Willem Dicke. Brilliant Clinical Observer and Translational Investigator. Discoverer of the Toxic Cause of Celiac Disease

David Yan[1] and Peter R. Holt, M.D.[2]

Abstract

We can admire and learn from physicians with acute clinical acumen and superb approaches to translational research. The observations and studies of Dr. Willem Dicke, a Dutch pediatrician, on the toxic effects of a protein component of wheat and rye demonstrate the highest quality of such investigations. From a clinical observation of one child with celiac disease, through years of historical questioning and empirical dietary suggestions of patient families, he concluded that such foods were toxic. When research became possible after the second world war and fecal fat measures as a hard end point became available he studied 5 children in detail to establish the validity of his clinical clues.

Keywords: celiac disease, translational research, diet

Progress in defining clinical disorders often requires the combination of careful observations of the patient's disease, intuition and the ability to perform the clinical translational research to prove a hypothesis. The story of William Dicke, a Dutch pediatrician, who had the birth of an idea from a case report from listening to his child patients' mothers, who then continued clinical questioning of families with children with the disease for almost a decade and then wrote his thesis on a remarkably careful series of clinical studies which resulted in basic understanding of the toxic effects of wheat protein in celiac disease, represents the peak of such clinical research.

Celiac disease (or Coeliac disease), also known as nontropical sprue (in contradistinction to tropical sprue), idiopathic sprue and celiac syndrome, was originally described principally in children. It is an autoimmune disease characterized by an abnormal small intestinal mucosa. The classic clinical features were described by Samuel Gee in England[1] and by Christian Herter in the United States, the latter emphasizing malnutrition and growth retardation.[2] Until the mid 20th century, celiac disease was known as Gee-Herter disease. The management of celiac disease was unclear in the 1930s when Dicke made his original observations; however, scattered observations suggested clinical improvement with several differing diets including an oyster diet suggested by Gee and the banana diet championed by Haas.[3] When Dicke completed his medical degree and internship in Holland in 1928, celiac disease was often fatal with a short-term mortality rate reported as between 10% to over 35% in different studies. Following Dicke's observations on the pathogenic effect of wheat protein and the adoption of a wheat/rye-free diet, patients rarely died.

The principal features of the disease described in pediatric textbooks around 1930 were malnutrition, inanition and growth retardation accompanied by the passage of bulky foul stools containing "an excess of soap, free fatty acids and to a lesser extent other components." It was only in 1938 that cystic fibrosis of the pancreas was separated as a diagnosis from "the celiac syndrome."[4] In his thesis, Dicke commented on the similarity of many of the clinical features of celiac disease with malnutrition in children who had lived in Japanese camps in the Dutch East Indies in the Second World War.[5]

Dietary management of celiac disease was a mainstay of treatment of celiac disease in the early part of the 20th century. One dietary approach was to reduce or eliminate dietary fat since the stools of patients had a greatly increased fat content. However, such diets were calorically severely deficient. Other clinical observation stimulated the conclusion that carbohydrate ingestion increased the weight and water contents of the stools.[6] Improvement in patients was noted when carbohydrates, including wheat products, were omitted from the diet;[7] however, clinicians also reduced ingested fat to lower fecal fat content, a calorically insufficient diet. This was the state of the nutritional art for the treatment of celiac disease when Dicke's attention was directed to case 3 in a report that suggested that lapses of diarrhea were preceded by consumption of bread and rusks.[8]

Following this singular report, Dicke would interrogate his patient's parents about the dietary components that appeared to result in either improvement or relapse of the symptoms in their children. He initiated uncontrolled clinical trials in his patients by encouraging families to experiment and provided celiac disease children with different diets, including wheat-free diets. He became convinced of the toxic effects of wheat and similar grains but continued clinical observations in his patients before he published a short report about the wheat-free diet in 1941 entitled W.K. Dicke "A simple diet for Gee-Herter's syndrome."[9] In 1941, the "accepted diet" for celiac disease children was a banana diet[3] or the Fanconi diet (consisting of fruit and vegetables);[10] however, at that time, during World War II, fruits and vegetables were not available in Holland. The generally popularized version of the discovery of the toxic effects of wheat ingestion was that Dicke's idea came during the winter of 1944/1945, toward the end of World War II, the so-called "winter of starvation" when even bread was unavailable in Holland. Celiac disease children paradoxically appeared to be clinically improved even though they were consuming a starvation diet (almost devoid of wheat products). When bread was airdropped in Holland, his patients rapidly deteriorated. Dicke certainly noted this but, as far as he was concerned, this was only "icing on the cake" for the clinical observations that he had made in the previous decade.

Dicke excels in translational research on celiac disease in his story-telling about his patients and the illness. Dicke's observations were not only qualitative but also quantitative and all his initial studies were performed in 5 patients. It is hard to believe nowadays that scientific papers could include such qualitative results. His accounts of each patient is a story by

[1]High School Student, Collegiate School, New York, New York 10024, USA; [2]Senior Research Associate, Rockefeller University, New York, New York 10065, USA.
Correspondence: Peter R. Holt (holtp@mail.rockefeller.edu)

DOI: 10.1111/j.1752-8062.2009.00167.x

itself and provides compelling evidence of his ideas on the cause of celiac disease. Dicke's clinical observations read like stories in a novel but this belies an insightful and creative research approach. He modulates patient diets with precision, adding butter milk here, or removing rusks there, to convince himself and the reader of his thesis that celiac patients could not tolerate certain types of grains. Dicke had to dispel the then current notion that certain food groups were better for celiac than others. He uniquely showed what celiac patients cannot consume and not what a patients should eat, making the celiac diet accessible to low-income families.

In his first study patients, A. Dr. and J. Tr., Dicke builds the evidence that a wheat-free diet is effective. He begins each subject's diets with basic necessities for survival, to establish an adequate initial baseline. As the patients' hospital stay lengthens he systematically adds specific foods such as mashed potato, apple sauce, and fried eggs and then wheat products to show relapse. After subjects had improved maximally in the hospital he continued out-patient observations, describing for example how J. Tr. "did not stick rigidly to the diet, after which the parents found the symptoms were returning."[11] Dicke describes A. Dr. as originally a "very small, pale, thin girl,"[12] but, after her hospital stay, her mother describes no apathy and an appetite that never existed before. Height graphs supplement his data and demonstrate that height curves rise steadily when wheat products were removed. In T.S. and Jo.T., for example, initially were several years behind the normal growth curve but with a wheat-free diet grew to attain normal height.

To prove that Dicke's diet improved the patients there is no better example than G.H., a patient who is irrelevantly described with a "family bad from a social point of view, totally unreliable."[13] Dicke followed G.H.'s progress over the following 10 years. He had recurrent relapses and hospital admission with remission of symptoms and height growth only to relapse when returned to his family. By inference, the family was not adhering to the grain-free diet and, as a result, G.H. suffered for it. It is important to point out that Dicke used not only gastrointestinal symptoms and weight end point but also increases in length. Haas already had previously stated that "increase in length is of much greater importance that gain in weight and no treatment that fails to produce normal growth in length can be considered satisfactory."[14] The next part of Dicke's research evaluates the effectiveness of treatment based on a patient's fecal fat reabsorption. Healthy children absorb 90–95% of dietary fat while celiac patients may retain 80% or less.

The clinical translational studies on celiac disease performed by Dicke and his collaborators became possible only because of the availability of an important hard end point—the quantitative determination of the amount of fat in the stools, a method developed by Van de Kamer.[15] In 1903 Cheadle had noted that the feces of celiac disease patients often contained abnormally large amounts of fat, but no quantitative test was available at that time.[16] Subsequently, methods for measuring the concentration of fat in the feces became available but Van de Kamer and another pediatrician, H.A. Weyers, who also worked with Dicke on celiac disease, noted that the fat content in individual patient stools varied greatly. Therefore, they developed the concept of the fat balance test representing the proportion of dietary fat that was not excreted.[17]

Variation in the speed of improvement with removal of wheat from the diet and the onset of symptoms after the reintroduction of the toxic components was noticed in several of the children in Dicke's studies and indeed sometimes could vary considerably in an individual patient from time to time. Therefore, the clinical observation on particular dietary components that Dicke performed often were repeated several times in the same subject before he accepted the data generated. Dicke commented that variation in some children was not surprising "since spontaneous improvement and deterioration in the disease were well known clinically so that test periods separated by some time should not automatically give the same results."[5]

Having initially established that removal of dietary whole wheat products regularly improved symptoms and growth retardation, Dicke studied the effect on his patients of other grains and wheat components including rye flour, wheat flour, wheat starch, rice flour, and cornstarch, each for several weeks at a time. Importantly, he distinguished the deleterious effect of rye and wheat flour from the other components. Each of these experimental studies involved clinical and hematological observations as well as daily fecal fat measurements. From these observations the importance of wheat protein as a toxic faction was deduced. Dicke's conclusions and "considerations" were as follows:

1. The active symptoms of celiac disease such as anorexia, vomiting and the characteristic stools disappear followed by recovery in body weight and growth when a wheat-free (rye-free, bean-free) diet is given.
2. If wheat, rye or bread is reintroduced, diarrhea occurs.
3. If wheat flour is provided instead of rice or corn flour or potatoes, diarrhea occurs.
4. With provision of wheat there is an increased quantity of fat in the feces.
5. Wheat flour is harmful but wheat starch is not harmful.

The previously published good results of diets such as the banana diet of Haas are explained by the absence of the harmful effects of dietary wheat. Dicke's final questions were: what is the nature and the specific substance that results in the harmful effects of wheat and why is wheat harmful to a celiac disease sufferer?

Following the observations of the effect of different diets in celiac disease patients published in Dicke's thesis and that of Weyers,[18] this data was published in Acta Paediatrica in January 1953.[19] At that time, the authors reiterated that wheat flour (as well as rye and oats) was deleterious and wheat starch, rice flour, potatoes, and maize flour was not. They proceeded systematically to study fractions of wheat that resulted in clinical deterioration in celiac disease.[5] These studies were performed in a single female child who regularly showed "an abnormally violent reaction to administration of any form of wheat—3–6 hours after administration, severe abdominal pain, vomiting, pallor and sometimes even slight signs of shock." Testing these fractions "in the usual way would take a long time." Gluten and gliadin was harmful[20] but gluten washwater, wheat flour, ash and fat and fiber fractions were not. Subsequently, since glutamine represented 43% of the amino acids in gliadin, they deaminated gliadin by treatment with hydrochloric acid abolishing the ill effects.[20] Several other follow-up studies examined the effects of a peptic-tryptic digest[21] and then hog intestine and showed this to be harmless when fed to celiac disease patients in remission.[22]

This data emphasizes that, from the time of Dicke's original studies in children in Holland in 1947–1948, patient volunteers with celiac disease continued to be used in clinical studies in order to determine the toxicity of components of wheat flour

and chemically altered gliadin products. The characteristic jejunal intestinal pathological changes of villous and submucosal infiltration and villous atrophy as well as changes in mesenteric lymph nodes were first clearly defined by Paulley in four celiac patients who underwent surgical laparotomy.[23] Subsequently, several instruments were developed that allowed biopsy of the upper small intestinal mucosa perorally. The initial method was developed by Royer and colleagues in Argentina in 1955[24] followed by a capsule by Shiner[25] and one year later by Crosby[26] and the peroral hydraulic multi-biopsy tube developed by Rubin and co-workers[27] which allowed for multiple biopsies at differing levels of the small intestine in an individual patient. This technique subsequently permitted *in vitro* studies of the injurious effects of gluten peptides[28] as well mucosal biopsy organ culture.[28] However, throughout this period and until at least 1983, when an accurate blood test was developed,[29] human subject volunteers continued to be the source of material for research studies of celiac disease. Perhaps the final chapter in the understanding of this unique disorder came very recently with the development of a mouse model resembling the disease produced by genetic manipulation of HLA antigens combined with the extraneous administration of gluten with indomethacin to enhance small intestinal permeability.[30]

Acknowledgments

This work was supported in part by the Rockefeller University Summer High School Science Outreach Program and the NIH Road Map for Medical Research, Rockefeller University.

References

1. Gee SJ. On the celiac affection. *St. Bartholomew's Hosp Rep.* 1888; 24: 17–20.

2. Herter CA. *On Infantilism from Chronic Intestinal Infection*. New York: Mac. Millan Comp., 1908.

3. Haas SV. The value of the banana in the treatment of coeliac disease. *Am J Dis Child.* 1924; 24: 421–37.

4. Andersen D. Cystic Fibrosis of the Pancreas and its relation to Celiac Disease. *Am J Dis Child.* 1938; 56: 344.

5. Dicke WK. *Coeliac Disease. Investigation of the Harmful Effects of Certain Types of Cereal on Patients with Coeliac Disease (Thesis)*. The Netherlands: University of Utrecht, 1950.

6. Sauer LW. Celiac Disease (Chronic Intestinal Indigestion) A simple, three-phased, high protein diet. *Am J Dis Child.* 1925; 29: 155.

7. Howland J. Prolonged intolerance to carbohydrates. *Tr Am Pediat.* 1921; S.23(II).

8. Stheeman HA. De intestinale infantilismus en zijn behandeling met ventraemon. *Ned T v Gen.* 1932; 76: 4823.

9. Dicke WK. Eenvoudig dieet bij het syndroom van Gee-Herter. *Ned T v Gen.* 1941; 85: 1715.

10. Fanconi G. Zoliakie. *Dtsch Med Wochenschr.* 1938; 64 1607.

11. Dicke WK. *Coeliac Disease. Investigation of the Harmful Effects of Certain Types of Cereal on Patients with Coeliac Disease (Thesis)*. The Netherlands: University of Utrecht, 1950: 23.

12. Dicke WK. *Coeliac Disease. Investigation of the Harmful Effects of Certain Types of Cereal on Patients with Coeliac Disease (Thesis)*. The Netherlands: University of Utrecht, 1950: 24.

13. Dicke WK. *Coeliac Disease. Investigation of the Harmful Effects of Certain Types of Cereal on Patients with Coeliac Disease (Thesis)*. The Netherlands: University of Utrecht, 1950: 27.

14. Haas SV. Celiac disease, its specific treatment and cure without nutritional relapse. *JAMA.* 1932; 99: 448.

15. Van De Kamer JH. Vet in feaces. *Academisch Proefschrift.* 1948.

16. Cheadle WB. A clinical lecture on acholia. *Lancet.* 1903; i: 1497.

17. Weijers HA, Van De Kamer JH, Dicke WK. Celiac Disease. *Advances in Pediatrics.* 1957; 9: 277–318.

18. Weyers HA. *Fat Absorption in Normal and Diseased Neonates and Children Especially in Patients with Coeliac Disease (Thesis)*. The Netherlands: University of Utrecht, 1950.

19. Dicke WK, Weijers HA, Van De Kamer JH. Coeliac disease. II. The presence in wheat of a factor having a deleterious effect in cases of coeliac disease. *Acta Paediatr.* 1953; 42(1): 34–42.

20. Van De Kamer JH, Weyers HA, Dicke WK. Coeliac disease IV. An investigation into the injurious constituents of wheat in connection with their action on patients with coeliac disease. *Acta Paediatr.* 1953; 42: 223–231.

21. Frazer AC, Fletchter RF, Ross CA, Shaw B, Sammons HG, Schneider R. Gluten-induced enteropathy: the effect of partially digested gluten. *Lancet.* 1959; 2(7097): 252–255.

22. Frazer AC. On the growth defect in coelic disease. *Proc R Soc Med.* 1956; 49(12): 1009–1013.

23. Paulley JW. Observation on the aetiology of idiopathic steatorrhoea; jejunal and lymph-node biopsies. *Br Med J.* 1954; 2(4900): 1318–1321.

24. Royer M, Croxatto O, Biempica L, Balcazar Morrison AJ. [Duodenal biopsy by aspiration under radioscopic control.] *Prensa Med Argent.* 1955; 42(33): 2515–2519.

25. Shiner M. Duodenal biopsy. *Lancet.* 1956; 270(6906): 17–9.

26. Crosby WH, Kugler HW. Intraluminal biopsy of the small intestine; the intestinal biopsy capsule. *Am J Dig Dis.* 1957; 2(5): 236–241.

27. Flick AL, Quinton WE, Rubin CE. A peroral hydraulic biopsy tube for multiple sampling at any level of the gastro-intestinal tract. *Gastroenterology.* 1961; 40: 120–126.

28. Katz AJ, Falchuk ZM. Definitive diagnosis of gluten-sensitive enteropathy. Use of an *in vitro* organ culture model. *Gastroenterology.* 1978; 75(4): 695–700.

29. Chorzelski TP, Sulej J, Tchorzewska H, Jablonska S, Beutner EH, Kumar V. IgA class endomysium antibodies in dermatitis herpetiformis and coeliac disease. *Ann N Y Acad Sci.* 1983; 420: 325–34.

30. Natividad JM, Huang X, Slack E, Jury J, Sanz Y, David C, Denou E, Yang P, Murray J, McCoy KD, Verdú EF. Host responses to intestinal microbial antigens in gluten-sensitive mice. *PLoS One.* 2009; 4(7): e6472.