IMPROVING BRAIN FUNCTION WITH BACTERIA
By Debby Hamilton, MD, MPH

What if you could take bacteria to treat depression or prevent the development of Alzheimer’s? Research is beginning to explain how the bacteria in our intestine can influence inflammation in the brain leading to changes in mood and cognition. Although the gut-brain connection is not a novel concept, understanding the gut-brain-microbiome connection is a new area of research. It is important for the medical community to comprehend how the head and body are connected by more than just the neck.

There appear to be multiple mechanisms of action to facilitate the gut-brain-microbiome connection. The digestive system contains a large portion of the immune system within its lining. When there is dysbiosis or an imbalance of beneficial bacteria in the intestine, the innate immune system is activated leading to an increase in gastrointestinal inflammation. Inflammation in the intestine increases the permeability of the intestinal lining allowing inflammatory markers to gain access to the circulation. Since the brain is connected to the body, this systemic inflammation leads to neuroinflammation. By decreasing inflammatory cytokines and suppressing NF-KB and gut microbiota short chain fatty acids, a healthy microbiome also improves markers of insulin metabolism and lipid profiles.

The intestinal microbiota is closely involved in the enteric nervous system with bidirectional communication through the vagal nerve. The autonomic and the central nervous system are connected through the enteric nervous system. To aid neural transmission, the intestinal microbiota produce neurotransmitters and neuromodulators such as GABA, noradrenaline, serotonin, dopamine, and acetylcholine. They may contribute to brain derived neurotrophic factor levels since research shows germ free mice have decreased levels of the growth factor.

Alzheimer’s treatment currently focuses on delaying progression of the illness. A recent randomized double-blind placebo controlled trial showed improvements in mini-mental state cognitive tests after 12 weeks on a probiotic supplement. The probiotic group showed a significant improvement in the mini mental state exam (p<0.001) versus a slight worsening in the placebo group. In addition, some metabolic markers affecting carbohydrate metabolism improved. Although the exact mechanism of action is unknown, the decrease in insulin resistance and inflammation may play a role. Alzheimer’s disease has been associated with increased markers of oxidative stress and inflammation along with insulin resistance and hyperglycemia.

While beneficial bacteria play a positive role in Alzheimer’s, studies show that pathological bacteria can be harmful. Gram-negative bacteria such as E. Coli have cell membranes with LPS or lipopolysaccharides that can trigger inflammation. These LPS components can be found in the human brain. Brain samples of patients with Alzheimer’s were compared versus age matched controls for LPS and E. Coli K99 proteins. Higher levels of K99 E. Coli levels were found in both the Alzheimer’s and the control group but this protein was localized to the neurons in the Alzheimer’s group. The level of LPS was increased in the brains of patients with a history of Alzheimer’s.

One of the first signs of Parkinson’s disease is constipation from involvement of the enteric nervous system. Due to this observation, it makes sense that the microbiome may play a role in Parkinson’s disease. A recently released study showed a disruption in the microbiome of patients with Parkinson’s with a significant difference in the microbiome composition between those patients and the control group. It is unclear whether this disruption came before or after the development of the disease. The development of Parkinson’s has been linked to toxic chemical exposure and the microbiome plays a role in processing xenobiotic toxins. Another mechanism of development may be the involvement of the enteric neurons contributing to alpha-synuclein misfolding.

Neurological diseases in children also appear to involve alterations of the microbiome as part of their pathology. Gastrointestinal disorders are seen frequently in children with autism.
spectrum disorders. Estimates are up to 70% of affected children. Alterations in the microbiome are common with decreases in Bifidobacterium and increases in different species including multiple types of clostridium\textsuperscript{10,11}. Based on studies of altered microbiome in children with autism, a microbiota transfer study was completed after pretreating with antibiotics to clear existing organisms\textsuperscript{12}. Positive results were seen with an 80% decrease in gastrointestinal symptoms along with significant improvements in behavior symptoms common in autism spectrum disorder\textsuperscript{13}. With the understanding of the significant incidence of gastrointestinal issues and autism, microbiome research is critical. The autism microbiome study is an ongoing study aimed at sequencing and understanding some of the genetic variations that exist with these children\textsuperscript{13}.

The prevalence of depression and anxiety are progressively increasing along with our neurodegenerative diseases. While multiple biologic and environmental causes are involved, the impact of the microbiome on mental health is becoming a more important factor. A change in the microbiome leads to inflammation which is transmitted to the central nervous system resulting in mood and cognitive changes\textsuperscript{14}. Stress plays a role by altering neural pathways through the HPA axis controlling cortisol and hormone regulation\textsuperscript{15}. Treatment for both depression and anxiety is complex but supporting the immune system and the microbiome needs to be considered part of a safe approach.

It is about time that medicine acknowledges the microbiome as an integral part of the gut-brain connection. The microbiome plays a large role in the immune system significantly impacting the level of inflammation in the body. If there is systemic inflammation, there is neuroinflammation with potential for cognitive and mood disorders. If we support a healthy microbiome and prevent, delay, or lessen these severe neurologic issues, we have the potential to make a significant impact for many people.

References:
13. www.microbiome.stanford.edu