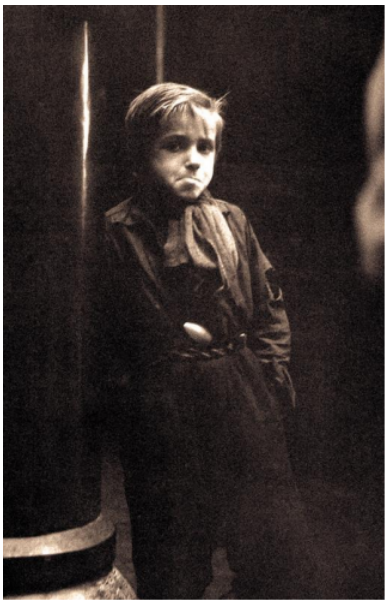
17.1: Prelude to the Organic Chemistry of Vitamins

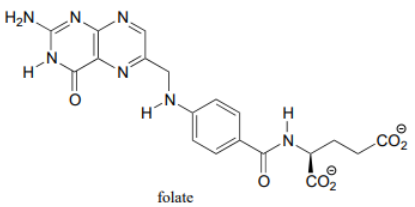
The old black and white photograph is haunting. A young boy, perhaps 10 or 11 years old, huddles against a wall outside a soup kitchen, his mouth in an odd twisted shape that could be expressing either pain or defiance, his eyes staring straight into those of the viewer. Tucked into his pants, almost like a pistol in a holster, is a metal spoon.



The photograph was taken in the Netherlands in 1945, at the height of what the Dutch people still refer to simply as "The Hunger Winter". With the western part of the country still occupied by the Nazis, the Dutch resistance government, based in London, had called for a railway strike with the aim of stopping German troop movements before a planned airborne invasion by Allied forces. In retaliation, the Germans cut off all food shipments to cities in the western Netherlands. The Allied invasion failed to liberate the country, and the winter of 1944-1945 turned out to be bitterly cold. With food supplies dwindling, rations were cut first to 1000 calories per day, then to 500. People resorted to eating grass and tulip bulbs just to stay alive. Over 20,000 people died of starvation before food shipments were restored in the spring.

As tragic as the Hunger Winter was for the Dutch people, some good did come from it. For medical scientists, the event became a unique 'social experiment': unlike most episodes of famine throughout human history, the Hunger Winter had a clearly defined beginning, end, and geographic boundary, and it occurred in a technologically advanced society that continued to keep thorough records before, during, and after the ordeal. Scientists knew exactly who suffered from famine and for precisely how long, and in the years that followed they were able to look at the long-term effects of famine, particularly on developing embryos. Researchers found that babies who had been conceived during the famine were born with a significantly higher incidence of neurological birth defects such as spina bifida, a condition in which a portion of the neural tube protrudes from between vertebrae which did not properly fuse together during fetal development. Later in life, members of this same cohort of 'famine babies' were more likely to be obese, and to suffer from schizophrenia.

These initial findings spurred interest in further research into the consequences of prenatal deprivation. In particular, carefully controlled studies later led to the recognition of the importance of the vitamin folate in ensuring proper neurological development in early-term fetuses.



folate

Folate - the conjugate base of folic acid - is an organic coenzyme: a helper molecule that binds in the active site of certain enzymes and plays a critical role in the biochemical reaction being catalyzed. Recall that we have seen coenzymes at work before: SAM, ATP, $NAD(P)^+$ and $NAD(P)H$, flavin and glutathione are all important coenzymes with which we are already familiar.

Because prenatal folate deficiency was found to be directly related to the incidence of spina bifida and other neural tube defects, health officials in the United States and many other countries changed their official guidelines to include a specific recommendation that women begin taking folate supplements as soon as they knew that they are pregnant, or better yet as soon as they begin trying to become pregnant. A number of studies conducted during the 1980s and early 1990s consistently showed that folate supplementation correlated with a 50-70% reduction in neural tube defects.

The molecular role of folate in prenatal neurological development is not understood in detail, but most researchers agree that it probably has a lot to do with DNA biosynthesis. Like S-adenosyl methionine (SAM), folate functions in 1-carbon transfer reactions, including several critical steps in the nucleic acid biosynthesis pathways. The rapidly dividing cells of the developing brain of an early term fetus appear to be especially sensitive to folate deficiency in the mother's diet: insufficient folate leads to impaired DNA biosynthesis, which in turn leads to defects in brain development.

Folate also serves as a 1-carbon donor in the pathway by which SAM is regenerated after it donates a methyl group. You may recall from the introduction to chapter 8 that methylation of cytosine bases in DNA by SAM results in permanent changes to a individual's genome - this was the reason why the two 'identical' twin sisters in that introductory story turned out to be, as they grew older, not so identical after all. It is likely that the folate deprivation that afflicted expectant mothers during the Dutch Hunger Winter also caused epigenetic changes (in other words, changes in the extent of DNA methylation) in their developing fetuses, which decades later manifested in the form of an increased incidence of conditions such as obesity and schizophrenia. All the more reason, we now know, to make sure that women get plenty of folate in their diet early in the first trimester of pregnancy.

In this final chapter, we focus on the organic chemistry of folate, along with three other coenzymes: pyridoxal phosphate, thiamine diphosphate, and lipoamide. Humans can synthesize lipoamide, but we depend on dietary sources for the other three: pyridoxal phosphate is a form of vitamin B6, and thiamine diphosphate is a form of vitamin B1. In a mechanistic sense, there is really nothing new in this chapter. All of the reaction mechanism types that we will see are already familiar to us, ranging from nucleophilic substitutions (chapter 8) to disulfide exchanges (chapter 15). We will soon see, however, how each coenzyme plays its own specific and crucial role in assisting enzymes with the catalysis of key reactions of metabolism. We will begin with pyridoxal phosphate and its various roles in amino acid metabolism.

Additional reading:

http://www.naturalhistorymag.com/fea...na-epigenetics
