From the Neolithic Revolution to Gluten Intolerance: Benefits and Problems Associated with the Cultivation of Wheat

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WHY ARE THERE SO MANY CASES OF GLUTEN INTOLERANCE?

It is difficult to believe that intolerance to one of the most common components of food (bread, pasta) in our environment might provoke such severe immunomediated reactions in any part of the human body. The list is endless, but to attribute malignancies, adverse pregnancy outcome, and impaired brain function to gluten intolerance would seem to be excessive. On the other hand, we have reported on a group of patients affected by drug-resistant epilepsy with cerebral calcifications, half of whom were cured by a gluten-free diet. All of them had atrophic jejunal mucosa, which recovered on a gluten-free diet [1].

In addition, we know that the majority of gluten-intolerant subjects, identified by family or population screening, do not have any complaints, although they do have flat intestinal mucosa [2]. It seems that a sizable proportion of our population (from 0.3 to 1%) is gluten intolerant and reacts with a wide spectrum of symptoms, from no apparent reaction to severe life-threatening diseases. This intolerance is strongly linked to specific genetic markers that have been selected over thousands of years, while environmental changes, for example, dietary changes, require only centuries to occur. Where do all these cases of gluten-intolerance come from?

HUNTERS, FISHERS, AND GATHERERS

Human beings have been on earth for over three million years, but *Homo sapiens* for only about a hundred thousand years. For about ninety thousand years he conducted a nomadic life, obtaining food by hunting, fishing, and collecting fruits, seeds, herbs, and vegetables. Ten thousand years ago the last glaciation came to an end: a neothermal period ensued, which marked the passage from the paleolithic to the neolithic age. The ice gradually melted from the equator to the poles over several thousands of years. While new fertile and humid lands were uncovered in Southeast Asia, all of Europe was still blanketed with ice; the northern countries had to wait up to another four thousand years to get out of a frozen environment. During this period some nomadic tribes started settling down as they developed the ability to gather enough food to store.

THE GREAT REVOLUTION

The First Farmers

The discovery of methods of producing and storing food has been the greatest revolution mankind has ever experienced. In the passage from collection to production of food originated the first system by which human labor gained income over long periods of time. The principle of property was consolidated, and fortifications to protect the land and food stores were developed. Archaeological findings suggest that this revolution was not initiated by the male hunter and warrior, but by the intelligent observations made by women. Women collected seeds, herbs, roots, and tubers. During this activity they probably observed the fall of grain seeds to the ground and their penetration into the soil with rain [(3)].

To our knowledge, the origin of farming practices must be located in the “Fertile Crescent”: the wide belt of Southeast Asia that includes southern Turkey, Palestine, Lebanon, and northern Iraq. In the highlands of this area, abundant rainfall was caused by the neothermal switch. In this area existed, and still exists, a wide variety of wild cereals. The majority of wild cereals had very few seeds [(2-4)], which easily fell on the ground at maturation. *Triticum dicoccoides* (wheat) and *Hordeum spontaneum* (barley) were commonly collected by the local dwellers.

The people from the Uadi el-Natuf Tell in Southeast Asia (7800 B.C.) provide the first evidence of a gradual shift from hunting to grain cultivation. Their economy was based on hunting of the gazelle, but their diet also consisted of collected grain seeds. The latter gradually came to form a substantial proportion of their energy intake, as cultivation practices grew. There were no grinding stones or mills, and it is most probable that gathering prevailed on cultivation. But during the Proto-neolithic superior, a cuneiform mortar appeared. One to two thousand years later (5000 B.C.), wild animals formed only 5% of the daily diet, while cereals and farmed animals became a sizable part of it [(3)].

Stable settlements were founded. The village of Catal-Huyuk in southern Turkey had a population of five thousand inhabitants 9000 years B.C. In that area a collection of sickles with oxidian blades, smoothed by routine contact with the siliceous stalks of cereals, has been found. The sickles indicate that it was possible to collect seeds not only by picking them off the ground but also by cutting the stems of plants, which retained the seed in an ear [(4)]. Populations in Mesopotamia developed a great civilization with large cities and powerful armies to defend their lands and food stores. In Egypt a civilization based on farming practices developed in the fifth millennium: they became specialists in the cultivation of wheat, barley (also used to produce beer), and flax.

EXPANSION OF THE FARMERS

While in Southeast Asia progressive drought made hunting difficult and encouraged farming, in Europe the Paleolithic culture of hunters and gatherers persisted for five thousand more years. In the Fertile Crescent, the availability of food stores and the gradual development of animal farming stimulated an unprecedented demographic explosion. In transmigrations, the mother could carry one infant, while the other family members were obliged to walk. Small children had less chance of surviving. Farmers most probably took advantage of all the hands in the family. In this way the size of families exploded and, as a result, the need to gain more lands was born. The expansions followed the waterways of the Mediterranean and the Danube throughout the times of the Egyptians, Phoenicians, Greeks, and Romans. The farmers' expansion lasted from 9000 B.C. up to 4000 B.C., when it reached Ireland, Denmark, and Sweden, covering most cultivable lands in Europe (5).

This expansion was not limited to the diffusion of agricultural practices, but was a migration of peoples characterized by a substantial replacement of the local mesolithic populations of Europe with the neolithic populations of Southeast Asia. More than two thirds of the actual European genetic makeup originates in this new population, while the native genetic background has progressively been lost or confined to isolated geographic areas. The genetic replacement of the native European population is marked by the B8 specificity of the HLA system. Cavalli Sforza and co-workers showed that the migration of farmers is paralleled by the expansion of HLA-B8. The prevalence of HLA-B8 is inversely proportional to the length of time of wheat cultivation. In practice, HLA-B8 appears to be less common in populations that have lived on wheat for a longer time, which seems to be caused by a negative genetic selection in wheat cultivators (6). The incidence of HLA-B8 seems to increase through Europe in a northwesterly direction: the highest incidence of HLA-B8 is found in the indigenous population of the west of Ireland, where wheat cultivation began only 3000 years B.C. and where a very high incidence of gluten intolerance has been reported.

EVOLUTION OF CEREALS

The early wild cereals of the *Triticum* (wheat) and *Hordeum* (barley) species were genetically diploid and carried few seeds, which usually fell on the ground at maturation, making any harvest difficult. A single couple of chromosomes (diploidicity) allowed for a wide genetic and phenotypic heterogeneity with remarkable variations in the content of protein and starches. Poliploid plants occasionally originated in nature but had few chances of surviving without artificial (cultivation) practices and thus were usually lost (7). The beginning of farming, with the use of irrigation, allowed for the survival and expansion of poliploid grains, which reduced genetic variations, causing an increase in genetic uniformity.

The first stable formation of poliploid grains dates from about 6000 years B.C. Genetic variability was essential in order to adapt the grains to different environmental conditions (8). *Triticum turgide dicoccoides* was crossed with *Triticum fanschii* to create *Triticum aestivum,* which is the progenitor of all our actual wheat. *T. aestivum* is an esaploid wheat with 42 chromosomes, versus the 14 chromosomes of *T. monococcum*. Such powerful grain replaced all existing wheat varieties: over the world there are 20 thousand species of the same unique *T. aestivum*.

For centuries grains had been selected in order to improve their homogeneity and productivity, but soon (in Greek times or perhaps earlier) another quality became desirable. It was necessary for dough to adhere better to improve bread making. Early bread making activities pushed toward cultivation of grains that contained greater amounts of a structural protein that greatly facilitated the bread making: gluten. Over the past two hundred years of our modern age, active genetic selection and genetic manipulation have changed the aspect of the original *Triticum* enormously, from few grains and a variable content of gluten to abundant grain very enriched in gluten (50% of the protein content), well adapted to cultivation practices, and ready to be handled by machinery. Gluten was not chosen because of its nutritional value (which was unknown at the time and which is far from special, since it is a protein with relatively low nutritional value), but for its commercial qualities. Only a small geographic area (Southeast Asia) developed gluten-containing cereals. In all of Asia rice was cultivated, while in America maize prevailed, as in Africa sorghum and millet had. Rice, maize, sorghum, and millet do not contain gluten. No leavened bread was prepared with them; the majority of mankind never lived on bread.

THE RISE OF GLUTEN INTOLERANCE

Did everybody adapt to such profound changes in basic nutrition over such a short period of time? Southeastern populations presumably adapted well to the new foods and replaced the mesolithic European dwellers who still lived from hunting and gathering. But a proportion of the local European populations persisted beside the invaders, and some hunters and gatherers did not adapt to the food changes induced by the cultivation of wheat. These people could not recognize gluten as a “tolerable” protein. They may not have had any complaints for centuries, since the content of gluten in the grains they ate was low, but when “industrial” quantities of gluten were introduced to improve bread making, their descendants were exposed to unbearable quantities of an intolerable protein. This population, genetically identifiable by its specific HLA pattern, generated a complex defense mechanism (an immunoresponse) against the gluten, which ultimately is the origin of the damage to their intestines and other organs. These fierce descendants of hunters and fishers, exposed to this subtle enemy, could not develop tolerance and, in the attempt to fight the unknown, ultimately acquired a disease from their excessive defense mechanisms.

Acute infectious diarrhea was the main killer of infants in Europe up to fifty years ago, and some 15 babies in every thousand died of this condition. In the suburbs of Naples only twenty-five years ago, 25% of the infant mortality rate of 100/1,000 live births was caused by diarrhea. The vast majority of cases of gluten intolerance occurred among these poor infants. In my own clinical experience twenty-five years ago, I observed several fatal gastrointestinal infections in babies with “celiac crisis,” which has now disappeared from our wards. Despite their lower chances of survival, people with an intolerance for gluten did not disappear.

These patients most probably had some selective advantages that counterbalanced the disadvantages of gluten intolerance. Breast-feeding most probably played a major role in preserving some children from the fatal infections of infancy [(9)]. The capacities of breast milk to protect against viral and bacterial attacks, the protection given by maternal antibodies, and the delaying effect on the manifestation of symptoms of gluten intolerance (in the predisposed subjects) may all have benefited the hunters and gatherers, who in this way survived and transmitted their genes.

HINTS ON THE EPIDEMIOLOGY OF GLUTEN INTOLERANCE

The epidemiology of gluten intolerance, as we know it today, is the complex result of the inheritance of hunters and gatherers. Nutritional attitudes have played a role in the manifestation of gluten intolerance in different parts of Europe: the example of Sweden compared with Denmark or Finland is paradigmatic. Nevertheless, when local incidence rates are compared with other regions' rates, the 95% confidence intervals are so wide that no clear-cut differences can really be shown in the incidence of gluten intolerance in Europe [(10)]. Wherever studies on symptomatic cases have been conducted, an incidence of one case per every 1,000 live births has been reached. Population screening studies invariably come to an incidence rate of one per every 250. This is close to the rate predicted by age-adjusted incidence density studies.

We have found our ancestral hunters and gatherers. Their descendants form a substantial proportion of our actual community and deserve a gluten-free alternative, not just as a therapeutic measure but also as an option in normal daily nutrition.

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DISCUSSION

Peña: Thank you very much for this fascinating presentation. Let's try to find some holes in this theory. Donald Kasarda, would you like to talk about gluten?

Kasarda: I agree with Dr. Greco in general, but I disagree on some details. There is no question that about ten thousand years ago man began to eat more wheat. I think, however, that hunters and gatherers had been eating wheat for a considerable time before domestication, although in lesser amounts. The crop scientist Jack Harlan once demonstrated that he could cut down (with a primitive stone knife) and recover the grain from wild stands of wheat still found in the Middle East today at a rate that would enable a person or small family to accumulate in one day sufficient grain to provide them with food for at least a week. No one knowns exactly when the tetraploids originated, but it appears that hunter-gatherers had been gathering wild grains, both diploids and tetraploids, for some considerable time before grain crops were domesticated.

I disagree that man has changed the gluten proteins in any significant way beyond the amounts that can be found in a single grain. The genes for wheat gluten proteins evolved thirty million years ago or earlier, which is still relatively recent in evolutionary time, but not as recent as the evolution of man. Wild wheats tend to have a higher protein content than modern wheats, but, of course, the grains are very small; a single grain of modern wheat might actually contain more gluten protein, even though the percentage in the grain is smaller.

Peña: Thank you very much for this addition. Now let's try to get a view of the genetics. I am a little uncomfortable talking about “changing” genes, because what really happens in evolution is that certain alleles with certain advantages are selected. The association between HLA-B8 and some diseases is fascinating because these people probably have genetic advantages, too.

Greco: Otherwise CD would have disappeared, like other diseases already have.

Meeuwisse: Before we stop discussing the matter of the incidence of CD, I would like to add something. It seems that the incidence of CD is one in 200 persons, or five in 1,000. But based on some features we are finding in Sweden, it is possible that the incidence is even higher. Where the incidence of a disease is as high as the one of CD in Sweden nowadays, we can observe features that are not evident when the incidence is lower. For example, we see, as Henry Ascher told us, that those children who have been breast-fed for a long time, do not manifest CD early. That means that we may expect more CD later among breast-fed children. We see, too, that there is a seasonal effect of the month of birth on the development of CD. If you are interested, I can show you a slide or two. It clearly shows that if a child is born in the summer, his or her chance of having CD is higher. I speak of a chance because I think it is an advantage to be diagnosed early.

Peña: Michael Marsh, could you tell us something about this while Dr. Meeuwisse is arranging his slides?

Marsh: We should also talk about tolerance, not only about intolerance. The genetic constellation of the DQ heterodimer is present in ≈10% of the population, isn't it?

Meeuwisse: Indeed, the susceptibility genes are present in ≈10% of the population, so we should actually expect that about one in 10 persons is susceptible to CD. We have had had periods of time in our area when the incidence was one in 100. Sometimes it seems that CD clusters in time and place and that it behaves like an epidemic disease. If you look at the whole country, you don't see it that way. But if you go area by area, then you can observe it. This slide shows you the incidence of CD by date of birth in different areas. You see that from April to September, there are many more cases than in the other half of the year. The next slide shows a varying incidence according to the year of birth; for example, in 1989 there were 130 cases. The incidence of CD is not constant; it changes over time from area to area.

Greco: But this could be a cohort effect as well. When you identify a cohort and follow it up, you find those changes. We actually failed to find any seasonal effect in 1,000 cases. We have observed such a phenomenon but failed to find statistical proof.

Meeuwisse: We found statistical differences, and there is one thing that is different between our countries. In Sweden we give the children high quantities of gluten when they are 6 months old. That means that those who are born in the summer will get a gluten load in the winter, when some of them may have damage to their intestinal mucosa because of viral gastroenteritis.

Ascher: I just want to comment a little bit on this. We have to be careful when we are analyzing small numbers of cases and considering variations in incidence according to the month of birth. In general, more children are born in the summer. But in a multicenter study in Sweden with a great number of cases, a statistically significant seasonal variation was found; children born in April and May had increased risk of CD.

Peña: Dr. Greco has just given us an excellent overview of this problem and has introduced CD into a wider field. At present he has convinced us that there is a large group in Europe at great risk of CD. The responsibility of physicians is to find a screening test to identify these people so that we can help them avoid the complications. This is one goal we have to achieve. Even more important for the future is this large proportion of people found by Heymans and Mulder to have abnormal intestinal permeability, as evidenced by the mannitol/lactulose test, without any histological abnormalities in the gut. Maybe this is the large population in Europe you were talking about that may or may not develop CD, depending on environmental or other variables. Take, for example, the identical twins story: they shared genes but were discordant for CD. We thought that environmental factors were important. That is not necessarily the case, because they may have differences in T-cell function.

Greco: We are now following a cohort of 373 young women with CD, who are in the fertile years and have had children. This cohort will produce and transmit. We will see more cases of CD.

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