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The Neolithic Revolution and Subsequent Emergence of the Celiac Affection

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Abstract Evidence suggests that celiac disease initially emerged as a distinct intestinal disorder sometime after organization of hunter-gatherers into human workforces capable of agriculture, especially wheat cultivation. This Neolithic revolution possibly developed to permit competitive survival over other hunter-gatherer groups. Recent archeological data suggests that wheat cultivation may have occurred in eastern Turkey, near the Gobleki Tepe, a recently discovered archeological site in the Fertile Crescent, about 10,000 to 12,000 years ago. DNA fingerprinting data suggests that diploid Einkorn wheat from this region was domesticated through hybridization into other more modern hexaploid grains with a higher more immunogenic gliadin content. Clinical features suggestive of celiac disease and recommendations for treatment are believed to have been first described by Aretaeus from Cappadocia about 250 AD, and later, by other clinicians from Europe and North America. In recent decades, celiac disease has become further defined as a clinical and pathological disorder developing in genetically predisposed individuals as a result of an immune-mediated reaction to specific peptides in wheat and other grains. Data largely from screening studies also suggests that the disorder is not uncommon, occurring in up to 2% of most populations studied. Detection is also increasing, possibly due to better clinical recognition, wider use of screening methods and, possibly, a true increase in celiac disease occurrence.

Keywords: *celiac disease, Areteaus the Cappadocian, Samuel Gee, gluten-free diet, Neolithic revolution, agriculture, wheat cultivation*

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1. Introduction

Celiac disease (also termed gluten-sensitive enteropathy) is a disorder that develops in genetically-predisposed individuals and represents a complex immune-mediated reaction to specific gluten-peptides in wheat and other grain products [1,2]. The precise initiating or precipitating cause of the disease in an individual resulting in clinical and pathological expression is unknown. Serological screening methods have estimated that the disorder affects about 0.5% to 1% of populations, perhaps more, inhabiting some European nations and the United States [3,4]. Historical studies using stored sera from male military recruits [5] and endoscopic screening studies of referred patients employing duodenal biopsies [6] have suggested that increased disease detection has occurred in recent decades, owing to greater clinical awareness, wider use of screening methods, and possibly, other hypothetical environmental factors, including increased use of emerging or novel pharmaceutical agents that cause sprue-like intestinal changes [7,8]. Finally, a real, but unexplained, increase in the disease may have occurred.

Information on celiac disease, prior to the past century or so is very limited. However, some evidence suggests that agricultural methods, particularly wheat cultivation, first evolved sometime after the dawn of civilization, estimated about 10,000 to 12,000 years ago near Urfa, Turkey in a region, called the Gobleki Tepe. Hunter-gatherers there became organized as a human workforce to secure a stable food supply.

Some believe that this "Neolithic revolution" resulted in an expansion of food sources and ultimately provided a critical survival advantage.

2. Wheat Domestication

In this region, wild Einkorn wheat species are also present on the slopes of the shield volcano, Karacadag, and subsequent DNA fingerprinting studies confirmed this to be the initial site of wheat domestication [9]. This ancient Einkorn grain is diploid (two sets of chromosomes), and predates emergence of a subsequent hybrid of Einkorn, so-called Emmer, with four sets of chromosomes, adapted and apparently more suitable for growing in other geographical areas and climates. Spelt is an even further hybrid of Emmer, possibly representing the oldest hexaploid species of grain. All three ancient grains are structurally "covered or coated", and, as a result, more labor intensive to process and mill.

Later, further hybridization and development of other easier-to-mill modern hexaploid varieties led to

emergence of newer grain species with higher gluten-peptide contents, yet still genetically-related to the native Einkorn wild species [9]. Interestingly, some more recent *in vitro* studies from Italy using an organ culture system showed a lack of intestinal mucosal toxicity with wheat gliadins from *Triticum monococcum* (an Einkorn variety) on celiac biopsies compared to exposure from bread gliadins [10]. Although ancient Einkorn grains apparently have reduced gliadin content, this study also indicated that modern grain varieties were more immunogenic.

3. Archeological Studies in the Gobleki Tepe

In recent decades, the historical record for this region has become even more intriguing in relation to human development and possible emergence of some human diseases. Some recent archeological studies have focused on this geographical area, as reflected in popular print media [11]. Urfa, birthplace of the prophet, Abraham, is located in southeastern Anatolia, only a short distance from the Syrian border. In the nearby countryside of the Gobekli Tepe, early Neolithic structures were first discovered. Initially, these "knolls of red earth" were reportedly surveyed in 1963 by Benedict, an archeologist from the University of Chicago. He also noted "small cemeteries" of apparently carved limestone, possibly, he thought, dating back to the Byzantine Empire [11]. Later, however, Schmidt, an archeologist from Heidelberg University became involved. He had earlier explored an archeologically important nearby site, Nevali Cori, with Hauptmann, also from Heidelberg University. This latter ancient settlement dated back to the ninth millennium BC and was first discovered in 1979, then lost in 1992 with the creation of a reservoir-lake resulting from construction of the Ataturk Dam on the Euphrates River. The dam (originally the Karababa Dam), developed as a hydroelectric power source, was re-named in honor of Mustafa Ataturk, founder of the Turkish Republic. In 1994, Schmidt is thought to have initially recognized the hills in the Gobekli Tepe as man-made and discovered flint Neolithic chards, similar to findings at Nevali Cori [11].

Subsequent archeological investigations revealed that this archeological wonderland, the Gobleki Tepe site, was over 10,000 years old and consisted of more than 60 multi-ton limestone pillars spread over 22 acres. Ironically, the Turkish words for Gobleki Tepe reportedly mean "fat hill" or the "hill with a potbelly" [11], would certainly not be terms used to detail the textbook clinical features of a patient with long-standing celiac disease causing malabsorption, nutrient deficiencies and weight loss!

Over subsequent centuries, it appears that wheat cultivation methods spread, first in local geographic areas of eastern Turkey, and later to more distant areas with different climates and growing seasons.

4. Aretaeus the Cappadocian

Although highly important from an archeological perspective, this region of Turkey was also geographically close to the site now attributed to an early clinical description of possible celiac disease. During the 2nd century AD, Aretaeus the Cappadocian, a Greek physician that lived there, provided an account of "*The Coeliac Affection*" as detailed in an 1856 translation of "*The Extant Works of Aretaeus, the Cappadocian*" by Francis Adams and provided as a lecture to the Sydenham Society [12]. Together, eight books were written in the Ionic dialect. In one, the coeliac state is described as a chronic disorder in adults with diarrhea and wasting caused by a "lack of internal heat". Symptomatic treatment with rest, fasting and prevention of chilling were recommended. Aretaeus first used the word "coeliac", apparently derived from the Greek word, "koiliakos", meaning "abdominal". Some believe this may have been the first recorded clinical description of a patient with malabsorption and diarrhea. Possibly, this represented the first case record of celiac disease, possibly not.

Cappadocia, also located in eastern Turkey, is known for its unique geological landscape characterized by unusual "fairy tale" like rocky pillars, now a popular tourist attraction. Interestingly, there is a striking regional occurrence of mesothelioma in some Cappadocian villages of eastern Turkey [13], perhaps 600 to 800 times more common than elsewhere in the world, and, in some at least, the late stages of peritoneal mesothelioma might have borne some clinical resemblance to advanced and long-standing celiac disease. Some studies have attributed this mesothelioma to tremolite, a prominent form of asbestos fiber in Cappadocia as well as a non-asbestos mineral identified as the fibrous zeolite, or erionite. These are present in stone commonly used for home construction in some villages. Recent reports describe mesothelioma as "epidemic" causing more than 50% of the total deaths in some of these "zeolite villages" [14,15]. To date, no infectious, particularly viral agent, has been discovered, however, a genetic pre-disposition to erionite carcinogenesis in Cappadocia has been hypothesized [16,17].

In spite of these elegant archeological, geological and historical studies focused on this geographical area of Turkey, the origins of celiac disease still require definition. For instance, another case of apparent celiac disease in antiquity has been suspected even earlier in a young woman from the first century AD. She was recently described by a group of Italian investigators to have anemia and reduced bone mass and noted artifacts in her burial tomb from an area known to be exposed to wheat cultivation methods [18].

5. The Post-Aretaeus Period

Several authors [19,20,21], but not all [22] popularly described Samuel Gee as providing one of the earliest descriptions of celiac disease in 1888 [23]. Gee (1839-1911) was a pediatric physician at the Children's Hospital on Great Ormond Street in London. In his report, also labeled *"The Coeliac Affection"* [23], Gee provided a detailed account of the clinical features of celiac disease, suggested that the disorder could occur at any age, including children, and noted that attention to the diet may ultimately lead to a cure. He also described a child who developed an improved clinical state with a diet of Dutch mussels, followed by relapse after the mussel season ended. Before Gee's description, other physicians had already detailed some clinical features of malabsorption

including Ketelaer, Bricknell and Baillie. It is not precisely clear from these reports, however, if celiac disease or other now recognized causes of malabsorption, besides celiac disease, were being described [22,24].

After translation of the writings of Areteaus by Adams, almost another century would pass before a more complete picture of the pathological features of celiac disease in the small intestine would emerge. In 1954, Paulley described his pathological findings based on studies of surgical specimens from patients with steatorrhea [25]. Also, a focus on rest and dietary treatment emerged. Positive results published by Haas in 1924 on a banana diet led to a popular treatment over decades [26]. Subsequently, Dicke and his colleagues documented evidence for gluten-free diet treatment. Studies included long-term growth measurements of affected Dutch children during periods of starvation and re-feeding as well as measured endpoints of intestinal absorption, specifically calculated coefficients of fecal fat absorption [27].

Later technological developments made the small intestine more accessible for direct imaging and histopathological evaluation while modern serological methods have offered new opportunities for screening. New data on virtually every aspect of celiac disease, including novel forms of possible treatment have emerged [28]. And even now, transition from hunter-gatherer to wheat cultivation in many distinct societies continues on a global scale. For example, immune-mediated disorders, including celiac disease, have only been recently reported in Coast Salish native populations on the west coast of Canada [29].

The Coast Salish attained a high level of cultural complexity in a rich maritime temperate zone climate. They lived in permanent villages of more than 1000 residents with social stratification, including slaves and ranked nobility, developed multiple linguistic dialects and one of the world's great art styles [30]. The Coast Salish of British Columbia subsisted largely on fish, fruits and berries without knowledge of soil cultivation methods and largely isolated from European influence. Possible sources of potato and wheat cultivation methods introduced into this area were hypothesized to include Russian settlements in Alaska, Spanish settlements in the Nootka Sound of British Columbia or later British settlements in the Fraser River Valley, associated with the Hudson's Bay Company [31,32]. Regardless of the precise source of wheat cultivation methodology, this change from a food gathering to a food producing society developed rapidly. While inherited factors are clearly important in the clinical expression of celiac disease, recent environmental changes, including the introduction of wheat cultivation methods, may have been important in the pathogenesis of celiac disease in this specific population.

Still, much remains to be examined about this intriguing disorder and the development of a special forum, like this new international journal, for clinicians and fundamental investigators focused on this disorder can be viewed as part of this global process.

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