Dr. David Perlmutter: New Steps to Targeting Brain Health and Alzheimer's Disease

Interview by Sheldon Baker

***David Perlmutter,** MD, is a Board-Certified Neurologist and six-time* New York Times *bestselling author whose work focuses on the intersection of neurology, nutrition, and brain health. A Fellow of the American College of Nutrition, he serves on its Board of Directors and on the Editorial Board of the* Journal of Alzheimer's Disease. *His books, including the #1 bestseller* Grain Brain*, have been published in 32 languages and sold over a million copies. Dr. Perlmutter lectures globally at leading institutions and has been featured on major media outlets including* 20/20, CNN, The Today Show, *and* Oprah. *His contributions have earned him numerous national and international awards for clinical innovation and leadership. His upcoming book,* Brain Defenders*, focuses on the pivotal role of microglia, the brain's immune cells, in protecting, repairing, and reprogramming the brain for lifelong resilience.*

Brain Defenders *reveals the powerful story of your brain's immune guardians (microglia), and how lifestyle choices can turn them into either fierce protectors or hidden saboteurs. The book directly challenges the notion that we now have meaningful treatments for diseases like Parkinson's and Alzheimer's. Despite FDA approval for drugs that reduce beta-amyloid, the book reveals that these drugs are not impactful and actually profoundly dangerous. Packed with cutting-edge science and practical steps,* Brain Defenders *helps readers take charge of their long-term brain health and unlock lasting cognitive vitality.*

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***Integrative Medicine: A Clinician's Journal* (*IMCJ*):** In your new book *Brain Defenders*, you argue that we've been targeting the wrong thing in Alzheimer's disease.

David Perlmutter, MD: For sure.

***IMCJ*:** What is the core fallacy behind the amyloid based treatment model?

Dr. Perlmutter: I think that it's quite obvious that the model gained so much traction in the late 1980s because there was this need, I believe, to find a single cause. Alzheimer's is not a disease characterized by a single cause or single event. There are multiple issues that lead to a good brain going bad. And I feel to be fair, the reason there's always been emphasis on looking for single cause, is it lends itself then to what's called monotherapy. If we could identify a single cause related to Alzheimer's disease then we might target a therapy at that single cause and next thing you know we have a blockbuster. The amyloid hypothesis was really based on flawed and doctored research. That is what's public knowledge now. Ultimately, the therapies that were an outgrowth of that hypothesis haven't worked. The idea that we could rid the brain of beta amyloid using monoclonal antibodies has been proven to be true. And yet, the effect on the disease course is almost none whatsoever in the face of potential death from the medications, or at least a significant risk of developing a potentially threatening side effect like ARIA which is amyloid-related imaging abnormalities. It basically means developing changes on your MRI scan that are either indicative of brain hemorrhages or areas of swelling.

***IMCJ*:** Where do we go from here or in other words, the next steps to treatment?

Dr. Perlmutter: The risk-benefit ratio of what has evolved out of the FDA approval of this medication, which is really at this time, the go-to approach for the treatment of Alzheimer's disease is, to be kind, lacking and unfair. We recognize now that a certain number of Alzheimer's patients do accumulate beta-amyloid in their brains. We also recognize that it's fairly common. But it is a consequence and not the cause. We certainly see the evidence of individuals developing aggressive Alzheimer's with no appreciable beta amyloid in their brains. Similarly, we see evidence of individuals who are randomly tested as part of research and have quite a bit of beta amyloid accumulating in their brains and yet are cognitively quite intact. These findings really cause us to call to question the whole amyloid hypothesis. And now, in the past several years, we recognize that there is a lot going on upstream of the accumulation of beta amyloid, that really represents mechanistically what is involved fundamentally in terms of the pathogenesis of that disease. Interestingly, this shift in immune functionality in the brain that we are talking about is seen to be involved across the spectrum of

neurodegenerative conditions. So, it's really quite an exciting development in neuroscience and neurology that we see such a global mechanism now being involved across the array of neurodegenerative conditions.

***IMCJ*:** You also say that Alzheimer's is not primarily a disease of plaques and tangles, but of misdirected immunity. So how do microglial cells reframe the entire conversation?

Dr. Perlmutter: What we're now recognizing with research is becoming very exciting and captivating. Over the past five years it has been the central role of the brain's immune system, the microglial cells, in really dictating the destiny of the brain. The changes in the function of the brain's immune system by microglial cells is very much upstream of the accumulation of both phosphorylated tau and the accumulation of beta amyloid. So, these are proximate events that we have to pay attention to. Our microglial cells in the best of times exist in their M2M2 phenotype. What does that mean? It means that these microglial cells can shift in their phenotype and their function. In the M2 supportive phenotype, they're nurturing neurons, enhancing synapse stability, and are shoring up the blood-brain barrier. They're really on our side.

***IMCJ*:** At the end of the day, the key to supporting a good brain lies in the microglial cells.

Dr. Perlmutter: Simplistically, the microglial cells can shift to being M1 configuration, or phenotype, and as such, can become the evil twin. They can become threatening so they can become destabilizing in the brain such that neurons are no longer nurtured, but synapses are. In fact, destroyed and the blood-brain barrier becomes less functional and more permeable allowing ingress of threatening issues into the brain which would normally have been excluded. This shift from the supportive to the threatening microglial cells is fundamental to what makes a good brain go bad. This shift is characterized by a profound shift in the metabolism of these microglial immune cells in the brain. When they're in their M2-supportive configuration their mitochondria and energy production is top notch. They're producing energy through oxidative phosphorylation meaning that in the presence of oxygen they are utilizing glucose to create the energy currency of life in humans called ATP. This is a very efficient process. When this is threatened by any number of issues that we will discuss, this shift in their metabolism changes immune function in the brain and is characterized by their shift from supportive M2 to destructive M1. This marries two seemingly disparate ideas, that is the idea of immunity and the idea of metabolism into a term that we call immunometabolism. A beautiful dance between metabolic function in these cells and their function as the arbiters of immunity. But what is so empowering about this understanding, and is fundamental, is that the metabolism of the microglial cells mirrors the metabolism of the entire body.

Why is that empowering? It's empowering because when we engage lifestyle factors to improve our body's metabolism we are directly targeting our microglial cell's metabolism and helping nudge them to be more supportive and less destructive. When they are destructive they are digesting away our vital synapses, our connections between neurons that form our neural networks and allow us to have the sophisticated cognitive experience that we all enjoy. It is the loss of synapses that most characterizes the Alzheimer's brain, not the accumulation of beta amyloid. The loss of synapses means the loss of connection at a cellular level and at a social level as it relates to this disease. The reason we use the term immunometabolism is to ultimately drive home the point that we, through our lifestyle choices, are the arbiters of our systemic metabolism, and as a consequence, the arbiters of the metabolism of our microglial cells, and determine whether they will be supportive or the evil twin.

***IMCJ*:** What does the science show about the triggers of dietary, metabolic, or environmental that shift microglial into a destructive pro-inflammatory state?

Dr. Perlmutter: The incredible number of threats to the microglial polarization, or the shift from supportive to destructive, seems to be expanding daily. We certainly know that changes in our body's metabolism directly target our microglial cells. When, for example, our blood sugar is elevated, we create glycated proteins to which this excess sugar can bind. People are familiar with that because hemoglobin A1C is a glycated protein, in this case hemoglobin that is measured as an indication of average blood sugar, and many people seem to be aware of that. But let's be clear, hemoglobin is certainly not the only protein in our bodies that becomes glycated. It's a rampant event when blood sugar is elevated. There are receptors called RAGE receptors on the microglial cells. Receptors for advanced glycosylated end products, and they respond to proteins when they are modified by binding sugar when blood sugar is elevated and help to morph these supportive microglial cells into being destructive. So, the rage receptor is one of the powerful inroads to make this happen, and interestingly, as well as importantly, Beta amyloid binds to that receptor. So, that creates a vicious cycle whereby increasing the activity of the M1 destructive microglial cells increase in beta amyloid, because it limits the way that our immune system would normally have phagocytized or destroyed and gotten rid of this beta amyloid. That process is compromised as our immune cells shift from being friend to being foe.

Now, that accumulation of beta-amyloid then further causes shift in these microglial cells from M2 supportive to M1 destructive by binding to that receptor, the receptor

for advanced glycated end products, or the RAGE receptor. Microglial cells are exquisitely sensitive to the chemical mediators of inflammation called cytokines. These can be produced within the brain, but they can actually enter the brain from anywhere in the body, meaning inflammation can be anywhere in the body and cause the microglial cells to turn their backs on us and shift to their threatening M1 phenotype. This is a very interesting idea because now, we have a good explanation as to why there's such a powerful relationship between the microbiome, changes in the gut microbiome, dysbiosis, and inflammatory diseases of the bowel, for example, and risk for neurodegenerative conditions, like Alzheimer's, Parkinson's, and even multiple sclerosis. It is because these shifts lead to increased permeability of the gut, or so-called leaky gut. The amplification of the production of these inflammatory cytokines in the body, making their way to the brain, and then shifting these microglial cells from M2 supportive to M1 supportive are destructive. We need desperately to preserve our brain defenders. The brain defenders being these supportive M2 microglia. When cytokines approach these M2 microglia, it shifts them away from being supportive.

A powerful source of the production of inflammatory cytokines in the brain are the M1 microglial cells. In other words, once we shift the microglial cells away from being our brain defenders to the M1 phenotype it dramatically amplifies inflammation in the brain.

Neuroinflammation is the cornerstone of what makes a good brain go bad. The destruction of the brain as a consequence of neuroinflammation has been talked about in the context of Alzheimer's for decades. But what we've created now is by shifting our microglial cells away from being supportive to being destructive, there's an increase in the very chemicals that are continuing this process. Those inflammatory cytokines then target neighboring supportive M2 microglia and shift them like zombies into being destructive. So, it spreads through the brain like a cancer. This is quite powerful.

***IMCJ*:** But is there a way to shift from M1 to M2?

Dr. Perlmutter: I'll answer that question in just a moment because we'll get there. Let me finish my previous point.

This understanding of the spreading of the shift of these microglial cells now helps us understand why events earlier in life set into motion a progressive decline. An example is CTE, chronic traumatic encephalopathy in people who engage in events that threaten brain trauma like professional football players. They're retired from football, are diagnosed with chronic traumatic encephalopathy, and they continue to decline long after they've retired from the inciting event. It's a feed-forward process.

We know that exposure to various toxins in the environment, including PM2.5 particles in the environment increase of inflammation including herbicides, or heavy metals that we are exposed to. The question then arises, and here's a great lead-in for your question, if that's the case, then what can we possibly do?

To shift these M1 microglial cells back to being supportive we can absolutely do that. I think job one is recognizing what I mentioned earlier, and that is that the metabolism which dictates the configuration of our microglial cells is mirrored by our body's metabolism. So, job one is to get our metabolic house in order and reduce the metabolic mayhem that so characterizes more than 90% of American adults at this time.

***IMCJ*:** As I often say, you're only as healthy as your gut.

Dr. Perlmutter: We live in a country where we have 40 million adults suffering from full-on diabetes. When you add in prediabetes that's 80 to 90 million. That's a huge metabolic insult on the body, and certainly on the brain itself, through the mechanisms that I just described as it relates to polarization of our microglial cells. We know that if you are, in fact, a type 2 diabetic that your risk of becoming an Alzheimer's patient may be as much as quadrupled. So, the issue then is to regain metabolic health, and that will nudge our microglial cells back to being supportive. How do we do that? Well, there are countless ways, including more exercise, getting better sleep, and socialization, a ketogenic diet, or a more ketogenic diet, a less inflammatory diet, reducing our consumption of ultra-processed foods are key. We recognize now that more than 60% of the calories consumed by American adults are derived from foods that are pro-inflammatory and lead to microglial polarization. It's no wonder that we're seeing the increase so drastically of these neurodegenerative conditions. More so, at least on a percentage basis, as it relates to Parkinson's, than as it relates to Alzheimer's, though Alzheimer's is certainly continuing to spread, like a pandemic.

***IMCJ*:** But as you state we need a multifaceted approach.

Dr. Perlmutter: Yes, but diet is certainly job one, but there's a multi-factor approach with exercise, ensuring we're getting adequate sleep, metricizing these issues, and the value, the duration, and the quality of our sleep, or being more aggressive with understanding our blood sugars, not just what our fasting blood sugar might be. Once a year getting a better idea as to what our fasting blood sugar is moment to moment for example, or using a continuous glucose monitor, or even less aggressively, checking not just our fasting blood sugars but fasting too. Checking our insulin level as well, as a powerful insight into where we are on the scale of the harbinger for prediabetes, which is insulin resistance. These are important things that we can do to rein in our metabolism, things that I think many people are familiar with. But beyond that, I touched upon earlier the notion that our

exposure to various toxins is certainly threatening through a number of mechanisms. Toxins can bind to specific receptors on the microglial cells and shift them away from being supportive.

***IMCJ*:** Our polluted, toxic air is everywhere.

Dr. Perlmutter: I recently took a trip to Egypt and used an app just to get a sense as to what the level of air pollution was day by day in Cairo and in Luxor, other cities that we visited. It was astounding to me the level of air pollution that we were experiencing. What recourse do we have? We requested an air purifier in our room. We also used PM, rather N95 masks whenever we were outside. I don't know what kind of social statement that makes, but PM2.5s are directly threatening to the brain. People who are exposed to higher levels of PM2.5s have a significantly increased risk for Alzheimer's disease, a disease for which there is no pharmaceutical fix.

I feel it's certainly valuable for us to assess our level of toxicity by doing blood tests that look at heavy metals, and what our exposure to these particulate matters that are in the air that we breathe, these threatening PM2.5s. The idea of actually measuring air quality, which we can do at home, or with various apps we can use, I describe in the book.

***IMCJ*:** Of course, it's not just the air we breathe that's harmful to our brain.

Dr. Perlmutter: People who become diabetic have such a risk that I just explained earlier. These are modifiable factors in our lives. We know that there's an increased risk of polarization of our microglial cells when we've experienced head trauma. What is the response? The response is to wear a seatbelt and use a helmet when you're involved in any activity that could threaten your brain, be it bicycling or riding a motorcycle, a horse, doing snowboarding or snow skiing. Any issue that could potentially increase your risk of head trauma needs to be taken care of. There are many issues we have significant control over that can help us keep our microglial cells in their M2-supportive configuration. One thing, a very sophisticated tool, that I often talk about that can be employed to determine risk of microglial polarization is simply a tape measure. A tape measure around the belly and around the hips determines your waist-to-hip ratio. The higher that is translates to a higher risk of Alzheimer's and other metabolic issues and certainly translates to risk of Alzheimer's as well. We know that increased amounts of body fat, depending of course on its distribution, correlates with increased inflammation.

Getting back to the mechanism we talked about earlier, the U.S. obesity rate is pegged right now at around 40-45%, with about 16% of Americans being diagnosed or categorized with extreme obesity. We used to say the standard American diet became the Western diet. It's now the global diet. The global diet is highly processed, pro-inflammatory, and dramatically increasing the risk of both obesity and diabetes worldwide. Anticipated that by 2035, we're going to have 1.5 billion adults categorized as being obese on our planet. Let's be clear, Alzheimer's is not a disease that suddenly begins in our 60s and 70s, when we start to manifest the clinical manifestations like we don't remember why we went into a room, the Wi-Fi code, or our grandchildren's names. The seeds are sown In terms of our metabolic dysfunction in our 20s, 30s, and 40s, I'm hopeful that this message can land on those individuals, because that's when we can begin to implement such changes targeting brain protection by reducing metabolic mayhem, and reining in overweight and obesity. Childhood obesity in America was 5% in the 1970s. It jumped to 20%. There was a four-fold increase by 2018 and continues to increase. Children who are obese become adolescents who are obese, teenagers who are obese, and kids in their 20s, 30s, and 40s carry that legacy and ultimately are setting the stage for declining brain function and everything else that goes along with metabolic dysfunction. These are inroads to what happens to our microglial cells just through the lens of what we can do from a lifestyle perspective. We can engage in things such as a variety of nutritional supplements that specifically target metabolism and therefore target the microglial cells.

***IMCJ*:** Which supplements do you suggest?

Dr. Perlmutter: Some are relatively new on the scene, like rosmarinic acid and dihydroxymiracetin. We know that things like Coenzyme Q10, and one of my favorites being creatine monohydrate, or creatine hydrochloride are helpful. We've seen recent interventional trials using creatine monohydrate that targets mitochondrial function and is central to the polarization of the microglial cells. A recent study, actually an interventional trial, showed significant change in early Alzheimer's patients who received a dosage of 10 grams twice a day of creatine monohydrate. It's inexpensive and tasteless, and I've not seen any side effects from the use of this nutritional supplement. So, why wouldn't anybody take it? Other things to consider are interventions like using Urolithin A, the new player on the block called spermidine, a type of oil that increases what we call mitophagy, or the body's natural ability to rid itself of defective mitochondria paving the way for replacement with more functional mitochondria. That's where the money is in terms of shifting our microglial cells to being supportive. It's targeting their mitochondrial function. I've been very impressed with the research on Himalayan tartary buckwheat in terms of its ability to bring about epigenetic changes associated with reduction in inflammation and various aging parameters as well as favorable impact on metabolism. Now, we can get more advanced with respect

to our interventions and use things like hyperbaric oxygen therapy where we oxygenate the body. We increase blood flow and we allow the growth of new blood vessels through hyperbaric oxygen therapy through its activation of something called hypoxia-inducible factor 1-alpha. It amplifies something called VEGF, vascular endothelial growth factor, which improves blood supply.

***IMCJ*:** Beyond supplements, what role is technology bringing to the forefront?

Dr. Perlmutter: Exciting technology is a background rhythm, a symphony that is played and we call it gamma oscillation. It's a beautiful sinusoidal curve that characterizes a normal, healthy, functioning brain with age. With a deterioration of the brain and deterioration of its functionality, this background rhythmicity gets threatened and we get a bit of cacophony. We're now using the metaphor of an orchestra. There's no longer a conductor, and people are not playing instruments in a way of synchrony, and creating this beautiful outflow, and the sound that characterizes a normally functioning brain. A forward-thinking researcher, Dr. Li-Wei Tsai at MIT discovered that. When you evaluate the Alzheimer's rodent model, the APP plus a rodent model that develops cognitive decline and all the pathological changes that we see in Alzheimer's, there's a decay of the gamma oscillation in the background, as expected, as there is in mammals across the board. But what Dr. Tsai noted was when these laboratory animals were exposed to a particular frequency of flashing light, 40 times per second, not 20 or 80. There was a significant change in the background rhythm with restoration of this gamma oscillation.

The next thing we would want to know, taking this a little further, is in addition to the restoration of the gamma oscillation in the background Dr. Tsai noted, a significant reduction in the accumulation of beta amyloid 1-40, as well as beta amyloid 1-42 in multiple areas of the brain in those animals exposed to a simple flashing light at 40 Hz, thinking that the rodent studies are interesting, but how does that play out for humans? In 2024, she conducted a study on humans which included 76 subjects. It was a six month interventional trial with a sham group as well that didn't get 40Hz light but was exposed to the delivery of light through the same goggles, but they didn't know if they were getting 40Hz light or not. The group receiving the 40 Hz treatment demonstrated a significant reduction in their cognitive decline as evaluated on two scales. First, it was Alzheimer's. A standard evaluation of Alzheimer's disease, and also an Alzheimer's disease assessment score that focused specifically on how individuals are able to perform their activities of daily living, like self-care, bathing, feeding, and other types of things. The difference between the sham group and the intervention group was breathtaking, especially in the context of how patients decline versus control when they are given the so-called Alzheimer's drug that targets beta amyloid. This was incomparable with respect to the results of the beta amyloid interventional studies and much more significant leveling off of their decline in terms of their amyloid load and their function which is really where the money is.

A bigger study is underway now, and these individuals are receiving not just a flashing light at 40 Hz but also listening to a sound at 40Hz as well, and the results are spectacular so far through this ongoing trial. We're hoping that it will be approved soon. There are companies, and there's one called Optoceutics that already makes a 40Hz light available to consumers. I have one and this technology is targeting our microglial cells. The original research demonstrated more than anything else in the rodents was not only an increase of microglial cells, but specifically an increase of the M2 supportive microglial cells, simply by shining a light in their eyes at a particular frequency.

I'm very taken by the simplicity and the elegance of this intervention. There's no downside that has been observed. I think that people who might have issues with flashing lights, photo-induced epilepsy for example, may not be able to avail themselves of this therapy. It's a very small number of people, but I feel it is something to be considered.

***IMCJ*:** Like I always say advancements in technology are great when it works as intended to do.

Dr. Perlmutter: Well, then let me just go to another place. One of the most profound interventions we've ever seen developed to target metabolism has been the GLP-1 agonist drugs. The way these drugs are improving metabolism, as we know, were originally developed for the treatment of diabetes, now are used globally for the treatment of overweight and obesity. But what research demonstrates is that, at least in diabetes, they have a profound effect on improving mitochondrial function. That's something to be aware of. In April 2024, in the *New England Journal of Medicine,* a published study, an interventional trial, included 156 patients. It was a one-year study, giving part of the group a placebo, and the other receiving, lixisenatide, a GLP-1 agonist drug. These people were evaluated after the trial with what is called the Unified Parkinson's Disease Rating Scale. It's a standardized scale used to determine functionality or degree of compromise in the Parkinson's patient. Parkinson's patients decline over time. It's incessant. These medications that are used in the treatment of Parkinson's today do not target Parkinson's disease, they only target Parkinson's symptoms, and they're certainly useful. There are medications for tremor and rigidity. It's an integral part of what my practice utilizes, or utilized, for the treatment of Parkinson's disease. It allows us to keep patients functional, but in the background, the disease continues to threaten their brains and they further decline. Mainstream treatment is focused on treating the smoke and ignoring the fire.

What the study demonstrated was that, as expected, the group receiving the placebo declined over the course of one year significantly in terms of the Unified Parkinson's Disease Rating Scale (UPDRS). The intervention group astoundingly not only stabilized but demonstrated a slight improvement with the utilization of an intervention, in this case, a GLP-1 agonist drug, that targeted their metabolism, and their mitochondrial function. As a result, I'm very excited about the future. Yes, I am sure there will be risks for long-term usage of GLP-1 agonist drugs. There are those that are already described. Do individuals seem to rebound with reference to their diabetes and weight gain after they stop these drugs? Yes, of course they do and I'm aware of that. But I think there's some incredibly valuable information here saying at the very least that when we target metabolism it is good for the brain in people who have neurodegenerative conditions because it shifts their microglial cells back to being supportive.

***IMCJ*:** Just to confirm, I think you said early lifestyle intervention is more powerful than any late-stage drug.

Dr. Perlmutter: Oh, I like that, and yes you could say that. That's actually a great quote, Sheldon. I was going say young Sheldon, but that's already taken.

***IMCJ*:** Thank you and yes it has. If you could distill *Brain Defenders* into one message about taking control of your range destiny what would it be?

Dr. Perlmutter: Simply, that it's time that we recognize the paradigm that has been presented to us. It's one of being passive, a patient, and being at the mercy of treatments that are developed. I think the most important message is that we should recognize that we can absolutely take control today and be the architects of our brain's destiny.

I think on a broader scale I write these books for empowerment. For individuals to read these books and see the other side of what we just talked about, that here's a whole different way of understanding of what can be done as it relates to your brain's destiny, and as opposed to being passive versus proactive. I think your quote just now was great. And that's been my mission across every book I've ever written. This is book number 16. I'm very taken by this book for a number of reasons. First, because it really brings together everything I've done. It explains why a high-carbohydrate diet that we described in *Grain Brain* ultimately threatens the brain. It's through the polarization of the microglial cells. It explains what I described in *Brain Maker* that focused on the relationship between changes in the microbiome and brain degeneration. Again, through the mechanism of inflammation, and how that polarizes our microglial cells. It explains what I wrote about with our son, Austin in the book *Brainwash* that looked at our disconnection from others and isolation. It relates to risk for brain degeneration, because we know that when we are isolated like that we experience less production of oxytocin. I talk about it in this new book. And oxytocin fundamentally signals our microglial cells to remain supportive. Think about that. The hormone of love is received by our nurturing microglial cells and keeps them doing their job. How profound. We're all aware of the research demonstrating that people decline very quickly, cognitively, when they're socially isolated. A key component is community and was one of the things that was seen in the *Blue Zones* research. Also having a purpose and socialization. People kind of underplay those things thinking that they don't have anywhere near the traction of a ketogenic diet that's rich in fiber, or getting a good night's sleep and exercise, things I mentioned earlier. But not true. These are profound inroads to better brain health and now we understand mechanistically why they work.

Everything has come together in *Brain Defenders*, and it's what I've been interested in for the past 40 years. I'm also very taken by the fact that here we are, a little over four months prior to publication, and the book has already been bought by 15 countries around the world and translated in 15 other languages. That's very exciting because I love my message becoming global. It just shows that there's real interest in this and moving away from being the passive patient to becoming the participant. It's also a recognition and I can see that it's happening globally, thus very exciting.