

# Epigenetics as Fuel for Brain Health

**David Perlmutter, MD, FACN, ABIHM**

**Q: How much power do we have to control brain health over the course of our lifetimes?**

**Dr. Perlmutter:** We have a great deal of power. Many of us grew up in a time of genetic determinism and had to labor through this dichotomy of “nature-versus-nurture,” which asks: “Are we the product of our genes or of our environments?” But now, we understand that our health and longevity actually represent a beautiful dance between nature *and* nurture—it is not one or the other. Our health is predicated on choosing how we interact with our genetic predispositions.

In fact, > 70% of genes that code for health and longevity are under epigenetic control. What a powerful concept, that through lifestyle choices, we have significant ability to control the transcription of those very genes that deal with health and longevity, including brain health.

Until now, the concept of epigenetics was foreign to most people in medical training. I was not taught in medical school that choosing certain lifestyle behaviors played a role in actually modifying our genetic expression and that we could unlock our genetic coding. But today, we have a greater understanding about the science behind epigenetics, and this is where we need to focus when dealing with brain health, resistance to disease, and enhancement of brain function. We are offered powerful tools through this understanding.

I want to point out that the term “epigenetics” was actually coined by Conrad Hal Waddington [CBE, FRS, FRSE; 1905–1075] in 1942 when he began to explain that genes and their expression are, in fact, interacting with our environments. This is not new information, but, just as the concept of neurogenesis, which is now hard science, was rejected by mainstream science for so long, it is difficult for people to shift their thinking. Ideas become ingrained, and they are very difficult to overturn.

For instance, we believe that each morning we look to the east and see the sunrise and then in the evening the sun sets in the west. It is great to think that is actually happening, but, in reality, it is not the sun that is moving; it is the earth that is rotating. This is part of the problem with people’s understanding and acceptance of epigenetics. There are still plenty of people who have this vision of our genes being locked in a proverbial glass case, and yet, that is not what science has demonstrated.

The question is not “is this real?” but rather “how do we take this reality and use it to our advantage?” Clinicians must be aware of this science in order to empower patients to help steer the course of their brain and bodily health.

**Q: Share with us the basics of what you are talking about when you speak of the role of epigenetics in modulating brain health.**

**Dr. Perlmutter:** We know that our genes are coiled around proteins that are called histones. Years ago, we recognized that histones have some reparative role to play in DNA, but we now understand that histones—beyond repairing DNA—actually play a role in allowing DNA expression.

So our DNA is wrapped around these histones, and the histones contain binding sites for various molecules, including methyl groups, acetyl groups, and others. When a histone is bound, it leads to changes in the conformation of the DNA, either tightening it up or opening it up; in other words, either making it unavailable or available for genetic transcription. Through the binding of what is called the epigenome—the combination of the DNA wrapped around the histone protein—we regulate the action of our genes.

As we consider the question of why this reality is not widely accepted in the medical community, the modern paradigm of medicine is treating illness after it has arisen, treating hypertension with medications, lowering blood sugar with drugs, and using anti-Alzheimer’s drugs—as if there were such drugs. That is the kind of reactive approach and it is a very Newtonian “billiard-ball” type of mentality that is pervasive throughout Western medicine.

Epigenetics points to a better way. For instance, we have known that the foods we eat contain the macronutrients of proteins, carbohydrates, and fats as well as micronutrients, such as minerals and vitamins—all of which produce various types of physiologic activity. But the concept that food represents information is really relatively new. The foods we eat and the lifestyle behaviors we choose are literally instructing our genomes.

**Q: When it comes to brain health, what are some of the key lifestyle behaviors that clinicians should be emphasizing with their patients? When should that education begin?**

**Dr. Perlmutter:** For me, the education begins within the first 5 minutes of the clinician–patient interaction. It is that profound. In essence, we have to communicate to the patient: “Guess what? What you are going to hear today is not focused on the coin of currency of medical practice, which is a prescription pad, but it is about you taking responsibility for your health in terms of the lifestyle choices that you are going to make from this moment forward. Here is the science that underlies it. Here are the epidemiologic studies that support that contention, and here are the tools that you need.” For me, that is job number one. The initial conversation is not focused on any medication or a specific supplement but rather on the data.

For example, a recent study demonstrated an actual increase in the size of the hippocampus in elderly individuals who engaged in 20 minutes of moderate-intensity aerobic exercise 3 days a week for 1 year.<sup>1</sup> The participants also experienced a corresponding increase in memory function and an increase in serum levels of brain-derived neurotrophic factor, or BDNF. However, the control group assigned to stretching and toning, experienced a decrease in hippocampal size over the same time period.

These findings are significant because, generally, as we age, we are losing ~1%–2% of hippocampal neurons in terms of size of the hippocampus every single year. The exercise intervention in this study did not just nullify that loss— aerobic exercise led to a *growth* of the hippocampus. That is powerful!

BDNF is coded for in our genes, and epigenetically, by doing aerobic exercise, for example, we enhance the epigenetic factors that lead to increased BDNF, which is basically growth hormone for the hippocampus. There is no pharmaceutical on the planet that can do that. There is no drug to treat Alzheimer’s disease. Yet, calorie restriction, physical exercise, taking a docosahexaenoic acid [DHA] supplement, and eating fish are all things that have been demonstrated to increase the size of the hippocampus and, more importantly, allow better memory function.

We have to look at the hippocampus when talking about brain health, as that is often the first area that degenerates, as demonstrated in what is called a voxel-based magnetic resonance imaging [MRI] study, in which it is possible to quantify the amount of tissue in a particular area of brain anatomy. Hippocampal degeneration, which happens in all of us, is also an early marker of Alzheimer’s disease. But the important message is that this degeneration can be reversed.

Another lifestyle factor that impacts the hippocampus and that clinicians must address with their patients is stress. Stress plays a very powerful role in the hippocampus and in our ability to preserve memory. The hippocampus is exquisitely sensitive to cortisol. Persistent exposure to cortisol with long-standing, even low-level stress in primates is demonstrated to play a significant role in initiating atrophy of the hippocampus, which is the manifestation of apoptosis, cell loss, and neuronal dropout. By the same token, acute high levels of cortisol can also lead to hippocampal destruction.

Individuals who have had post-traumatic stress disorder [PTSD] or who have been exposed to severe trauma in the

past, have a dramatically increased risk for Alzheimer’s disease, even if that stress occurred during childhood. But again, if a person has experienced PTSD or childhood trauma, it is not “Doomsday” in the least. This loss of function is recoverable. We have this incredible ability to regain both structure and function as it relates to the hippocampus. Now 20 years ago no-one would have even considered that fact or that this whole process of neurogenesis is real. But we now know that we have a second chance for health, and we have the ability to regrow the hippocampus. How exciting to actually get another chance!

Glucose control is another key point that clinicians must address. An interesting study in *Neurology* entitled, “Higher Normal Fasting Plasma Glucose is Associated with Hippocampal Atrophy: The PATH Study,” brings to our attention the role that glucose and glycated proteins have in increasing free radicals and, therefore, oxidative stress and hippocampal neuronal dropout.<sup>2</sup>

In this study, researchers measured participants’ fasting blood sugars and then followed the subjects for 4 years. The scientists checked the size of the subjects’ hippocampi by MRI at the beginning of the study and 4 years later. The scientists found that individuals with the highest blood sugar levels had a significant degree of hippocampal atrophy, compared to people with lower blood sugar levels. The important point here is that the highest level of glucose that was used in the study was only 110 mg/dL. That is a value that we have considered normal until now. The study authors comment that their findings suggest that, “even in the subclinical range and in the absence of diabetes, monitoring and management of plasma glucose levels could have an impact on cerebral health.”

For the study participants with the lowest level of blood sugar, the degree of hippocampal atrophy was actually in the negative range, meaning that their hippocampi were growing throughout the lifetimes of these elderly individuals.

There is a profound relationship between brain atrophy and excess blood sugar but also with hemoglobin A1c levels. When a patient’s hemoglobin A1c is 5.6–5.8—levels that are generally considered acceptable—these levels are dramatically related to brain atrophy and are directly proportional to the degree of brain atrophy.<sup>3</sup>

Clinicians need to understand that hemoglobin A1c is not simply a marker for how well blood sugar is controlled, but that hemoglobin A1c is a marker for free radical-mediated stress and directly relates to the risk of brain atrophy. When clinicians monitor hemoglobin A1c, they have got to view the results in this new light. We cannot control the



Alzheimer's gene—that is inherited. Yet, we can control hemoglobin A1c.

These are just a few examples of the hard science behind epigenetics. These examples highlight the lifestyle issues that clinicians should share with their patients.

**Q: What is being discovered in terms of the role of integrative therapies and genetic expression?**

**Dr. Perlmutter:** Let us start by looking at nutrition. First of all, neuronal degeneration and brain degeneration in general is predicated on mitochondrial failure, and all that we do from our integrative and complementary perspective is focused on

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nurturing mitochondria. What we now understand is that mitochondria tend to function better when they are burning fat as a fuel as opposed to carbohydrates. A diet that is extremely low in carbohydrates but that favors a little bit of ketosis provides the brain with  $\beta$ -hydroxybutyrate, which is powerfully therapeutic for mitochondria.

This is a brand new idea that we should be eating ~ 70% of our calories from fat, and yet, it has only been what we have consumed for 2.6 million years. Our collective genome has not evolved to handle carbohydrates, so the best and most therapeutic diet from an integrative and complementary medicine perspective for brain cells is a higher fat diet that reduces carbohydrate. The best fuel for mitochondria is fat, which allows them to function more efficiently, reducing their production of free radicals, increasing the mitochondria's adenosine-5'-triphosphate production, and increasing mitochondrial biogenesis.

When a person cuts back on fat and follows a low-fat diet that is so widely recommended in Western medicine today, by default, calories will come from carbohydrates, which is the worst thing a person could possibly do. Why? When a person increases carbohydrate consumption, that person begins to glycate his or her proteins, which increases the production of free radicals by as much as 50-fold.

The good news is that we can reduce the glycation of protein by, number one, reducing carbohydrate in the diet. A low-carbohydrate diet is, far and away, the most important first step. A study in *The New England Journal of Medicine* comparing the effectiveness of a low-carbohydrate, Mediterranean, or low-fat diet on weight loss, showed that, in every cardiovascular parameter, whether C-reactive protein or high-density lipoprotein/low-density lipoprotein cholesterol ratios, the low-carbohydrate diet beats the low-fat diet hands down in terms of improvement.<sup>4</sup>

Second of all, various nutritional supplements are antiglycating agents, such as benfotiamine,  $\alpha$ -lipoic acid, taurine, DHA,

and resveratrol. *N*-acetylcysteine is very powerful in that regard. Aspirin and carnosine are also effective.

We have to reduce our glycemic load of the foods that we eat and, therefore, reduce our glycation of proteins.<sup>5</sup> Glycation of proteins not only increases radical formation, but it is also a dramatic upregulator of cytokine formation, which is the type of chemical that increases brain inflammation. At the end of the day, brain inflammation is the cornerstone of conditions such as Alzheimer's and Parkinson's disease.

**Q: How can mind-body therapies improve brain health epigenetically?**

**Dr. Perlmutter:** We have covered neurogenesis and the ability to grow back new brain cells, but let us explore, for just a moment, the notion of neuroplasticity, the ability of the brain to make new connections. We know that neuroplasticity is a process that is occurring throughout the human lifetime and is aggressively happening during the formative years, but it also occurs when people are 95 years' old.

Neuroplasticity is the ability of the brain to form new networks and to provide better connections to various brain areas. One of the areas that is really useful in terms of developing more as humans is, obviously, the prefrontal cortex. The prefrontal cortex, as it has developed in our species, has become very advanced, and, if there is an area of the brain that is devoted to allowing us to feel empathetic and compassionate and socially aware, and for us to understand the future implications of our actions today, it is the prefrontal cortex.

Lifestyle factors will enhance our abilities, should we so choose, to make better connections through neuroplasticity to the prefrontal cortex. Endeavors to make better connections to the area that mediates those positive factors are practices such as meditation and prayer.

When a person meditates or is involved in prayer, that person's body is connected to the prefrontal cortex and tends to actually make less connection to, for example, the amygdala, the emotional response center of the brain, and even the parietal lobes, which mediate the sense of three-dimensionality or where a person is in relation to other people or objects. The person will tend to shut that down and become less concerned about where he or she is physically—and what might be threatening physically or emotionally—and make a better connection to the prefrontal cortex. This allows a person to become more socially aware, more empathetic, and more compassionate.

There is a wonderful book entitled *“How God Changes Your Brain,”* written by a neuroradiologist, Andrew Newberg [MD] and Mark Robert Waldman, who have demonstrated, in various types of brain imaging studies, the physical changes that are permanent and that happen when people meditate.<sup>6</sup>

Whatever we can do to enhance the process of neuroplasticity will enhance the ability of our brains to connect to our prefrontal cortices, and we enhance neuroplasticity through a number of epigenetic techniques. Calorie restriction and fasting also turn on BDNF production. It is interesting to note that the idea of fasting has been pervasive in all major religious doctrines throughout the history of humankind, whether it is

the fast of Ramadan, the fast of Yom Kippur, or Jesus fasting for 40 days before his public ministry.

When one fasts, of course, it makes one think about things because one becomes hungry. But interestingly, from a physiologic perspective, it is an epigenetic modulator turning on BDNF production, allowing the person who is fasting to make better physical, structural, and functional contact with his or her prefrontal cortex.<sup>7</sup>

**Q: Why is it important for clinicians to understand the concept and the science behind epigenetics, and where can they find learning opportunities?**

**Dr. Perlmutter:** “Doctor” means “teacher”; it does not mean “healer.” The information and science behind epigenetics provides the most powerful teaching platform that clinicians could have ever imagined and allows them to impact people’s lives to the degree that these clinicians never could have imagined. That is really the focus of epigenetics.

At the end of the day, as sophisticated as medicine has become, the most important factors in health and longevity are diet and lifestyle. I have spent the last 20 years deeply involved in the most challenging biochemistry that one can imagine in terms of my teaching and writing. Now I have come to realize, that it is all about things that Hippocrates talked about. We now understand the mechanism that, yes, Hippocrates was right: “Let food be your medicine and medicine be your food.” It is humbling, but it is empowering.

Learning opportunities for clinicians are available at The Institute for Functional Medicine (especially Applying Functional Medicine in Clinical Practice), the American College of Nutrition, and the American Academy of Anti-Aging Medicine. Many of these organizations’ lectures are now focused on an understanding of epigenetics.

Let me conclude by sharing a quote by Louis Pasteur, which is that “chance favors the prepared mind.” We have the chance

to be very effective and share with patients the therapies that help them turn the corners and achieve better health outcomes, but this requires preparation, homework, and academic pursuit. My point is that an understanding of epigenetics can become one of clinicians’ most powerful tools in terms of guiding patients to those therapies that will bring about the biggest changes in health and longevity. ■

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