The Second World War and Epigenetic
Part2: The Ukraine and Dutch Famine

Historical catastrophes that underline the importance of understanding epigenetic effects

The relatively late abolishing of the food ratio in Britain, which focused on a tremendous sudden increase in the consumption of sugar, sweets, and candies, allowed to study the advantage of limited sugar intake after conception and 1000 days after birth in later life, reducing the risk for T2DM and hypertension. The investigation might be the only study of a positive effect on human metabolism based on what happened during and around WWII (1).

Most population studies about starvation during pregnancy and on infants during the two World Wars and in between had adverse outcomes on T2DM and insulin resistance for middle-aged adults and during aging. One of these studies focused on population groups in Ukraine. In between the two World Wars, parts of Ukraine ended up integrated into the Soviet Union (2).

Background of the Ukraine famine

Stalin, the ruler of the Union of the Soviet Socialist Republic (USSR) at that time, forced the collectivization of agriculture in 1930 (2473). This caused food shortages and famine in several parts of the Soviet Union. The most affected area, however, was the Ukrainian. Although there was a bad harvest for 1931 and 1932, farmers were ordered not only to return the grain they produced up to target but also potatoes and poultry. In 1932, the grain shortage increased dramatically, which also happened in the forthcoming 12 months and resulted in 3.9 million excess deaths and an estimated 0.6 million lost births (3).

T2DM in adults with mothers suffering from the famine during gestation

A retrospective study examined 43.150 T2DM patients, 40 years and older, selected from a diabetes mellitus register, borne between 1930 and 1938. More than 1.4 million individuals born simultaneously in Ukrainian regions served as a reference, either with extreme or severe famine or not being affected. The odds ratio (OR) for those with T2DM borne during the extreme food shortage was 1.47 (95% CI 1.37–1.58), and for areas affected by severe famine was 1.26 (1.14–1.39). No increased risk with an OR 1.00 (0.91–1.09) was recognized in famine-free areas (4). Similar outcomes of famine and hunger during fetal exposure in terms of hyperglycemia and T2DM in adulthood were found for a famine from 1959 to 1961 in China and during various occasions experienced by the Austrian population at the end of WWI, shortly at the beginning and the end of WWII (5, 6).

Background of the Dutch Hunger Winter

That severe food shortage for mothers during pregnancy and their newborns, toddlers, and infants might not only develop a high risk as adults for having T2DM, insulin resistance, and obesity but could suffer from a range of diseases even through forthcoming generations. This could be proven by investigations into the well-known Dutch Famine, or Hunger Winter, as

remembered in the Netherlands. At almost the end of WWII, the underlying historical background has been used for two movies with doubtful historical accuracy. The ‘Battle of the Bulge’ (1965) and ‘One Bridge Too Far’ (1977). Both movies are available on YouTube. They illustrate the background of what happened from November 1944 to May 1945, the war's end in Europe.

After the Germans were driven out of France, the Allied forces swiftly moved to the borders of Germany, Eisenhower with the Americans in the West and Montgomery with the British in the North. When the more agricultural part of the Netherlands was liberated, the exiled Dutch government in England ordered a railway strike to impair the movement of weapons and soldiers from the Germans to the front, expecting an immediate end to the German occupation. The German occupying forces retaliated by interrupting the food supply to the cities still in the North of the Netherlands. Unexpectedly, from the Allied forces, the German army launched on the 16 December 1944 a counterattack with modern tanks known in history as the Ardennes Offensive. The tanks approached out of the wintery dense forest, driving the Americans back. Montgomery, the general commander of the English forces, trying to have an advantage above Eisenhauer, he disliked, trying to be in Berlin before him, more or less failed at the Arnhem bridge in a daring crossing over the river Rhine, unaware of the immediate starting German offensive.

Decreasing food ratios

The German attack lasted until the 25 of January 1945, finally breaking down because of a shortage of supply in weapons and fuel and the intensifying fighting of the American forces. In between the events, an agreement was reached with the German occupying administration to enable food supply again. The catastrophe worsened since the railway was destroyed and the very harsh cold season froze the channels from the West to the East of the Netherlands. The most affected cities were Amsterdam, Rotterdam, and The Hague, with an estimated population of 1.8 million. The food ratio after November dropped to 750 calories per capita and, at the end of the ordeal, decreased to 370 calories (7).

Mortality during the Dutch Famine

An excess of 23.000 deaths in the urban areas of the famine-effected areas are estimated from September 1944 to July 1945, and another 12.500 in the rural regions. Another 26.500 excess deaths in the country are estimated, not due to hunger but most likely up for fighting during the liberation of the Netherlands (8). The main culprits of the famine were the children under 14 years old, particularly in the three main cities affected.

Infant mortality increased from 109 deaths per 10.000 before the famine to 922 deaths per 10.000 during the Hunger Winter for the ages one to four. The mortality of those between five and fourteen accounted for 27 deaths per 10.000. Over 60% of the deaths took place during the first year (9, 10). From a cohort study of 2.414 adults born at the time of the Dutch Famine observed at a hospital between the ages of 50 and 58, glucose intolerance, atherogenic lipid, and an increased risk of suffering from coronary heart disease were discovered (11). Despite the metabolic consequences, such as increased risk for T2DM, mental and cognitive alterations were observed, along with rapid aging (12).

DNA mutations outside the Mendelian inheritance

It is now established that events like the Dutch Famine and similar disasters connected to the unruly past decade, especially related to both World Wars, follow a general rule that 'transgenerational effects from the environment to future observation' are not necessarily due to DNA mutations as known as Mendelian inheritance but to epigenetic modification. Non-communicable diseases (NCDs) are, to a great extent, linked to the environment (13, 14). At least for the academic sector of public health, basic knowledge in genetics, including epigenetics, is an urgent necessity (15, 16).

Understanding epigenetics through the Agouti mouse model

The Agouti mouse model can help to provide a better understanding of what epigenetics is all about. The Agouti mouse has a yellow coat because of its Agouti gene alleles. It is also fat and tends to develop cancer and diabetes. Feeding a pregnant Agouty female mouse a diet supplemented with methyl donors, i.e., choline, folic acid, betaine, and vitamin B12, the phenotype of the offspring is of the standard size of a laboratory mouse and has a brown-colored coat. The nutritional environment changed the phenotype through epigenetic means (17).

Epigenetic mechanisms

One of the major control mechanisms related to epigenetics is DNA methylation. A methyl group at the 5^{th} carbon of the cytosine base is added to a CpG dinucleotide pair. Other main epigenetic processes are linked to non-coding RNA (ncRNA) and histone modification. Originally, epigenetics was defined as the interaction between genetics and the environment. A more accurate definition refers to gene functionality not encoded into the DNA sequence but can be hereditary (18). A shorter definition refers to a 'mitotically heritable alteration in gene expression potential' (19). What happened between the World Wars and particularly WWII includes many unthinkable terrible occurrences and can hardly just be described as 'environment.' Yet, quite some of these events enlightened the importance of the maternal 'environment' on the 'development and health and diseases of the fetus hypothesis,' discussed as DOHaD (20). (The historical origins of the hypothesis should be well known in the academic circles of public health but cannot be discussed here. Astonishingly, the economic sector gives a comprehensive, easy-reading review (21)).

Extrinsic and intrinsic factors of the DOHaD

According to DOHaD, the maternal environment is influenced by extrinsic factors, such as toxins, pollution, and chemicals, and intrinsic factors, such as eating behavior, metabolism, lifestyle, and stress. The effect on the child's phenotype and pathological developments in later life, such as the metabolic syndrome, including T2DM, as mentioned above, has been extensively conveyed, but what happens on the molecular basis on the genome is not very well known yet (13).

Key regulator of methylation linked to T2DM

For instance, genes involved in the epigenetic causes of T2DM were recently identified in pancreatic islets associated with HbA1c. T2DM methylation was evident in regions bound to beta-cell transcription with reduced expression. The methylation key regulator RHOT1 (a protein-coding gene) was linked to mitochondrial dysfunction and might be a blood-based biomarker for T2TM diseases (22, 23).

Epigenetic changes explored in humans and animals

In addition, based on individuals whose mothers suffered from undernutrition in the Dutch famine and along an example from Gambia, following seasonal diets, DNA epigenetic modification in humans has been explored. Methylated DNA was related to low birth weight, CVD, low lipoprotein levels, and the risk for metabolic diseases. The Gambian example shows DNA methylation during food shortage at conception but, so far, no direct association to specific epigenetic changes. Various outcomes were observed in laboratory animals, pigs, and two primates, similar to the findings in humans, so to low- and high-fat diets. Besides non-alcohol steatohepatitis phenotype, fatty acid liver, depression behavior, brain disorder, breast cancer, and neural tube defects were linked to the animal experiments (see Table 1 (13)).

Conclusion

Historical reflection helps to understand the background of worldwide political developments and often enlightens important findings in science, medicine, and public health. The value of the thrifty gene hypothesis, with surprising effects not only on those suffering from political crimes and wartime but also on the genetic setting of their offspring, even through generations, could be impacted. In the future, more genetic alteration through these events will be laid open by advances in genetic sequences. The basic what is known as ‘epigenetic modification during development’ is nicely summarized by Peral-Sanchez et al. (2022) (see Fig. 1 (13)). Notably, in the future, biomarkers will identify epigenetic risks not only for treatment in medicine but for prevention in public health.

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