Editorial: Conference Issue-2nd International Conference on Autoimmunity 2018; Where have we Gotten to?

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Our second annual conference was held June 20, 2018, at New York City Health+Hospitals/Woodhull. Synergy Conferences partnered with Woodhull to put together a learning and networking experience which was rewarding for everyone who participated as a speaker, poster presenter, session chair, or audience member.

I would like to extend warm thanks to the other members of the Scientific Committee who helped in suggesting lecturers for the invitation, including Dr. Gŭl Bahtiyar, Dr. Jocelyne Karam, and Dr. Yong Zhao.

I would like to thank our organizers at Synergy Conferences/Synergy Publishing, including Ahmed Ullah, Organizing Secretary, Noman Pirzada, Sadaf Idrees Khan without whose hard work, infrastructure, web, and financial support the conference could not have taken place.

An enormous debt of gratitude also goes to our Woodhull support team from the Department of Medical Communications: Stephanie Lugo, Patrick Ashley, and Ray Gibson-who did much on short notice, the Department of Community Affairs: Maria Hernandez, Andre Marie Suarez, Sammy Rodriguez, and to Anthony DiVittis, Associate Director for Planning and Public Affairs, our Executive Director, Gregory Calliste, our Senior Associate Director of Graduate Medical Education, Chermain Cross, our Department of Medicine Program Director, Susan Grossman and our chief medical residents, Kevin Singh and Pawel Szurnicki for arranging for our medical residents to attend, our department administrator, Bibiana Soto and our executive associates: Yolanda Dawson, Mary Hayes, Jinette Maldonado, Jovanie Santos, and Gail Charles for organizing the on-site registration and assisting with catering arrangements. We should also like to thank our Food/Nutrition Dept. for their breakfast and morning coffee break arrangements. No conference is possible without speakers/presenters and session chairs and we were fortunate to have a wonderful group of speakers/presenters from administrative, clergy, political, clinical, translational, epidemiologic, and basic science backgrounds sharing their unique perspectives.

Mr. Gregory Calliste, Woodhull's Executive Director, opened the conference with an eloquent greeting to all those attending the conference, stressing the impact of autoimmune disorders on the Brooklyn community.

The inspiring invocation prayer was offered by Woodhull Chaplain, Sister Lilia Njoku.

Our Chief Guest, Brooklyn Borough President, Eric Adams, inaugurated the conference, emphasizing the impact of autoimmune disease on the people of Brooklyn and sharing his inspirational personal experience of controlling his Type 2 diabetes through use of a low calorie, vegan diet, and a regular exercise program, shedding considerable weight in the process.

The first academic session was chaired by Dr. Yong Zhao from the Department of Biomedical Research at Hackensack University Medical Center.

Dr. Harold Lebovitz, Emeritus Professor of Medicine and former Chief of the Endocrine Division at SUNY Downstate Medical Center, kicked off our scientific program with a lecture entitled *Autoimmune Polyglandular Syndrome: a Merger of Endocrinology and Immunology* in which he updated us on Autoimmune Polyglandular Syndrome (APS) 1, a rare, autosomal recessive disorder in which there are mutations in the autoimmune regulator (AIRE) gene with early onset and clinical findings of hypoparathyroidism, mucocutaneous candidiasis, and adrenal insufficiency, APS 2, a polygenic disorder, unlike APS 1, which is monogenic, involving mutations

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in genes in the major histocompatibility locus, typically with an adult clinical onset and often presenting with Type 1 diabetes, Addison's disease, autoimmune thyroid disorders and primary hypoparathyroidism as well as other autoimmune disorders, and X-linked immunodysregulation, polyendocrinopathy, and enteropathy (IPEX)-a very rare FOX-P3 disorder presenting in infancy with neonatal Type 1 diabetes, autoimmune enteropathy, eczema, and other autoimmune disorders.

The next speaker in the scientific program was Dr. MaryAnn Banerji, Professor of Medicine and current Chief of the Division of Endocrinology and Metabolism at SUNY Downstate Medical Center who spoke to us about *Autoimmunity in Type 2 Diabetes*, a disorder that, traditionally, has not been thought of as autoimmune. She discussed the fact that "Flatbush" diabetes often presents with diabetic ketoacidosis, much like in Type 1 diabetic patients, however, most of the Flatbush diabetic patients do not develop circulating antibodies to insulin or islet cell antigens and have a clinical course typical of type 2 diabetics, often not requiring the use of exogenous insulin after initial treatment. "Typical" Type 2 diabetic patients, initially well-controlled with lifestyle measures alone or in combination with oral agents may quickly progress to insulin dependence and develop antibodies to islet antigens, suggesting that they have subsequently developed Type 1 diabetes or latent autoimmune diabetes of adults (LADA), although many LADA patients never require insulin. Many patients with Type 2 diabetes with or without circulating antibodies against insulin or islet cell antigens demonstrate T cell reactivity to islet cell antigens. Chronic, low-grade inflammation participates in the pathogenesis of type 2 diabetes with a build-up of innate immune cells in adipose and other metabolic tissues resulting in the increased release of inflammatory cytokines, such as TNF-α and IL-1β, which cause both insulin resistance and autoimmune β-islet cell damage (as occurs in Type 1 diabetes). In addition, type 2 diabetes is often associated with other autoimmune disorders including psoriasis and vitiligo.

The second session was chaired by Dr. MaryAnn Banerji (previously introduced).

After his stellar poster and lecture last year, Dr. Yong Zhao, from the Department of Biomedical Research at Hackensack University Medical Center, returned to this year's conference as a member of the Scientific Committee and updated us on the subject of *Stem Cell Educator Therapy and Type 1 Diabetes: From Bench to Clinic* with some data on this therapy for autoimmune alopecia as well. This therapy is a closed-loop system that moves the patient's blood through a blood cell separator and then briefly co-cultures the patient's lymphocytes with cord blood stem cells expressing autoimmune regulator (AIRE) in vitro and then returns the 'educated" lymphocytes *only* to the patient resulting in durable reversal of autoimmunity; acting, in effect, like an artificial thymus. Key to the therapeutic effectiveness of this procedure is the presence of platelet mitochondria possessing immune tolerance-associated markers that allow beta islet cells to be reprogrammed to proliferate, with good viability and restoration of normal insulin production. This therapy may help many patients with Type 1 diabetes, Type 2 diabetes, and autoimmune alopecia with minimal invasiveness and avoid ethical and risk concerns associated with transplantation or use of embryonic stem cells.

The third session was chaired by Dr. Alan Sacerdote, Chief of the Division of Endocrinology at NYC Health+Hospitals/Woodhull, Clinical Professor of Medicine at SUNY Downstate Medical Center and NYU School of Medicine and Professor of Medicine at St. George's University. Dr. Jocelyne Karam, Director of the Division of Endocrinology at Maimonides Medical Center, Affiliate Site Program Director of the SUNY Downstate Endocrine Fellowship Program, as well as Clinical Assistant Professor of Medicine at SUNY Downstate Medical Center, gave a very informative lecture entitled *Thyroid Autoimmunity and Pregnancy*. She shared data showing that more than 12% of women of reproductive age have positive anti-thyroid peroxidase (TPO) antibodies and that the presence of these antibodies is associated with an increased risk for poor pregnancy-associated outcomes including, spontaneous abortion, pre-term delivery, subclinical hypothyroidism, and post-partum thyroiditis. More limited data suggest that low dose l-thyroxine treatment of euthyroid anti-TPO ab positive pregnant women to achieve/maintain the serum TSH<2.5 MIU/ml reduces the risk for both spontaneous abortion and pre-term delivery and recent guidelines suggest that it be considered in this patient group.

The next session was chaired by Dr. Behzad Dorotaj, Chief, Division of Hematology/Oncology, NYC Health+Hospitals/Woodhull. This session was a lecture on *Primary Biliary Cholangitis* given by Dr. Nora Bergasa, Chief of the Hepatology Clinic at NYC Health+Hospitals/Woodhull, Director of the Dept. of

Medicine, NYC Health+Hospitals/Metropolitan. This disorder, previously known as primary biliary cirrhosis is an autoimmune disorder characterized by chronic, non-suppurative, progressive inflammation of septal and interlobular intrahepatic bile ducts, often culminating in cirrhosis and liver failure. Liver function tests are consistent with cholestasis. Characteristic symptoms are pruritus and fatigue. The research of Dr. Bergasa and others supports increased opiodergic tone as a possible cause for the itching. Most patients have high titers of anti-mitochondrial antibodies and high IgM levels. Current treatment is primarily with ursodeoxycholic acid which can delay the need for liver transplantation, with non-responders who meet certain criteria being offered obeticholic acid.

The fifth session was chaired by Dr. Marie-Alex Michel-Vincent, Chief of the Nephrology Division, NYC Health+Hospitals/Woodhull. This session was a fascinating lecture on the *Influence of the Gut Microbiome on Autoimmunity* presented by Dr. Maria S Maritato, Chief of the Infectious Disease Division, NYC Health+Hospitals/Woodhull and Clerkship Co-Director, Woodhull Medical and Mental Health Center, St. George's University. In her talk, Dr. Maritato highlighted those autoimmune disorders which have been most closely associated with alterations in the gut biome. She explained how dysbiosis resulting from antimicrobial drugs, diet, and other influences in the gut can lead to weakening of the innate immune system via increasing gut permeability and exposure of the adaptive immune system to antigens in microbes, food, and other ingested materials which may be similar to self-antigens (molecular mimicry), resulting in an immune response directed against one's self. Such changes may also be associated with weight gain and subsequent insulin resistance with increased inflammatory chemokine and cytokine production, sustaining the autoimmune response.

The sixth session on autoimmune renal disease was chaired by Dr. Jocelyne Karam (previously introduced as a speaker). The first lecture in this session was given by Dr. Paul Byssainthe, Attending Physician in the Nephrology Division at NYC Health+Hospitals/Woodhull, who spoke on *IgA Nephropathy*, one of the most common autoimmune renal disorders. He reviewed the pathophysiology and varied clinical presentations of this disorder as well as the most up to date therapies, which include both immune system-targeted therapies and therapies which are useful in chronic kidney disease generally such as dietary protein/phosphorus restriction and drugs which block the renin-angiotensin system.

The second lecture in this session was given by Dr. Marie-Alex Michel-Vincent, Chief, Division of Nephrology, NYC Health+Hospitals/Woodhull, who spoke on the myriad presentations of *Lupus Nephritis*, another of the most common autoimmune, chronic renal disorders, using a case-based approach. The presentations range from mild to those that cause end-stage renal disease. These presentations, based on renal biopsies performed at Woodhull, are: mesangial lupus nephritis, focal lupus nephritis, diffuse proliferative lupus nephritis, membranous lupus nephritis, advanced glomerulosclerosis, crescentic presentation, lupus interstitial nephritis, double antibody disease with anti-glomerular basement membrane antibody, and double antibody disease with anti-myeloperoxidase (MPO) antibodies- antineutrophil cytoplasmic antibodies (ANCA). Some patients were very ill systemically with dramatic extra-renal manifestations, but with very mild renal involvement, while others had significant renal involvement with minimal or no systemic manifestations and were not diagnosed until renal biopsy had been performed.

The plenary lecture session following the lunch break was chaired by Dr. Paul Byssainthe (previously introduced). The lecture, entitled *Helminth Immunomodulation in Autoimmune Disease* was delivered by Dr. Sara Lustigman, Head, Laboratory of Molecular Parasitology, Lindsley F. Kimball Research Institute, New York Blood Center. Here we see the influence of the gut macrobiome as we did with the microbiome in Dr. Maritato's lecture. She began by reviewing the observations of many people that parasitic worm infections can last for many years, often triggering very little host immunopathology and generally resulting in a predominantly Th-2 host immune response, favoring persistence of the parasite within the host. This response is in contrast to the typical Th-1 response seen with viral infections and in autoimmune disorders. The "old friends" hypothesis suggests that this tolerance to helminth parasites exists because, during evolution, mammalian immune systems have evolved in continuous contact with these helminth pathogens.

Epidemiologically, it has been observed that as helminth infections have been reduced through vaccine programs, mass anti-helminthic drug distribution, and improved hygienic/socioeconomic conditions there has been a concomitant rise in the prevalence of

autoimmune and allergic disease. There has recently been a striking inverse relationship observed between the prevalence of nematode infection and several autoimmune disorders including, T2DM, RA, and SLE. Public health initiatives, e.g. deworming, have been associated with an increased incidence of atopy. It has been observed that helminth-associated molecules may have potent regulatory effects on mammalian immune systems and redirecting the immune-regulating abilities of nematode worms and their secretions to treat human inflammatory (including autoimmune) disorders is now a subject of intensifying research. This work ties in nicely with work by Larralde *et al.* [1] showing that in the helminthic disease, cysticercosis, the parasite estrogenifies the host to create a more hospitable environment. Subsequent work by the same group in Mexico [2] showed that use of the selective estrogen receptor modulator (SERM), tamoxifen, significantly reduced the parasite burden in mice. Later, our group successfully treated a patient with neurocysticercosis-induced polycystic ovarian syndrome (PCOS) with the SERM, raloxifene as well as metformin, resulting in both resolution of the PCOS and a decrease in her CNS parasite burden [3] as well as a reduction in the elevated serum level of 1, 25 (OH)2-Vitamin D3 associated with the parasitosis. In addition, research is being advanced into the development of an immuno-stimulatory helminth-associated molecule as an antigen-sparing adjuvant for the influenza vaccine to improve its effectiveness.

The next session was chaired by Gŏl Bahtiyar, MD, MPH, Attending Endocrinologist, NYC Health+Hospitals/Woodhull, Clinical Associate Professor of Medicine, NYU School of Medicine, Associate Professor of Medicine, St. George's University, and Clinical Assistant Professor of Medicine, SUNY Downstate Medical Center. The session speaker was Nanette Alexander-Thomas, MD, FACP, FACR who spoke to us about *State of the Art Treatment of Rheumatoid Arthritis* (RA) involving the early use of disease-modifying medications including methotrexate, TNF-α blockade, and monoclonal antibodies directed against inflammatory cytokines and chemokines. Though cure remains elusive, the appropriate use of these agents has dramatically changed the outlook for RA patients from the dismal recent past, when RA was frequently a crippling, disease with a shortened life expectancy, to a manageable chronic disorder with a virtually normal life expectancy, much less disability, and a reasonably good quality of life.

The following session was chaired by Dr. Marie-Alex Michel-Vincent (previously introduced) and featured a lecture by Dr. Alan Sacerdote (previously introduced) entitled *Non-Classic Adrenal Hyperplasia, Vitamin D, Insulin Resistance, and Autoimmunity*. Dr. Sacerdote began by reviewing concepts and data from his lecture at last year's meeting and highlighting relevant data acquired since then. Key concepts from this lecture include:

- Almost all patients with autoimmune disorders investigated to date have non-classic adrenal hyperplasia (NCAH). Possible reasons for this are discussed in the companion article summarizing his lecture.
- Both NCAH and classic CAH are characterized by insulin resistance (IR).
- Hypovitaminosis D is generally present in both NCAH and autoimmune disorders.
- Interventions which reduce IR, including metformin, thiazolidinediones, lifestyle changes, bariatric surgery, **Vitamin D**, ashwagandha, biotin, zinc, copper, beta-carotene, and Vitamin C have been reported to ameliorate NCAH and classic CAH clinically and biochemically as well as to ameliorate or prevent a number of autoimmune disorders.
- Worsening and protracted Vitamin D deficiency has been reported to exacerbate NCAH.
- IR and autoimmunity have much in common including an alteration in the gut biome to one that is less numerous in total number of organisms and less varied in terms of species and an increase in many pro-inflammatory cytokines/chemokines, lower mean serum 25-OH-vitamin D levels compared to healthy controls and amelioration reported with vitamin D replacement.

The next session was chaired by Alan Sacerdote (previously introduced). This session featured a lecture by Dr. Mohamed Boutjdir, Professor of Medicine at NYU School of Medicine and SUNY Downstate Medical Center and Attending Cardiologist at the New York Harbor Healthcare System, entitled *Autoimmune Channelopathies as a Novel Mechanism in Cardiac Arrhythmias*. He told us that congestive heart failure and coronary artery disease remain the most common causes of cardiac arrest. However, in 5-15% of

patients, there are no identifiable structural abnormalities present at the autopsy. In some of these patients mutations involving proteins within the cardiac ion channels have been reported (inherited channelopathies), however, in almost 70% of patients with structurally normal ion channels no responsible mutations have been identified. Recent evidence suggests that autoimmunity may be responsible for some of these arrhythmias. Several arrythmogenic antibodies targeting potassium and calcium ion channels in the heart have recently been identified. Both preclinical and clinical studies have shown that these antibodies can promote conduction abnormalities and dangerous tachyarrythmias by precipitating electrophysiologic changes in these channels. Most of the available data has involved anti-SS/Ro antibodies in patients with concurrent autoimmune connective tissue disease. It is, of course, possible that these antibodies, as well as any associated cellular immune responses, may exacerbate channel dysfunction due to coronary disease, heart failure, or inherited mutations of channel protein genes.

The next session was the poster session wherein 5 posters were presented by trainees, a nurse, and an attending surgeon related to autoimmunity and/or NCAH, which were as follows: Inoue T, Soni L, Bahlol M, Fenteany G, Bahtiyar G, Sacerdote A. *Worsening and Prolonged Hypovitaminosis D is Associated with Biochemical Exacerbation of Non-classic 11-Hydroxylase Deficiency*, Sultana T, Inoue T, Gattorno F, Soni L, Fenteany G, Bahtiyar G, Sacerdote, initial *Empagliflozin Use in Type 2 Diabetes is Associated with Remission of Adrenal Hyperandrogenism*, Karen Simon MS, BSN, RN, Taiga Inoue, MS, MD, Gabriel Fenteany PhD, Gul Bahtiyar MD, MPH, Alan Sacerdote, MD *Ashwagandha Root in the Treatment of Prediabetes*, Christopher Albergo, MD, Galina Glazman, MD, Alan Scott Sacerdote, MD, FACP, *A Novel Case of Normokalemic Thyrotoxic Periodic Paralysis in an Elderly Haitian Woman*, Eliza Sharma, MD, Christine Resta, MD, Elizabeth Sedlis-Singer, MD, Luba Rakhlin, MD, Jocelyne Karam, MD. *Amiodarone-Induced Cure of Graves' disease*. Great interactions between poster presenters and other attendees were observed.

Following the poster session, Dr. Alan Sacerdote presented, what was originally scheduled to be the Keynote Address of Dr. Mayris Webber of the Department of Epidemiology and Population Health, Montefiore Medical Center, Albert Einstein College of Medicine, and the Fire Department of the City of New York, Bureau of Health Services. Her topic was *Post-September 11, 2001, Incidence of Systemic Autoimmune Diseases in World Trade Center-Exposed Firefighters and Emergency Medical Service Workers*. Dr. Webber was unable to appear in person but graciously furnished her PowerPoint presentation. Their goal was to estimate the incidence of selected systemic autoimmune diseases (SAIDs) in nearly 14,000 male rescue/recovery workers enrolled in the New York Fire Department's (FDNY) World Trade Center (WTC) Health Program and to compare this incidence to that of demographically similar males in the Rochester Epidemiology Project (REP), a population-based database for Olmsted County, Minnesota (location of the Mayo Clinic). They calculated the incidence for specific SAIDs (SLE, RA, psoriatic arthritis and others) combining SAIDs diagnosed between September 12, 2001, and September 11, 2014, and produced expected age and gender-specific rates based on REP rates. The incidence rates were stratified by the level of exposure to the WTC site (Ground Zero) (higher vs lower). They next calculated standardized incidence ratios (SIRs) which were the ratio of the observed number of cases of SAIDs in the FDNY cohort to the expected number of cases based on REP incidence rates. Ninety-five percent confidence intervals for the SIRs were then computed. The authors identified 97 SAID cases in the FDNY cohort. The overall FDNY incidence rates were not significantly different from the expected (REP) rates (SIR 0.97; 95% CI, 0.77-1.21). The lower WTC exposure cohort had 9.9 fewer SAID cases than expected, while the higher exposure cohort had 7.7 more cases than expected.

In interpreting these results Dr. Webber's slides refer to the fact that in most published studies of occupational exposure, what is called 'the healthy worker effect" reduces the association between exposure and outcome by about 20%-this is about what they observed in the lower exposure WTC cohort. The healthy worker effect takes into account that, in general, people who are working are somewhat healthier than the general population, which would include more ill and/or disabled people. This may be especially true in occupational groups such as firefighters and EMS workers for whom a certain level of physical fitness is a job requirement. The overall FDNY SAID incidence rate obscured differences in incidence according to the level of WTC site exposure because the higher exposure group was small.

Continued surveillance of this population for early detection of SAIDs, as well as other autoimmune disorders, is warranted, especially in the higher exposure cohort.

The conference was concluded with inspiring closing remarks from our hospital's Associate Director for Planning and Public Affairs, Mr. Anthony DiVittis, who had such an important role in coordinating the logistics of our conference.

After chairing the Scientific Committees for Autoimmunity in 2017; Where Are We Now? and 2nd Conference on Autoimmunity 2018; Where Have We Gotten To? I shall be passing the torch to a younger, more energetic future chairperson. It has been a rare privilege to work with so many talented and dedicated people to make these 2 past autoimmunity conferences a reality. My hopes and prayers for future, even more successful, conferences are with my successor.

These findings may have relevance for people and animals exposed to planned demolition sites as well as those that are terrorism or war victims

Alan Sacerdote, July 26, 2018.

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