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A Dialogue with Professor Hugh Freeman

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Abstract Here, we continue to interview interesting persons in the field of celiac disease. Professor Hugh James Freeman, a member of our editorial board is introduced. Readers will likely know him from his publications in different international journals related to intestinal disorders, including celiac disease.

Keywords: *interview, journal questions, a great personality*

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1. Could you introduce yourself to the readers? When/where were you born? Where did you attend school and university? Where did you obtain specialty training, particularly in Gastroenterology and Gastrointestinal Pathology?

I was born in Edmonton, Canada in 1947 and received support as a Queen Elizabeth II Scholar to complete my undergraduate education that included a B.Sc. (Honors) from the University of Montreal in 1968 and a M.D., C.M. (University Scholar) from McGill University in Montreal in 1972. Over the next 4 years, clinical training was completed in Internal Medicine and Gastroenterology at the University of Alberta, Edmonton, Canada, followed by the Royal College (FRCPC) as well as American Board examinations (FACP and FACG) in Internal Medicine and Gastroenterology. While at the University of Alberta, I became very interested in celiac disease, its clinical complications, especially lymphoma, and the use of intestinal biopsy for clinical investigation under the direction of Dr. Wilfred (Fred) Weinstein who had distinguished himself with histopathological studies on celiac disease, the relationship with dermatitis herpetiformis, including use of the term latent celiac disease, and the initial clinical and detailed pathological description of collagenous sprue. As a result, my initial experience extended into the intestinal biopsy laboratory, at the time, a very unique hospital facility for microscopic study of the gastrointestinal tract mucosa jointly within the Departments of Medicine and Pathology. From 1976 to 1979, I pursued further research training through the Medical Research Council of Canada, as a post-doctoral fellow in Gastroenterology at the University of California, San Francisco under Dr. Young Kim. Although initially trained as a clinician, Young became a very distinguished basic research faculty member under Dr. Marvin Sleisinger at the VA Hospital. There, Young established the Gastrointestinal Research Laboratories for the University of California at San Francisco, then one of largest fundamental intestinal research units in the world. In this setting, my work extended into development of novel investigative methods with labeled lectins to explore the small intestinal cell surface structure, correlate findings with structural and functional changes in the small bowel (specifically, nutrient transport) using animal models of adapting intestine and chemically-induced models of intestinal carcinogenesis.

2. Where have you worked since your training was completed? What was your daily routine job description in Canada and what was your clinical and research focus in Gastroenterology?

In 1979, I returned to Canada and the University of British Columbia, Vancouver, pursued a clinical and research career over a duration of almost 40 years. During this time, I established a new university hospital academic and clinical center in Gastroenterology that included a modern endoscopic facility with biopsy research laboratories and a clinical investigation unit in a new hospital. The histological review of biopsies done on my patients with intestinal diseases became a critical element in my clinical care. I served as University Head of a 4-hospital Gastroenterology division at the University of British Columbia (including UBC Health Sciences Center, St. Paul's Hospital, Shaughnessy Veteran's Hospital and the Vancouver General Hospital, then the single largest hospital in the British Commonwealth) for 12 years, and continued with my own intestinal clinical and research focus. For more than 3 decades, I practiced clinical gastroenterology, largely focused on intestinal diseases, especially in celiac disease as well as inflammatory bowel diseases, and taught specialty trainees in Gastroenterology, medical resident physicians and medical students. I was fortunate to receive competitive research funding from national and international agencies and published almost 500 peer-reviewed manuscripts related largely to intestinal

diseases, particularly celiac disease, its clinical and pathological complications, clinical and endoscopic features of inflammatory bowel disease and colonic neoplasia, including colon cancer.

3. From a training perspective, is there anything very different from then and now?

Yes, absolutely. Then, trainees were encouraged to take time and learn about the investigative aspects of the speciality, in addition to clinical care. Now, it is a bit different. For the clinician specialist, there is much less interest in exploring basic and fundamental physiological, cell biological and genetic aspects of diseases of the intestinal tract. Of course, there are rare exceptions, but the emphasis now is largely on procedural aspects of the specialty. In large part, the incentive is the financial reward associated with expert performance of a procedure rather than attempt at new discovery of a fundamental biological mechanism of disease.

4. What and who stimulated your interest in celiac disease?

Two patients in 1974, both 43-yr-old females with celiac disease, were seen as a medical resident at the University of Alberta in Edmonton. The first had classic features. She had numerous overt clinical changes including short stature, marked weight loss and diarrhea, steatorrhea, iron deficiency anemia, bone demineralization, long-standing structural changes suggesting childhood rickets, and clubbing of her extremities. The second was an obese, but otherwise well lady with iron deficiency anemia, diagnosed with occult or clinically silent disease. These 2 women illustrated the wide spectrum of clinical changes that could occur in celiac disease. Strong encouragement from the clinical faculty, including Dr. Weinstein, only increased my resolve to pursue a career in intestinal disease. It was pretty obvious to me that any interested physician could learn a great deal about all of medicine, just from patients with celiac disease. As a result, I pursued training in Gastroenterology, and within a few months, accumulated a small series of patients with intestinal lymphoma and celiac disease. During this time, I began studies of the intestinal tract using endoscopic biopsies along the length of the small intestine and did extended pathological and epithelial cell kinetic studies using the Quinton hydraulic instrument. The hospital clinical facility was exceedingly active and became an important asset, not only in supplying biopsy material, but also in allowing me to develop truly “hands-on” technical skills to prepare fixed biopsy material, recognize the critical importance of careful orientation of mucosal biopsies in paraffin blocks and the value of serial sections. Eventually, and in retrospect, expertise in pathological interpretation of biopsy material developed from scheduled weekly sessions, not only in the interpretive histopathological description of biopsies with expert pathologists, but also correlation of macroscopic findings visually observed at endoscopy with microscopic changes in biopsy materials. This rarely occurred in other clinical training programs then, and even now, but in retrospect, became an important, additional skill set that would eventually complement my endoscopic skills as a clinician and investigator in later years. One winter evening in 1975, this weekly descriptive routine became injected with something really novel: the excitement of an unanticipated discovery of an entirely new pathological colonic mucosal disorder in a patient with celiac disease and continued diarrhea, later eventually termed collagenous colitis.

This initial training was later complemented by an extended research experience with a new mentor in San Francisco, Dr. Young Kim, over a 3 year period. In retrospect, he quickly recognized my energy and skill set and allowed me to pursue a multitude of research projects in his laboratory. He was a man full of enthusiasm, intensely driven and always present in the laboratories. He was perfect for me and provided me with great opportunities. During those years, this laboratory was very impressive collection of numerous basic scientists, post-doctoral fellows and trainees from every continent, largely focused on basic enterocyte biology and cell surface membrane structure and function of intestinal tract in health and disease. During this time, my research funding was provided by the Medical Research Council of Canada along with some added faculty support from the University of California to complete my research training experience. It was a busy time, but one that I deeply valued. It taught me, not only about research skills, how to communicate results at meetings and publish, but more importantly, about the actual performance of research in an exceedingly competitive environment, especially for funding. After this added research training, I was ready to return to Canada to function an independent clinician and investigator in intestinal diseases.

5. Where do you work now?

I work at the University of British Columbia in Vancouver, but with decades of clinical experience behind me, I elected to change directions and focus largely on teaching and research, focused on intestinal diseases. Our medical school, like many has a need to revise and update its curriculum and my energies have been directed there, not a small task. In addition, my direct clinical activities have lessened but the ongoing experience of participating with my clinical colleagues has continued to draw me to our weekly subspecialty sessions. Finally, I have taken on a new, but extremely interesting task involved in clinical research ethics for our university. This is really an essential element that has really developed over most recent decades with the emergence of large scale clinical trials in different disciplines presenting many challenges to physicians caring for their patients.

6. What has changed in clinical and investigative activities related to celiac disease?

Celiac disease still presents a challenge in diagnosis and management. A lot of descriptive work related to clinical

aspects of celiac disease has been done, and serological testing has undoubtedly impacted screening in research studies as well as a case-finding tool in clinical practice. However, there is a huge need to more fully understand the immunological etio-pathogenesis of the disease. What actually initiates the clinical disorder in a genetically-predisposed individual? Why does a gluten-free diet actually have an impact? Questions like these require a lot of work at the molecular biological level to provide any answers. So far, we are only scratching the surface, and in many respects, probably only witnessing the end results of many years of persistent inflammatory disease in the small intestinal mucosa and elsewhere. Essentially, we are evaluating a disease, often that may have first developed many years before, a process that may already be decades on in its pathogenesis.

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

I think we are still waiting. That is not to say some very important work has already been concluded. Many early physicians believed that a dietary factor was responsible for the disease, leading to the use of different regimens, such as the banana diet, for symptom control. Then, recall Dicke's work during World War 2 in Holland provided new evidence for gluten effects on the absorptive process in children with celiac disease. To accomplish his studies, he developed a team of expert colleagues, including van de Kamer, for development of a standardized method to determine fecal fat results with different diets. I don't think this effort to establish the role of gluten in celiac disease is the final word though. We still don't know what causes the disease *per se* even though we now think and define celiac disease as a gluten-sensitive enteropathy. Another important development was purely technological. The developments related to small intestinal biopsy were critical. Efforts by Rubin and his trainees in Seattle (Brandborg, Quinton, Trier, Tytgat, Brow, Weinstein and many others) were very important. The work of Walter MacDonald who was a research fellow there was especially interesting. He showed that even the ileum was histopathologically sensitive to gluten infused through long intestinal tubes, along with evidence for a proximal-to-distal gradient of disease severity in celiac disease. I thought the work of Kagnoff was also really intriguing. He was a Canadian from Vancouver, working in San Diego. His idea was that a viral agent (i.e., adenovirus 12) with a specific E1B protein could immunologically mimic the gluten peptide sequence. This was conceptually very interesting, and seemed, initially, at least, to hypothetically suggest a possible etiopathogenetic mechanism. Like much of scientific endeavour, it was never confirmed but it was still a novel and understandable way at looking at the disease. Given recent interest in the intestinal microbiome (and perhaps, virome), the clue may be there. There certainly seems to be a lot of interest in this field of endeavour now.

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

Wow, that is a really tough question. I think it depends on how one defines the disease. I was always clinically focused on adults, not children, and sometimes, I even wonder if the disease in children and adults is different. To me, adult celiac disease is a disorder affecting primarily the small bowel mucosa, particularly, the duodenum and, sometimes, as the disease becomes more severe, further distally into the jejunum and ileum. At present, we define celiac disease as a gluten-dependent disorder. We know now that the tests that we employ to make a diagnosis, including serological markers and biopsy, both have issues. None are perfect and there are passionate and vocal proponents of both, especially in public meetings. Although we have traditionally chosen small intestinal biopsy as the gold standard test, we now all recognize that the changes are pretty non-specific and a lot of other disorders can cause similar, even very severe, histopathological changes. This list will probably expand, now that we have started to recognize that a number of medications can induce celiac-like biopsy changes, for example, olmesartan. It is not too big a jump to worry about a lot of other medications as a cause of similar biopsy changes, or at least, precipitating the disease in an individual pre-disposed to celiac disease. A big advance for screening and case-finding purposes has been the detection of tissue trans-glutaminase antibodies. These tests are not perfect though, either for specific diagnosis or later clinical follow-up. But they still represent an important advance.

9. What are the frequent problems seen in your clinical practice of celiac disease?

Actually, most patients with celiac disease have few problems, once initiated on a diet. Most often, the main symptoms were classical diarrhea and weight loss. Most often, these symptoms usually resolved in most patients within a few months. In my career, I was fortunate to work with dietitian that was really interested in the disease, and willing to devote the necessary extra time to work with these patients and provide them with a lot of good information and source material. She also proved to be a bit of an expert detective when it came to issues related to compliance and detection of foods (and pills) with gluten. Of course, in a tertiary care setting, one does see more unusual problems, often soon after clinical onset. Many had extra-intestinal presentations, like autoimmune thyroid disease and dermatitis herpetiformis. Some, like lymphoma, proved to be pretty devastating for the minority that developed this complication. Anecdotally, celiac disease seems to be an even less significant clinical disorder than a couple of decades ago, although it seems more frequently diagnosed. Perhaps, this is simply a product of wider recognition, more community screening and more case-finding by clinicians ordering tests for serological markers.

10. What questions have your celiac patients verbalized before and after diagnosis?

Most patients with diarrhea and weight loss are most interested in the tests that will be needed to define the cause of their problem. Celiac disease *per se* is rarely noted before a diagnosis is apparent, except in those that are referred because of a prior diagnosis of celiac disease in a family member or because of a positive screening test. After the diagnosis though, there are a multitude of questions. These usually revolve around complications, such as bone disease or malignancies, risk to family members, and the gluten-free diet. As noted, a dietitian was always a useful resource, especially if access was made available to a recently diagnosed patient. In our hospital, a local lay group of celiac patients developed for both adults, and usually, the parents of children diagnosed by our pediatricians. Often, these meetings were useful to convey information to patients and other family members by specialist physicians and others, including dietitians, focused on some aspect of the disease. The internet has become a useful resource for some celiacs, but sometimes, the information provided is not optimal and physicians need to be prepared for questions that result from internet readers and social media users.

11. Do you think that celiac disease will one day be fully curable and a gluten-free diet will not be required?

Short answer: no, at least not until we figure out what actually precipitates the disease. Fortunately, we have a dietary form of treatment. A lot of work is being done to find an alternative to the gluten-free diet, but at the moment, none has convinced me that these will fully replace a gluten-free diet. Right now, I think a lot of the approaches being taken are really interesting, but will likely only be an adjunct to a strict-gluten free diet. Admittedly, I probably have a bias and would love though, to be proven wrong.

12. What role do you think the IJCD has for the readers of this journal?

Important question. I think it is an important global forum for clinicians and investigators focused on the disease. It is really an excellent journal already and will only improve as more and more clinicians discover it. I think the editors, Drs. Samasca and Makovicky, deserve a lot of credit for their efforts as well as support from the investigative and clinical communities dealing with celiac patients. I think it will continue to serve the readership as an excellent source for information, provide a forum for discussion of important issues and concerns for clinicians caring for celiacs, and likely already provides a source of information for many patients that have access around the world to information technology.