

A Dialogue with Professor Aaron Lerner

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Abstract We continue to interview other personalities in the field of celiac disease. Professor Aaron Lerner, a member of our editorial board is introduced. His researches are well known by our readers.

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1. Would you be so kind and could you please shortly introduce to the readers? Where are you born? Some information about your education and eventually some interest from this period?

This is the easiest part of the interview. I was born in Milano, Italy. I immigrated to the new independent state of Israel, while breast fed. My first 3 years of medical school (1969-1972) were in French, in the school of medicine in Strasbourg, France. I graduated as an M.D. in 1976, at the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel. I finished my 5 years of Pediatric specialization in 1985, at the Department of pediatrics, Carmel Medical Center, B. Rappaport School of Medicine, Technion-Israel Institute of technology, Haifa, Israel, founded by Prof. Iancu Theodor. Here I have to pay tribute to Prof. T. Iancu, who imbedded the love and patience for children in me and was a role model for future career as Pediatric Gastroenterologist. In the midst of the pediatric residency, I specialized in pediatric Gastroenterology and Nutrition, at the Pediatric Gastroenterology and Nutrition Institute, Children Hospital at Buffalo, State University of N.Y., USA. My second tribute is allocated to its founder and the famous head of the Institute, Prof. E. Lebenthal, who put the foundation for clinical, as well as research pediatric Gastroenterology and Nutrition, expanding the profession worldwide, with more than 30 fellows, from all over the world. Here I spent two influential years, 1982-1984, being exposed to numerous clinical, academical, laboratory, endoscopic, as well as basic science research aspects. The third tribute is donated to Prof. Lee PC, who instructed me numerous laboratory techniques and taught me how to write a scientific manuscript. Without those three mentors I would not have reached my position and accomplishments during my career.

During 1985-1987, I specialized in adult Gastroenterology, in the Gastroenterology Institute, Rambam Medical Center, B. Rappaport School of Medicine, Technion-Israel Institute

of technology, Haifa, Israel. The M.H.A degree in health system management was acquired in the Ben Gurion University, Beer Sheba, Israel, during 1996-1998.

Since then, I established the Pediatric Gastroenterology, Hepatology and Nutrition unit, in Carmel medical Center, where I served for 30 years, including 10 years as the head of the department of Pediatrics (1995-2005).

In addition to my fellowship in Buffalo, I spent 3 years as Sabbaticals: Hahnemann University, Philadelphia, PA, USA 1990-1991, 2004-2005 in the Department of Medicine, Division of Gastrointestinal Diseases, State University of North Carolina, Chapel Hill, North Carolina, U.S.A. headed by Prof. Sartor B. and lately at the AESKU.KIPP Institute, Wendelsheim, Germany, 2014-2016, headed by Dr. T. Matthias. It seems to me that the multi-specialization (pediatrics, Pediatric Gastroenterology and Nutrition, Gastroenterology and medical management) and the eminent tutors mentioned above, along my learning curves, established my clinical and scientific progression.

2. Where are you currently work and on what position? Some information about daily routine job description?

I am currently in my second year of research Sabbatical from the B. Rappaport School of Medicine, Technion-Israel Institute of technology, Haifa, Israel. I am working as a senior scientist at the AESKU.KIPP Institute, Wendelsheim, Germany. My main research avenues are new serological markers for celiac disease (CD), side effects of gluten that might compromise human health, nutritional additives in the food processing industries that breach intestinal permeability integrity and autoimmunity. In this regards, we are developing the hypothesis that the food additive, microbial transglutaminase, that functionally mimics tissue transglutaminase and is heavily consumed by the food industries, is a new environmental inducer of CD. Interestingly, the neo-complex of gliadin cross-linked to the microbial enzyme is immunogenic in celiac patients and now we explore its pathogenicity in the gluten associated conditions.

My daily routine is very diverse since I am involved in laboratory bench work, experimental design planning and executing, and recruiting sera bio-banks of autoimmune diseases, scientific and strategic brain storming, writing and publishing the results (30 publications in 1.5 year). I see the sunrise, but miss the sunset...never a dale moment.

3. When you come in directly contact with celiac disease?

I have to dig my memory. The sick babies with failure to thrive, chronic diarrhea, protuberant abdomen and malnutrition were the first patients with CD that I have seen in the ward, in the late seventies. For the diagnosis, we were struggling with the Crosby suction capsule, under X rays irradiation, to get a good duodenal sample, to orient it under the optic microscope for pathological examination. But the major drive toward pediatric gastroenterology came from Prof. Iancu T that in addition of being an eminent pediatrician, was a gastroenterologist that taught me to use the optic microscope, to orient the biopsies and disclosed to me the electron microscopic features of intestinal and hepatic samples.

4. Readers know that you are working in the clinics, but also in the research with orientation to the Celiac disease. Would you be so kind and can you tell us what connections between clinics and research are and how the clinicians can use this information in your daily practice?

I was fortunate enough to mix clinical aspects with clinical/basic science research. During the last 35 years I gathered vast experience, treating, following and discussing thousands of patients and we know how important the experience in the medical practice is. In parallel, I never gave up the scientific pathways and always explored the pathophysiology, etiology, potential risks, improve diagnostic modalities and search for alternative or better therapies. I remember being involved all the way, with basic science people to question and trying to resolve clinical jigsaws. I encourage the cross-talks between the scientific community and the clinicians and always created a mutual team work to widen the medico-scientific rainbow. I sincerely believe that understanding the pathophysiology, actively asking questions, putting question marks on medical axioms transmitted during generations, is the clue for present and future medical progress, for the benefit of human kind. A curious clinician who understands the genetics, biochemistry, immunology, environmental influences, psychology, epidemiology or pathophysiology of the patient's phenotype will offer a better therapy and improve the satisfaction of his client.

5. Is the current all world research of Celiac disease correctly oriented and the

results are available for practice. What do you think about future research of Celiac disease?

I think that we are witnessing a gorgeous era in CD research. It should be emphasized that the disease is very frequent and our knowledge exceeds many other autoimmune diseases. The environmental inducer and its toxic and immunogenic peptides, the autoantigen, the specific diagnostic serological markers, the intestinal luminal, as well as mucosal events, the immune activation of the adaptive and innate immunity, the pathological damage, the extra-intestinal manifestation and the relationship to other non-celiac gluten associated conditions, are continuously explored. Many of the scientific understanding and revelations are continuously spread to the treating physician and their clients. No doubt that the present CD populations are much more aware of the disease and its gluten free diet therapy.

I believe that unraveling additional environmental inducing factors, exploring the CD associated dysbiosis and its metabolome and proteome, further understanding the luminal metabolism, absorptive pathways, toxicity, side effects and immunogenicity of gluten, understanding the transglutaminase and its autoantibodies functions in the disease initiation and progression and improving the gluten free diet aspects and awareness, will advance future therapeutical strategies in CD management. It seems to me that the strategies of enzymatic degradation or binding of gluten, decreasing intestinal permeability towards gluten, local inhibition of the TGase, blocking HLA-DQ2 and -DQ8 presentation by a pseudo peptide, suppressing the gluten peptides stimulation of the adaptive and innate immune activation and their harmful messengers, finding or developing gluten free prolamins or alternative nutrients and finally, developing a vaccination, will eliminate the long dark tunnel of CD. Nowadays, it is difficult to predict what strategy will win the race of future therapy.

6. What was the most progressive and most important moment in the research of celiac disease?

There were several pivotal discoveries and major progression in the modern life course of CD. The celiac disease is an ancient pathology, present since the introduction of the wheat to the human diet. Gluten appeared as a consequence of agricultural practices initiated 10,000 years ago in the Fertile Crescent of southwest Asia. The first description of the compatible clinical symptoms and signs goes back to 250 A.D. The major breakthroughs in the last 100 years were:

- a. The doctoral thesis of Wim Dicke of 1950 established that exclusion of wheat, rye and oats from the diet led to dramatic improvement. The toxicity was shown to be a protein component, referred to as gluten.
- b. Dicke's colleagues, Weijers and Van de Kamer, showed that measurement of stool fat reflected the clinical condition.
- c. The small intestine histological features were demonstrated by Paulley in 1954 and techniques of per-

oral biopsy described by Royer in 1955 and Shiner in 1956 afforded reliable diagnosis.

d. The monozygotic twin's concordance and the HLA-DQ2/8 genetic predisposition.

e. CD associated serology, including AGA-1953, EMA-1983, anti tTg-1997, anti DGP-1997, anti neo-epitope tTg-2008 and anti neo-epitope microbial transglutaminase (mTg)-2016, were very instrumental for the disease screening, diagnosis, follow-up and monitoring dietary compliance.

f. CD relationship with dermatitis herpetiformis was suggested by Samman in 1955 and established by Shuster and Marks in 1965 and 1968, respectively.

g. The Coeliac Society was founded in 1968 (Coeliac UK) and similar societies now exist across the world, provide an extremely valuable service.

h. Since then, numerous clinicians and basic science researchers contributed pivotal information and contributed substantially to our current state of knowledge.

7. Are the clinicians, others medical, or research workers and general public sufficiently informed about Celiac Disease? Are there some differences between countries?

To my personal opinion, a gap in knowledge and updating exist, in multiple aspects of CD. The lack of information exists not only in the public domains, not only between clinicians, nurses, dieticians and patients, but also between professionals like pediatric and adult gastroenterologists. The awareness of this 1000 faced disease, extra intestinal manifestations, changing epidemiology at the age of onset, presenting symptoms, complications, morbidities, expending serological biomarkers, nutritional deficiencies and difficulties in sticking to gluten free diet, are far from being sufficiently informed. Even the geo-epidemiology of CD is changing continuously. Some of the reasons might be the Westernization of the dietary habits in the east, the decrease in rice and surge in wheat consumption worldwide, the changing environment, increase in industrial processing and additive usage, the hygiene hypothesis and finally the microbiome/dysbiome interplay.

It is well known that there is a North-South and West-East gradient in CD incidence, influenced by HLA-DQ2/-DQ8 prevalence and degree of wheat consumption.

8. Do you think there are differences in the concept of disease between some countries?

Absolutely so. One can't compare the awareness and the conceptual knowledge between developed/underdeveloped countries, the availability of CD laboratory markers and endoscopic detections, free media and professional medical information, established CD local societies, wheat/rice dominant nutritional habits and compliance with the diagnostic flow chart of the CD professional societies.

9. How do you think the situation will change in the near and possibly in to the distant future?

In the near future the public as well as the professional awareness, rate of diagnosis, gluten food labeling, gluten withdrawal compliance, media coverage and patients' satisfaction will improve.

In the long run, in parallel to our increased understanding of additional environmental factors that affect autoimmunogenesis, including CD, the unraveling of the dysbiota and immunological event in the luminal eco-system and inside the mucosa, respectively, future therapeutical strategies will be implemented to replace or decrease the patient's dependency on gluten consumption.

10. Do you think that celiac disease will be one day fully curable and patients will not need and not follow gluten-free diet?

This ideal scenario is far from being realized, but without efforts and hope, the tunnel's end will not be reached. There are several unraveled aspect in CD initiation, progression and maintenance: Additional environmental inducers, CD specific dysbiota characterization and its proteomic and metabolomics functions, clarification of the gluten metabolic events in the lumen and its cross-talks with its luminal partners and its mucosal internalization, the immunological cascades of the innate and reactive immune pathways, the lack of a reliable animal model and the relation to other gluten non-celiac dependent conditions. We are at the beginning of a fascinating era, were breakthroughs in CD are achievable and realistic.

11. I think that for readers will be interesting, what are your future objectives?

Actually, we are conducting, in the AESKU.KIPP Institute, Germany, headed by Dr. Torsten Matthias, several lines of research on the following objectives:

1. To improve the serological diagnostic, follow-up and predictive performances, by developing new bio-markers for CD.

2. Since we observed that the complex between the industrial food additive mTg and gliadin, is immunogenic in CD, we are exploring its pathogenicity.

3. To study the intestinal luminal events that relay to remote organ autoimmunity, (gut-peripheral organs' axes).

12. What would you conclude briefly referred to the readers of IJCD?

I congratulate the publisher, the editors, Prof. Samanska and Prof. Makovicky and the editorial board and team for putting forward a Journal dedicated for CD.

It is a great platform to disseminate and propagate CD knowledge worldwide. Personally, it seems to me that the J. offers several unique advantages:

A. concentrates on one disease and gluten related conditions,

B. open access J.,

C. publishes pediatric and adult studies,

D. opens the stage for multiple editorials, debates and experts' personal opinions,

E. becomes the leader and important source of information for the clinicians and scientists dealing with CD, and for the gluten affected populations.