

Chapter 2

A History of Celiac Disease

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Abstract

Celiac disease is known since ancient times. This chapter describes Aretaeus of Cappadocia's contribution, approximately 2,000 years ago and up until recent times when Marcelo Royer in Buenos Aires and Margot Shiner in London each independently designed a technique for peroral duodenal biopsy under fluoroscopic control. Over the centuries, doctors tried to treat this disease using different diets since the exact pathogenesis of CD was not clear. Special attention is given to the early history of celiac disease in Spain, highlighting the work of Santiago Cavengt and later writings by other Spanish doctors. The elucidation of the cause of celiac disease is due to Willem Karel Dicke. He published his first findings in 1941 in a Dutch Journal in an age when medical literature was based on the empirical knowledge that the diets by proposed by Fanconi and Haas were best for the treatment of the disease. The introduction of intestinal biopsy was the key in confirming the diagnosis of celiac disease since it revealed the characteristic flattening of the mucosa exposed to gluten and the response to a gluten-free diet. Afterwards came new, great advances in the knowledge of the pathophysiological mechanisms of the disease. But that is another history.

“Upon first sight the child appears to have a great pallor... he gives the impression of a balloon held up by two sticks”

(Recalde Cuestas JC, Travella EA.
La Medicina de los Niños. 1935; 36: 326-41)

Celiac disease is one of the nosological entities which has generated more writing in modern pediatric gastroenterology and in pediatrics in general.

Knowledge of the pathogenesis and treatment of the disease has progressed significantly since Willem Karel Dicke established the relationship between the consumption of gluten and the appearance of the disease's symptoms. However, celiac disease has been known for a long time. For centuries, doctors tried to treat it with different dietary regimes since they did not know its exact pathogenesis.

1. Aretaeus of Cappadocia and Gerónimo Soriano

Aretaeus of Cappadocia (85?-138 AD) was a physician, influenced by Greek culture, who flourished in Rome during the age of the Emperor Nero. He brought the clinical dimension of medical practice to the forefront, intensifying the return to the Hippocratic tradition.¹

He hailed from Cappadocia (in what is now Central Turkey). Apparently, he studied at Alexandria in Egypt, where dissection was allowed. Aretaeus must have practiced it in order to acquire the profound and accurate knowledge about the internal structure of the human body he possessed. His work contains the best ancient descriptions of diseases like diabetes, tetanus, leprosy and pulmonary tuberculosis. He described the aura and hallucinations that precede epileptic seizures. His first description of diphtheric angina and croup are noted for their originality.²

His main work is a comprehensive treaty which has not been fully preserved. It consisted of four books which dealt with the causes and symptoms of acute and chronic diseases, plus four others on their treatment.¹ His work was printed in Venice in 1552. The first four books were published under the title *De Causis et Signis Acutorum et Diuturnorum Morborum*. They were regarded, together with the best Hippocratic texts, as classical antiquity's greatest contribution to clinical medicine and they exerted a significant influence on its development.¹ In Book IV, section VII, Aretaeus described the chronic disorder of *pepsis* and *anadosis*, terms which can be translated as “digestion” and “absorption”, respectively. For contemporary physicians, *anadosis* included two phases, the passage of food from the intestines to the liver and, from there, to the tissues. According Aretaeus, the celiac condition consisted mainly in fecal elimination of undigested food and in a partially raw state. Being a chronic disease, it made the patient felt very weak “because of the body's hunger”. The term “celiac” comes from the Greek word *koiliakos* (*koelia* means

“belly” in Greek), which describes a characteristic symptom of the disease in children who begin exhibiting a classic clinical feature (i.e., bloating).

The explanation Aretaeus gives to this mixed disorder of digestion and assimilation was based on the then-current theory of digestive functions. It was based on the concept of “natural heat”: as the heat of the sun is necessary for ripening fruit or as the heat used in cooking softens food, the “natural heat” of the stomach was thought to be necessary for the preparation (concoction) of ingested food as requirement for their subsequent absorption. To Aretaeus, the celiac state was thus caused by a cooling of the “natural heat” necessary for the *pepsis* and the *anadosis* of food. For this reason, celiac patients would be haggard, hungry, pale and devoid of the energy needed to perform their usual activities. The exclusion of “peptic” activity would lead to deterioration in the color, smell and consistency of their stools.

In Book VII, section VIII, Aretaeus explains the treatment for said disease. It was aimed at promoting *pepsis*, preventing cooling and restoring the “natural heat”. The treatment included rest and fasting along with then current therapeutic measures to prevent flatulence and diarrhea. The prescribed diet was mentioned without excessive details, but it suggested that drinks should be taken before solid foods.

The first Spanish reference to celiac disease is found in a book written nearly three centuries before the work of Samuel Gee.³

Gerónimo Soriano, an aragonese physician born in Teruel, published, in 1600, one of the first Spanish language books on pediatrics, *Método y Orden de Curar las Enfermedades de los Niños* (“The Method and Order by which to Cure the Diseases of Children”).⁴ The book consists of 39 chapters, each referring to a pediatric disease, including topics as diverse as the treatment of fainting, cataracts and epilepsy. The second edition, which also appeared in Zaragoza in 1690, included a new chapter on the treatment of carbuncles.

In Chapter II, which dealt with the treatment of diarrhea, Soriano states that there are different types of diarrhea, one of which is characteristic of “those which are celiac” in which “that which is emptied is with little alteration or mutation”. A few lines further on, he writes that “Regarding all these differences in diarrhea, we dwell long in the book on our medical experiments. Here you will find wonderful remedies”.

2. Samuel Gee and Subsequent Works until the Late Nineteen Forties

London’s St. Bartholomew’s Hospital was founded in 1123. For centuries, numerous doctors and surgeons tried to alleviate the ills of their fellow citizens through the use of the methods, techniques and drugs current in the era in which they lived. Samuel Gee was one of the physicians who worked here (Figures 1 and 2).

He was born in London, on September 13, 1839. He died 72 years old, on August 3, 1911 in the English town of Keswick.⁵ He began his medical studies at *University College Hospital* in London

in 1857 and graduated from the University of London in 1861. Soon he began working at the prestigious *Hospital for Sick Children* in the same city and, in 1865, was appointed member of the Royal College of Physicians, the year in which he earned his doctorate. A year later, he began working at St. Bartholomew's Hospital.⁵



Figure 1. Samuel Jones Gee (1839-1911).



Figure 2. Samuel Gee in 1900. Picture taken in the yard of St. Bartholomew's Hospital, London. Dr. Gee is the second figure from the right, sitting, wearing top hat.

On October 5, 1887, Gee was invited to lecture at the *Hospital for Sick Children*. The contents of this lecture, published the following year in the journal *St. Bartholomew's Hospital Reports*, is the first recognizably modern description of celiac disease in children.⁶ Gee describes a disease characterized as a kind of chronic indigestion which could be observed in all ages, although it mainly occurred in children aged between one and five years. This disease is characterized by the presence of soft, unformed stools, though not liquid, bulkier than the amount of food eaten, pale, as if devoid of bile, frothy and, sometimes, emitting a striking stench as if food had undergone putrefaction rather than *concoction* (digestion). Gee conducted autopsies on some of his patients and found no injuries to the stomach or intestines or other digestive organs, although he could not tell whether the atrophy which could be observed in the intestinal glandular crypts could be important to the pathogenesis of the disease. He thought that certain errors in the diet could be the cause of the disease, which led him to conclude that "if the patient can be cured at all, it must be by means of the diet".⁶

Indeed, he found that a patient who had been prescribed a daily "pint" of the "best" Dutch mussels thrived "wonderfully", even though he relapsed when the mussel season ended. The following season there was no way to repeat the experience.

In 1908, Christian Archibald Herter (1865-1910), who worked in New York, published his findings on new cases of the disease, which he called "intestinal infantilism". This author attributed this

condition to an infection linked to abnormal persistence of acidic digestive flora (bifid bacilli) in the newly born; this theory was quite influential. Following the publication of his book⁷ CD became known as the *Gee-Herter disease*.

In 1909, Johann Otto Leonhard Heubner (1843-1926), director of the Children's University Hospital at Berlin (Charité), described some cases of "serious digestive insufficiency" in which he supposed there might be a problem caused by starch fermentation, due to a faulty congenital disposition of the entire digestive tract.

In 1918, George Frederick Still (1868-1941), professor of pediatrics at King's College Hospital in London, considered the disease to be a serious digestive disorder and noted that bread particularly aggravated its symptoms, but was not aware of the importance of this observation.⁸

In 1924, Sydney Haas (1870-1964) reported success with eight children who were fed a diet based on bananas and which excluded bread, cereals and sugars, which ought to be maintained indefinitely. The author was right to recommend a gluten-free diet even though he did not understand the reason for his success, since he believed that what really mattered was the sugar content of the diet. It is possible that he may have based his recommendations on his observation that in Puerto Rico, "the inhabitants of the city suffer from sprue while farmers, who mostly live on bananas, never do".^{9,10} (Figures 3 and 4)

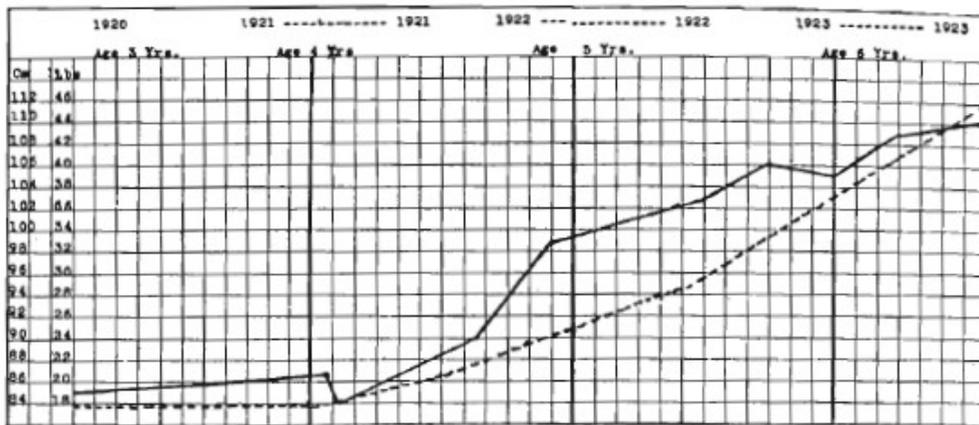


Figure 3. The effectiveness of Sydney Haas' banana diet. Case 2). Progress S.D. The dashed line indicates height; the solid line, weight.⁹

In 1928 Guido Fanconi (1892-1979) suggested the possibility of the existence of profound metabolic changes in children suffering from this disease, such as hypocalcaemia, hypophosphatemia, vitamin C deficiency and, especially, metabolic acidosis. He therefore recommended that they be nourished with vitamin C-rich foods. The diet should be based on fruit and their juices, adding raw or pureed vegetables, crossing out flour, sucrose or baby food since they tend to be poorly tolerated by the small intestine and tend to produce acidosis.¹¹ This author, along Uehlinger and Knauer, published in 1936 a memorable article in which they revealed a new disease, mucoviscoidosis or cystic fibrosis.¹² Two years later, Dorothy Andersen (1901-1963) established the histopathological differences between this disease and celiac disease.¹³ In 1947, Dr. Andersen defined celiac disease as “the disease which causes recurrent or chronic diarrhea in children between six months and six years, with no demonstrable pathological or bacteriological basis, showing intolerance to the food proper for their age and leading to a progressive increase in the volume of the stomach and halting of body weight gain”.¹⁴ In the late nineteen forties, Emery published some articles on carbohydrate¹⁵ metabolism and on the tendency to hypoglycemia, with afebrile perspiration¹⁶ in celiac children.

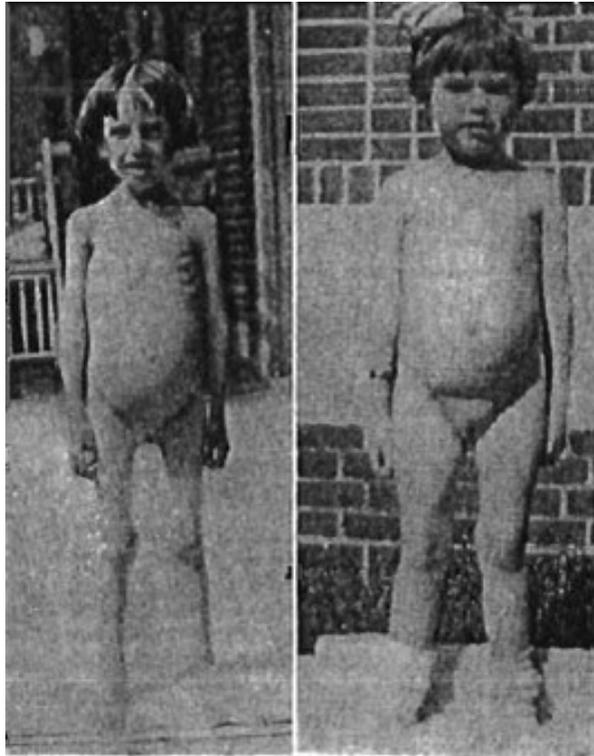


Figure 4. These pictures show the rate of change in celiac disease after the introduction of the gluten-free diet. The image on the left shows patient RB at age 7 years and 7 months, the right, at the age of 7 years, 10 months.¹⁰

3. Celiac Disease in Spain; Santiago Cavengt and the Later Writings of Spanish Physicians

In pediatrics textbooks as widely used in Spain as Apert's (1917) no reference is made to this entity, and the only thing that could be found approaching it was only a brief description of chronic dyspepsia, in which a distinction is made between "fatty dyspepsia" and "atrophic dyspepsia". Spanish pediatricians were aware of what was known as "serious digestive insufficiency" through the equally titled chapter in *Treatise of Children's Diseases*, edited by the German physician Bernardo Bendix and translated into Spanish in 1913. The author, who named to Heubner as his teacher, stated that this disease numbers among its symptoms "general depression, moodiness, loss of appetite, change in the appearance of the stool, bowel movements and halting of weight gain and growth. The abdomen may be distended". This text mentions a study by Herter which had shown an increase in the fecal excretion of calcium salts which might later help explain, at least in part, the osteomalacia and hyperoxaluria that can be seen in celiac children. Drawing from his experience in the treatment of the disease, which is defined as "faulty or weak congenital disposition of the entire digestive apparatus", Bendix recommended the exclusion of milk from the diet. Decades later, this decision would later be explained by the transient lactase deficiency that occurs in this disorder. The drugs that were recommended then were "occasionally, lactopepsin, acidolpepsin, pancreatin and pancreon tablets" a result of the fact that, by that date, celiac disease had not yet been differentiated from cystic fibrosis.

Santiago Cavengt Gutiérrez was one of the great Spanish pediatricians from the first half of the last century (Figure 5). He was a staff member at the of the *Hospital del Niño Jesús* at Madrid, where the *La Pediatría Española* ("Spanish Pediatrics") magazine was edited under the direction of Martin Aurelio Arquellada, a pediatric surgeon. Cavengt taught at the *Escuela Nacional de Puericultura* ("National Childcare School") and became Director of the *Dispensario Municipal de Puericultura* ("Municipal Childcare Dispensary"). In 1922 Santiago Cavengt wrote *Endocrinología Infantil* ("Child Endocrinology") with a foreword by Gregorio Marañón. This was the first book written in Spain on the subject of pediatrics. Chapter 12 of said book is titled "Infantilism or *Patocativismo*" (this last Spanish-language term has fallen into disuse and it was used to denote a pathologically weak constitution).¹⁷ The author recalls the different classifications made by contemporary writes on the different types of infantilism. Thus, he refers to Bauer's division of infantilism into two groups: thyroid infantilism or Brissaud's and "all the other types, that is to say (sic.) infantiles of the Lorain type, not regarding them as truly ill, but simply as constitutionally weak, physiologically miserable; he named them *chétivistes* (*chétivisme*), name which Marañón successfully rendered into Spanish as *cativistas* (*cativismo*)". Later that same chapter, Cavengt goes on to expound on "pluriglandular infant *patocativismo*" and one of them being "intestinal in origin". He quotes Herter, as the first author who studied this disease but he states that "Charrin and Le Play already in 1904 wrote about lack of intestinal development of toxic origin". He goes to say that "this *patocativismo* has also been described by Stoops, from Berne, who defines two varieties: one that begins during the second year of life (Herter type) and another one which features gastrointestinal disorders during the first year (Heubner type). The author goes on to relate the case of a child with a medical history absolutely typical for this disease, since it began with "vomiting since birth, without respite up until four years of age, sometimes not defecating for six or seven days, living in a state of athrepsia". Further on he adds

“before, as an infant, he was very constipated, alternating between normality and ill-smelling diarrhea”. At nine years old, the patient measured only 90 cm. The abdomen was distended and blood tests showed “decreased hemoglobin and red blood cells”. This data suggest that the patient was affected by Hirschsprung’s disease, rather than celiac disease. He closes the chapter admitting knowledge of the term “celiac infantilism” but points out that “the authors call it so, as they could name it otherwise, they are really cases of intestinal infantilism”.¹⁷

Four years after the publication of his book, Santiago Cavengt publishes in *La Pediatría Española* reports on two new celiac disease cases, this time under the term *digestive infantilism*.¹⁸ The author repeats concepts already mentioned. He admits knowledge of Gee’s work: “thus, Samuel in 1888 speaks of the celiac affliction”. He also mentions new concepts, such as the relationship of the disease with bone metabolism so that “along with Marfan, we admit that, among the root causes of rickets, the most common is chronic gastrointestinal toxicity; other authors such as Lehmann, Bluhdorn, Stollte and talk about osteoporosis”. It is striking that these cases’ symptoms began quite soon during lactation. Unless dietary cereals were introduced quite early, which is quite likely, it might be considered “that these children have actually suffered from diseases such as intolerance to the proteins in cow’s milk or cystic fibrosis”. Thus, the second patient acquired “pertussis one month after being born, which lasted a long time; the parents assure that he still coughs occasionally, catching cold quite easily”.



Figure 5. Santiago Cavengt Gutiérrez, the Spanish pediatrician who published the first cases of celiac disease in Spain. He was President of the Spanish Association of Pediatrics (1949-1952).

The nineteen thirties, especially near the end of the decade, were not conducive to promoting research and scientific development in Spain. In that span of time there are only two known papers written on the subject. In 1932, Tenerife pediatrician Isidoro González Hernández published the first known case described in the Canary Islands.¹⁹ In 1935, Dr. Martínez Vargas, Professor of Pediatrics at the Faculty of Medicine, Barcelona, published in the journal *La Medicina de los Niños* ("The Children's Medicine") an article which now did use the term *celiac disease*. Actually, it was an article written by two Argentine authors, Recalde Cuestas and Travella, who had already presented it at the V National Congress of Medicine at Rosario and in which they pointed out that "most of these children are neuropathic, capricious, and prone to anger, to lack of appetite and bulimia". Martínez Vargas, simply restricted himself to writing a few comments at the end of said text.²⁰

The pediatric journals that were published in 1936, such as *La Medicina de los Niños* (Barcelona), *Archivos Españoles de Pediatría* ("Spanish Pediatrics Archives", Madrid), *La Pediatría Española* (Madrid) and *Pediatría y Puericultura* ("Pediatrics and Childcare, Granada) disappeared forever as a result of the civil war. Interestingly, in that decade, between 1934 and 1936, Dicke began his first experiments with wheat-free diets.

After the war, in 1943 Spanish pediatric journals reappeared with *Acta Pediátrica* ("Pediatric Act"), co-founded by Santiago Cavengt and which continues to this day. It was this author who would publish in the journal's first issue his *Contribución al Estudio Clínico del Síndrome Celíaco* ("Contribution to the Clinical Study of the Celiac Syndrome").²¹ In this article, in which he already accepts celiac terminology, he also recognizes that it was Gee who gave the disease an "independent scientific personality"; he also reported the case histories of two new patients, the second of which was born with imperforate anus. The author, who no longer used the term *patocativismo*, summarized the three pathogenic theories at the time current at the time he wrote: "the one which defends the toxic influence of a bromo-infective origin, which would impinge upon the intestinal mucosa's function and absorption, the one that assigns the main role to altered adrenal glands and the one that posits the intervention of avitaminosis". This last hypothesis, then in vogue, was proposed by Dubois, who sought to explain the pathogenesis of celiac disease from a point of view essentially based on vitamins linked to lactoflavine, the vitamin B2 complex's thermostable factor. The author postulated that "it appears that vitamin B2 would be able to intervene in regulating the absorption process of the intestinal mucosa". Cavengt quoted data on mortality from various contemporary works and which ranged from 11% in the Shaap series up to 50% from Knofelmacher's. Discussing the issue of treatment, the author mentions renowned French pediatrician Marfan, who stated that "given the darkness that prevails about the aetiopathogenesis of this disease, treatment must depend on an empirical basis". Experience had already shown that a good way to start feeding the children again was based on rice flour and fruit juice. The author mentioned diets advocated by Haas and Fanconi, as well as those recommended by Marfan's, based modified milk compounds (albuminous milk, kefir) or more "exotic" ones, like Ribadeu-Dumas' comprising "heliotrope aleurone, vegetable protide, porridge made with water, sour milk or beef broth". In all these diets, experience had shown, in an empirical but effective way, to withdraw certain cereals and, in many cases, lactose from the diet of celiac children.

In 1945, Manuel Suárez Perdiguero, who then held the chair of Pediatrics at the University of Zaragoza, published the most comprehensive national study, consisting of 17 celiac children.²²

From the point of view of the bodily functions, he mentioned that these patients had a flat glucose curve when the test was performed orally but a normal curve when checked intravenously. He mentioned as well radiological images obtained from the intestinal tract showing slow transit of pap in the small intestine, atonic dilated loops or “rainy” images. Dr. Suarez insisted on establishing differential diagnosis of celiac disease with pancreatic cystic fibrosis, lambliasis or B2 hypovitaminosis, rejecting the current pathogenic theories listed above, and thought, along with other authors like Stolte and Parssons, that the disease was due to functional impairment of the small intestine, which behaved like an infant’s, able to accept only the “biological food of a woman’s milk”.

In 1948, Guillermo Arce, Chief of Pediatrics at the *Casa de Salud Valdecilla* (“Valdecilla House of Health”), at Santander, published a review summarizing current knowledge concerning chronic dyspepsia between three and six years of age.³ The author reviewed contemporary etiologic systematizations including those of authors such as Nobécourt, Andersen, Hodges, Ramos and Fanconi, among others. The author explained his personal classification of the subject, in which distributed “chronic dyspepsias” into five subgroups, namely, simple chronic dyspepsia, chronic dyspepsia with accompanies genuine celiac disease, pseudoceliac chronic dyspepsia, chronic dyspepsia due to pancreatic insufficiency and dyspepsia with chronic enteritis or colitis.

In 1949 a work was published by one who would become one of the most internationally-minded Spanish pediatricians in the second half of the last century, Ángel Ballabriga Aguado. In this article, which had been awarded the Nestlé Prize by the *Sociedad Pediátrica de Madrid* (“Madrid Pediatric Society”), he mentioned that “it is more important to maximize the elimination or restriction of carbohydrates from the diet than the elimination or giving low-fat diet”, and that this restriction “must be imposed on certain carbohydrates. Therefore, the administration of carbohydrates will take the form of disaccharides”.²⁴ The reason for the removal of cereals is explained as done “in order to avoid or minimize hydrocarbon fermentation which causes bloating and diarrhea”. The author advocated the effectiveness of a diet based on bananas, carob and buttermilk. The second part of this work mentioned the development of a new biochemical technique in Spain, referring to the determination of aminoacidemia levels following Krauel’s micromethod. Ballabriga showed that the increase of these levels followed the administration of casein hydrolyzates, whose use he recommended.

Finally, in 1950, *Acta Pediátrica Española* published a reference to a meeting of the *Sociedad de Pediatría de Madrid* (“Madrid Pediatric Society”), which included a paper entitled *Consideraciones Clínicas sobre la Celiaquía* (“Clinical Considerations on Celiac Disease”).²⁵ The author was none other than Santiago Cavengt, who, by then must have been 67 years old and yet still had enough enthusiasm to continue studying the disease he had made known in Spain. Little did he imagine that the question of its origins had already been solved.

4. The Elucidation of the Cause of Celiac Disease. The First Intestinal Biopsies

Willem Karel Dicke (1905-1962) (Figure 6) began his experiments in 1932 using wheat-free diets, inspired by Stheeman's report of the case of a child who experienced diarrhea after eating bread and biscuits. He published his first results in 1941 in a Dutch magazine, when literature had already empirically established that the Haas and Fanconi diets were the most suitable in the treatment of this disease.²⁶ At the International Congress of Pediatrics (New York, 1947) Dicke submitted comments about the bread or cookies aggravating celiac disease. He was not taken seriously.²⁷ With the help of colleagues from Utrecht, Weijers, a pediatrician and Van de Kamer, a biochemist who developed the fecal fat quantification technique, Dicke was able to show that the removal of wheat from the diet of celiac patients reduced fecal fat, while its reintroduction increased steatorrhea. These findings were presented at the International Congress of the International Pediatric Association (IPA) (Zurich, 1950).²⁷ The publication of the article which contained these results was delayed because it was rejected by a noted American magazine. It was later published in 1953 in *Acta Paediatrica Scandinavica*.²⁸ At the same time, Anderson et al. in Birmingham, noted that most of the fecal fat was of dietary origin and that it was due to a defect in intestinal absorption. This group concluded that improvement occurred only when a wheat flour component, gluten, was strictly removed.²⁹ This was what the Dutch group called the "wheat factor".³⁰



Figure 6. Willem Karel Dicke Stock (1905-1962) during the period in which he was Director of the Wilhelmina Children's Hospital at Utrecht.

The introduction of intestinal biopsy was instrumental in confirming the diagnosis of celiac disease, it highlighted the characteristic flattening of the mucosa when exposed to gluten. This finding was defined by Paulley in 1954, by means of laparotomy-obtained samples from adult individuals affected by idiopathic steatorrhea.³¹ The difficulty in obtaining samples able to yield data suggested the need for a viable method to obtain intestinal biopsies from these patients. Wood et al. designed in Melbourne a simple biopsy tube which was flexible and could be used to perform gastric biopsies without the aid of a gastroscope or an X-ray screen; it was soon used to establish the histological diagnosis of diffuse lesions such as chronic gastritis or atrophic gastritis.³² Marcelo Royer et al. in Buenos Aires³³, and Margot Shiner, in London³⁴, each developed separately a technique for peroral duodenal biopsy under fluoroscopic control, based on a device designed by Wood (Figure 7).

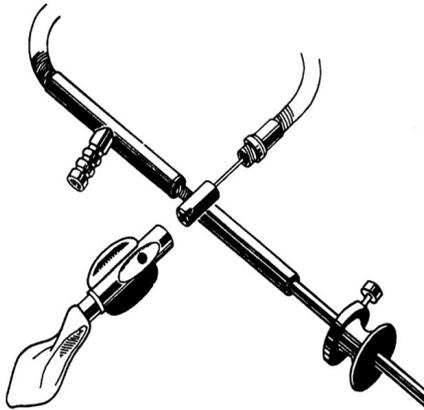


Figure 7. Margot Shiner's jejunal biopsy tube.³⁴

Subsequently, other authors found flattening of the intestinal mucosa in celiac patients and that mucosal recovery followed the introduction of the gluten-free diet³⁵ (Figure 8).

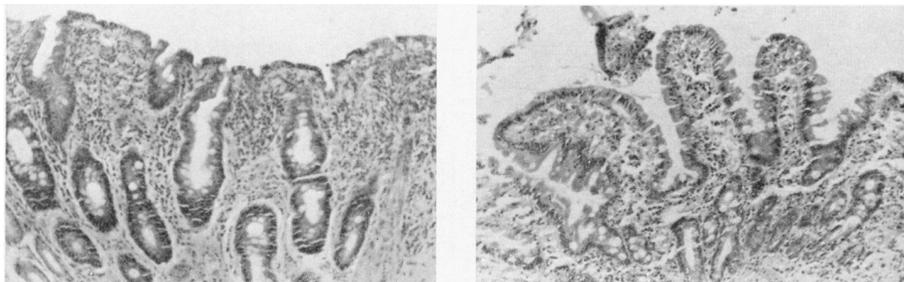


Figure 8. Left: initial biopsy. Right: Marked improvement in duodenal biopsy after 12 months of treatment with gluten-free diet.³⁵

New and significant advances in the understanding of the pathophysiological mechanisms of the disease are yet to come. But that is another story.

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