Chapter 3

History of Celiac Disease

Few diseases in medicine enjoy a history as rich and intriguing as celiac disease. Its story spans eighteen centuries and it is not reasonable to describe it all in one chapter. However, a brief summary is being presented which should be of interest to both patients and health professionals. The history of celiac disease also provides examples of how careful observations by astute clinicians can lead to important medical discoveries. Being a paediatric gastroenterologist, I have an added interest in this topic as most of the pioneers in the history of celiac disease were paediatricians!

An Ancient Disease

Celiac disease is one of the oldest gastrointestinal disorders described. The earliest known record of what seems like celiac disease was given around 250 A.D by Aretaeus an ancient Greek physician born in Cappadocia, a Roman province in Asia Minor and who practiced medicine in Rome and Alexandria. He referred to his patients as "*koiliakos*," which meant "suffering in the bowels." The name *koiliakos* comes from the Greek word "*koelia*", meaning abdomen. Francis Adams (1796-1861) translated the original text from Greek to English for the Sydenham Society of England in 1856, giving the sufferers of this disease the name "celiacs".

Describing this debilitating condition, Aretaeus wrote, "if the stomach be irretentive of the food and if it pass through undigested and crude, and nothing ascends into the body, we

call such persons coeliacs". His description contains references to chronic diarrhea with pale, fatty stools, abdominal pain, weakness and emaciation in adults. Diet is mentioned in his writings but no details are given. He recommended "drinks taken before meals, for otherwise bread is very little conducive to trim vigour." Although, interestingly, a reference to bread is made in this statement, it seems to refer to food in general and not to bread in relation to its significance in gluten intolerance. Aretaeus did not make any connection between wheat and celiac disease.

Next Discovery

Another seventeen centuries went by before the next clinical account of celiac disease came from a Dr. Mathew Baillie in the early 19th century. Baillie published his observations on a chronic diarrhoeal disorder of adults causing malnutrition and characterized by a gas-distended abdomen. He even suggested dietary remedies, stating “Some patients have appeared to derive considerable advantage from living almost entirely upon rice.”

This was the first clue that diet may have something to do with celiac disease. What that connection was remained an enigma.

Trial of Treatment

The credit for the modern description of celiac disease goes to Dr. Samuel Jones Gee (1839-1911), a renowned paediatrician at the famous St. Bartholomew’s Hospital in London, England. Gee first drew attention to the disorder that he later described as "a kind of chronic indigestion which is met with in persons of all ages" in a lecture delivered in October 1887 at the Hospital for Sick Children, London. He also noted that that it was "especially apt to affect children between one and five

years old." In 1888, Gee gave a notable account of what he chose to call the “coeliac affection” (Gee S. On the coeliac affection. *St. Bartholomew’s Hospital Report* 1888;24:17-20). This remains one of the most accurate descriptions of the clinical state which at that time was named “Coeliac affection of Gee” and is still called coeliac disease.

The most important discovery Gee made was recognizing the importance of diet in the management of celiac disease. He treated a young patient by eliminating foods from his diet and giving him mussels to eat. He wrote, “Child was fed upon a quart of the best Dutch mussels daily, throve wonderfully but relapsed when the season for mussels was over. Next season, he could not be prevailed upon to take them. This is an experiment I have not been able to repeat, but if the patient can be cured at all, it must be by means of the diet.”

Celiac disease carried a very high mortality in those days. Gee is said to have performed over 600 autopsies in his career. During these examinations he could not detect any structural abnormalities and concluded, “naked-eye examination of dead bodies throws no light upon the nature of the coeliac affection: nothing unnatural can be seen in the stomach, intestine or other digestive organs. Whether atrophy of the glandular crypts of the intestine be ever or always present I cannot tell.”

Gee did not feel that he had discovered a new disorder but rather what Aretaeus and others had already described in the past. Although he had noted that “the allowance of farinaceous food must be small” and “to regulate food is the main part of the treatment”, the true nature of celiac disease remained shrouded in mystery.

More Documentation

In 1908, an American physician, Dr. Christian Archibald Herter (1865-1910), wrote a book on children with celiac disease titled "Intestinal Infantilism". He noted that these

children had retarded growth and that fat was better tolerated than carbohydrate in their diet. The eponym Gee-Herter disease was used to acknowledge his contributions in the field of celiac disease along with those of Dr. Samuel Gee.

A Sweet Therapy

The next major advancement in celiac disease came from Dr. Sidney Valentine Haas (1870-1964) when be developed an effective dietary treatment for celiac disease. Dr. Haas was an accomplished paediatrician from New York who achieved notice in 1924 when he published a medical paper describing his use of a banana diet for the treatment of children diagnosed with celiac disease.

Earlier observations had shown dramatic improvement in patients with celiac disease when carbohydrates were eliminated from their diet. However, this diet, consisting mainly of protein and fat, was much less varied, nutritious or palatable. Haas's research led to the development of the Specific Carbohydrate Diet, a nutritional regimen that restricted the use of complex carbohydrates and eliminated refined sugar and starch from the diet.

While in Puerto Rico, Haas had first noted the higher incidence of sprue in urban populations as opposed to farmers whose diet contained a large proportion of bananas. Previous research that children with severe diarrhea did very well on banana flour (made of 70% ripe banana) and plantain meal led Haas to try this on children with celiac disease. Carbohydrates (including bread, crackers, cereals and potatoes) were removed from the diet and bananas were gradually added to the diet from the 4^{th} to 8^{th} day. Ripe bananas were then fed in large quantities. Haas concluded that bananas enabled the breaking up of starches and the conversion of cane sugar into fruit sugar, preventing the debilitating diarrhea of celiac disease. With

time, the focus was on the beneficial effects of banana rather than removal of carbohydrates in celiac disease.

Based on a previous successful experience in treating an anorexic child, Haas treated eight out of ten children suffering with celiac disease using the banana diet. He claimed to have clinically “cured” these eight children. The two children who were not on the banana diet died. It is recorded that, during his career, Haas treated over 600 cases of celiac disease with his Specific Carbohydrate Diet. The patients were kept on the diet for at least a year, some indefinitely. He found the prognosis for celiac disease to be excellent and noted, "there is complete recovery with no relapses, no deaths, no crisis, no pulmonary involvement and no stunting of growth."

In 1951, Dr. Haas and his son, Dr. Merrill P. Haas, published their famous book *Management of Celiac Disease,* believed to be the most comprehensive medical text ever written on celiac disease. It detailed his years of success in using diet to treat various intestinal disorders including celiac disease.

For the next several decades, the banana diet (including elimination of all bread, cereals and crackers) remained a very popular treatment of celiac disease and likely helped reduce the burden of illness for many patients. In Britain during World War II, children with celiac disease were allocated supplies of dried bananas as a supplementary ration.

A few years ago, I personally met a gentleman at a celiac conference in Canada who informed me that he was a “banana baby”. This individual was in his 70’s and had been on Dr. Haas’ famous diet as a child.

Despite this major advance in management, the connection between gluten-containing grains (wheat, barley, rye) and celiac disease was not yet made.

Making the Connection

The credit for connecting wheat to the causation of celiac disease goes to a Dutch paediatrician, Dr. Willem-Karel Dicke (1905-1962). In 1952, Dicke recognized that celiac disease is caused by the ingestion of wheat. He made some astute observations during World War II when there was a shortage of bread and other cereals and food supplies became severely restricted. People turned to uncommon foods including vegetation such as tulip bulbs for survival. Dicke noticed that children with celiac disease improved significantly during that period of starvation. However, these children became ill again when the Allies dropped bread from planes into the Netherlands. During the period of bread scarcity, the mortality in celiac disease decreased from over 30% to almost zero.

Dicke was convinced of the beneficial effect of a wheat-free diet even before this period. Events during the bread shortage further reinforced his beliefs. In the 1930s, he had started to conduct experiments with wheat-free diets, and then published his first report on a wheat-free diet titled *A Simple Diet for Gee-Herter Syndrome* in 1941. (At the time, celiac disease was still called Gee-Herter's syndrome, after Samuel Gee and Christian Herter). Dicke was aware of the effectiveness of Dr. Haas's banana-diet but did not have easy access to fruits during World War II. He wrote, "Therefore, I give a simple diet, which is helping these children at this time of rationing. The diet should not contain any bread or rusks. A hot meal twice a day is also well tolerated. The third meal can be sweet or sour porridge (without any wheat flour)."

In 1953, Dicke wrote his doctoral thesis for the University of Utrecht based on his observations that the ingestion of wheat proteins specifically, and not carbohydrates in general, was the cause of celiac disease. In his seminal thesis, Dicke described the results of the detailed dietary study he conducted over

several years on a patient with celiac disease at Juliana Children's Hospital, The Hague, Netherlands. While admitted to the hospital, the child was given a wheat-free diet which led to a resolution of symptoms and normalized his growth. However, when at home, the child became sick as he was unable to maintain a strict wheat-free diet. He described these findings in his thesis as: "if certain types of meal, such as wheat and rye are replaced in the daily diet, the patient improves" and "deterioration and acute attacks of diarrhea re-occur, if the objectionable types of meal are added to the diet too soon"

After World War II, Dicke conducted a series of experiments involving exclusion or addition of wheat or rye flour over long periods in the diets of children with celiac disease. Children were challenged with different cereals under a strict dietary protocol with measurement of fat in the feces. (Fat in the feces is a good marker of malabsorption). Collaboration with other scientists resulted in the development of techniques for measuring fecal fat content. Based on these findings, Dicke concluded that wheat flour, but not well-purified wheat starch, and also rye flour, triggered the loss of appetite and the fatty stools common in patients with celiac disease.

Although Dicke had made a very important connection between wheat and celiac disease, the exact mechanism of how wheat proteins were causing the problem remained unknown.

Discovering the Culprit

In 1953, a British research team from Birmingham, England discovered gliadin to be the toxic portion in wheat responsible for causing injury to the bowel of patients with celiac disease. How and what damage wheat was causing to the bowel remained a mystery. The diagnosis of celiac disease remained

largely based on clinical symptoms as there were no means for obtaining the intestinal tissue from patients for examination.

Examining the Bowel

In 1954, a British physician Dr. John W. Paulley recognized the characteristic lesion of villous atrophy in celiac disease. Paulley was able to examine biopsies of the small intestinal mucosa (lining) taken from patients during abdominal operations. This discovery concerning the abnormality of the small intestinal mucosa became the most essential feature on which the diagnosis of the celiac disease could be based. Furthermore, it was observed that if a patient remained on a strict gluten free diet, the mucosa of the small intestine returned to normal.

The mystery around the pathophysiology of celiac disease was beginning to unfold. However, a significant challenge remained. How does one obtain a biopsy from the intestine of a patient in a non-invasive manner without an operation?

In a Capsule

In 1956, Dr. Margot Shiner (1923-1998), a paediatric gastroenterologist working at the Hammersmith Hospital in London, developed a quick and safe method to perform biopsies of the small intestinal mucosa by oral route for diagnosis of celiac disease. However, Shiner's biopsy tube was cumbersome. Dr. William Holmes Crosby (1914-2005), a Lt. Colonel in the U.S. army, recognized the need for a more flexible instrument for obtaining samples. In 1957, he and Heinz W. Kugler a U.S. engineer developed the Crosby-Kugler capsule for obtaining the small intestinal mucosal biopsies needed for the diagnosis of celiac disease.

The metal capsule, attached to a long tube, is swallowed by the patient. The other end of the tube remains outside the

patient's mouth. The capsule contains a tiny spring-loaded blade and has an aperture. When the capsule has reached the desired section of the small intestine as seen by X-ray, suction is applied to the tube with a syringe. This suction triggers a mechanism in the capsule which causes the blade to sweep across the aperture, slicing away any protruding mucosa. The capsule is then pulled out of the body and the biopsied tissue is retrieved from within the capsule chamber.

The capsule biopsy procedure had limitations. It was uncomfortable, often requiring sedation or anesthesia for children. Essentially a blind procedure, occasionally a specimen could not be obtained. Other complications included the inability to retrieve the capsule, bleeding and perforation of the bowel. Despite these limitations, the ability to take biopsies opened a new era in the understanding of the pathology, diagnosis and treatment of celiac disease and other small intestinal disorders.

In 1965, Dr. Cyrus E. Rubin from the USA reported on the successful use of an improved biopsy tube for taking intestinal biopsies. The instrument, called the Rubin tube, used suction and a hand-operated guillotine-type blade for taking multiple intestinal biopsy specimens through the oral route. The procedure of small bowel biopsy had been rendered safer and more practical.

For the next two decades, these devices remained the diagnostic tool for celiac disease until the advent of fiber optic endoscopes.

End of the Dark Ages

I call the pre-endoscopy era the “Dark Ages” of gastroenterology. Without a doubt, the invention of the flexible fiber optic endoscopy has been the greatest advancement in the field of clinical gastroenterology. Rigid endoscopes had been

around for a long time but could only examine the esophagus (food-pipe). For adequate examination of the stomach and small intestine, an instrument was required that was flexible and had a source of light that could be transmitted from one end to the other.

The breakthrough came while glass fiber technology was being developed. Dr. Basil Isaac Hirschowitz, a gastro-enterologist in USA and his associates used glass fiber in their endoscopes to take advantage of its ability to transmit light from one end to the other even when it was bent. In 1956, Hirschowitz invented the first glass fiber flexible endoscope for clinical use. Finally, there was light; the Dark Ages had ended!

Celiac disease, like many other gastrointestinal disorders, has been one of the major beneficiaries of endoscopy. Endoscopic small intestinal biopsies are now the routine method for confirming the diagnosis of celiac disease. The procedure is safe, effective and well tolerated by patients.

Further technical refinements in endoscopy and its wide availability have made easy access to intestinal tissue possible. This has led to rapid advancement in the knowledge of the pathophysiology of celiac disease, including the role of the immune system in causing intestinal injury. Through the efforts of researchers like Dr. Michael Marsh from the U.K. and others, it became evident that the villous lesion in celiac disease goes through various stages (Marsh classification). Criteria for the histological diagnosis of celiac disease became established.

Itching to be discovered

Dermatitis herpetiformis was first described by Dr. Louis Duhring in 1884. It was almost a century later in 1967 that Dr. Janet Marks from England discovered the link between dermatitis herpetiformis and celiac disease. This intensely

itchy, blistering skin rash was not responsive to the usual remedies. A gluten-free diet provided an effective therapy for dermatitis herpetiformis which is often referred to as “celiac disease of the skin”.

Checking the Blood

One of the major advances in celiac disease has been the availability of serological tests for screening suspected cases. Patients with celiac disease produce a variety of antibodies in response to gluten ingestion. In the 1980s, the anti-gliadin antibody (AGA) test became available to screen for celiac disease. This was followed by the discovery of the anti-reticulin antibody (ARA). However, this set of antibodies was not very sensitive or specific for celiac disease.

The discovery and clinical availability of endomysial antibody (EMA) in the early 1990s changed the landscape for serological screening. This test is highly sensitive and specific for celiac disease and can be used not only in suspected cases of celiac disease but also, to a certain extent, for monitoring compliance with the gluten-free diet. It also provided a means to do population-based studies on large numbers of individuals, making prevalence data from different countries possible. Along with this data came the realization that celiac disease is much more common in the general population than originally thought. The “celiac iceberg” model was developed to highlight its various clinical forms; typical, atypical, silent and latent. Its connection with other autoimmune disorders became established. Suddenly, there was a surge in interest in celiac disease around the world.

What exactly the antigen against which EMA was being produced had been a mystery. That mystery was solved in 1997 when tissue-transglutaminase (TTG) was discovered to be the antigen in humans which was targeted by auto-antibodies in the

serum. Rapid advancement in this area made TTG widely available and affordable as a blood test to screen for celiac disease.

The last few years have seen the development of a new class of serological test called the deamidated gliadin peptide antibody (DGP) test.

Along with this came advances in the genetics of celiac disease. In the last decade, there has been an explosion of knowledge in this area especially in our understanding of how determination of genetic markers like DQ2 and DQ8 can help predict susceptibility for celiac disease.

The panel of serological tests, coupled with genetic testing, will one day open a new chapter in how the diagnosis of celiac disease is established.

Celiac disease in the 21st century is an old disorder with a new face. A disease which had been on the backbenches until recently, is now in the forefront of gastrointestinal research. Things are now moving so fast in the area of celiac disease that, as they say, we have to run in order to stay where we are! If the past is any indication of how intriguing celiac disease can be, its future will no doubt be full of surprises.