental and inflammatory toxins that impair mitochondrial function and oxygen signaling? Automobile mechanics know well how their engines get clogged and lose efficiency and mileage. In 2004, the author published data concerning impaired mitochondrial function in chronic immune-inflammatory and metabolic disorders.[1] His observations were validated by the work of others as well as his follow-up studies.[23]

3. Osteocrin, Making Connections, and Autism[16]

Ataman et al. linked osteocrin, a gene expressed in muscles and bones, to a new primate-specific enhancer sequence that binds to a myocyte enhancer factor 2 (MEF2.) (ref. 1). MEF2C mutations resulting in haploinsufficiency represent a form of intellectual disability in humans. (ref.2,3). MEF2A- and MEF2C-binding sites are enriched in genes associated with idiopathic autism spectrum disorder (ref. 4).

This new osteocrin work is especially important for integrative clinicians who care for autism and other disorders of developmental neurobiology. No pharmacologic agents to treat autism spectrum are available at this time. However, it is well established that neuronal activity triggers distinct transcriptional responses in different neuronal subtypes (ref. 5) This offers an opening for integrative clinicians to investigate the potential benefits of non-pharmacologic approaches to enhance neuronal activity to evoke desirable neurological responses for improved clinical outcomes. Notable among these are dietary, nutritional, metabolic, and gut mircobiota-directed therapies, as well as educational and behavioral programs. Specifically, the use of injectable and oral glutathione, methylcobalamine, taurine, calcium, magnesium, vitamin B complex usually yield gratifying results in treating atism (ref. 6,7).

The work of Ataman et al inspires this writer to pursue his impeded progenitor cell progression model of autism (ref. 6). He put forth this unifying model as a frame of reference for establishing clinical priorities to improve clinical results by identifying and addressing all prenatal and postnatal challenges to developmental neurobiology which seem relevant to the pathogenesis of ASD. The core tenet of

this model is impeded neuronal progenitor cell progression to mature neurons during antenatal and postnatal lives caused in autism is disrupted oxygen signaling (ref. 6,8,9) resulting from: (1) Krebs cycle dysfunction (ref. 10); (2) overdriven immune-inflammatory dynamics (ref. 11); and (3) disruptions of insulin homeostasis and IGF1-dynamics (ref. 12,13). The members of this trio amplify challenges to progenitor cell progression posed by one another, and impede progenitor cell progression during antenatal and postnatal lives.

4. Insulin.Autism.Hypothalamus[24]

The work of Stanley et al. points out how their constructs targeting glucose-sensing neurons will also be applicable to other areas, including insulin signaling. I have two specific reasons for celebrating this work. First, my work with hyperinsulnism and diabetes led me to recognize a clear need for a shift of focus from glycemic status to insulin homeostasis for stemming the tide of Type 2 diabetes in children (ref. 2-4). Second, I have special interest in the subject of hyperinsulinism in children with neurological challenges, such as autism and dysautonomia. (ref.5) Readers might find the following data concerning four children with hyperinsulinism, two with autism and two with dysautonomina, interesting. The insulin and glucose profiles were obtained with blood samples drawn at fasting and 1-hour, 2-hour, and 3-hour after a 75-gram challenge. I also include an insulin profile of a healthy subject with unimpaired glucose tolerance as a control. Insulin and glucose concentrations in 3-hour insulin and glucose profiles of four children given below are expressed in uIU/ml and mg/mL respectively.

Table 7. Insulin and Glucose Profiles of Two Children each With Autism, and Dysautonomia, and One Control Child .

	Fasting	1-Hr	2-Hr	3-Hr
Autism Case 1				
Insulin uIU/mL	24.4	73.8	71.6	28
Glucose mg/mL	95	79	79	69
Autism Case 2				
Insulin uIU/mL	6.2	40.3	41.5	24.8
Glucose mg/mL	96	131	109	57
Pediatric Dysautonomia Case 1				

Insulin uIU/mL	9.3	90.7	119.9	53.8
Glucose mg/mL	78	165	141	99
Pediatric Dysautonomia Case 1				
Insulin uIUi/mL	3.9	49.59	13.1	7.8
Glucose mg/mL	84	96	71	77
Control Subject Without Any Neurologic Disorder				
Insulin uIU/mL	<2	18	4	<2
Glucose mg/mL	77	109	74	52

5. Darwin Moms, Nursing Milk, and Antibiotic Resistance[25]

Darwin moms have much to teach clinicians like me. To cite one example, women in Punjab diligently follow the family tradition of mustard oil rubs over their bellies daily for forty days after delivering a baby. I recommend this simple remedy to my American patients who nearly always find it beneficial in improving bowel health and reducing abdominal fat. They also report good results with castor oil rubs for their colicky babies.

Darwin moms have taught me much about many other remedies for controlling pregnancy-related digestive-absorptive disruptions and for improving their nutritional, metabolic, and immune status, as well as of their children. Such measures profoundly affect the nourishing quality and safety of nursing milk, a crucially important immune booster. This approach can be expected not only to reduce the need for antibiotics but also diminish the frequency and intensity of their adverse effects when antibiotics cannot be avoided.

APPNA and Global Challenges of Disrupted Oxygen and Insulin Signaling

In closing**,** APPNA has an impressive world-class "clinician capital." What might it contribute to the daunting challenge of stemming global tides of diabetes? Hyperinsulinism is recognized not only as the primary pathogenetic mechanism for Typ2 diabetes but also as playing central roles in diverse developmental, diffferentiative, immune-inflammatory, cardiovascular, neurologic, hepatic, endocrine, and cellular repair-

related pathologies. Within the broader evolutionary context, the incremental "non-metabolic effects" of disrupted insulin homeostasis inflict diffuse cellular injury in nearly all organ systems of the body. The case of a 13-yr-old with total loss of vision in one eye presented in Table 6 and those of children with autism and dysautonomia in Table 7 offer intellectual and clinical challenges worthy of APPNA physicians. The integrative clinical Protocol guidelines proposed here also harness myriad low-cost indigenous therapies. The oxygen-insulin dimensions of the Protocol provide the scientific underpinning and rationale for gauging and engaging therapeutic aspects of molecular biology of oxygen and insulin.

In this light, APPNA clinicians considering the Protocol may look forward to exploring rewarding new dimensions of the new global realities of health and healing. Excerpts from the writer's comments published online by the journal Nature provide windows to some of these dimensions. I add here that I consider publications in Nature analogous to the U.S Supreme Court admitting cases – to be presented, argued for and against, and then to be ruled on.

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