

## New Movement in Neuroscience: A Purpose-Driven Life

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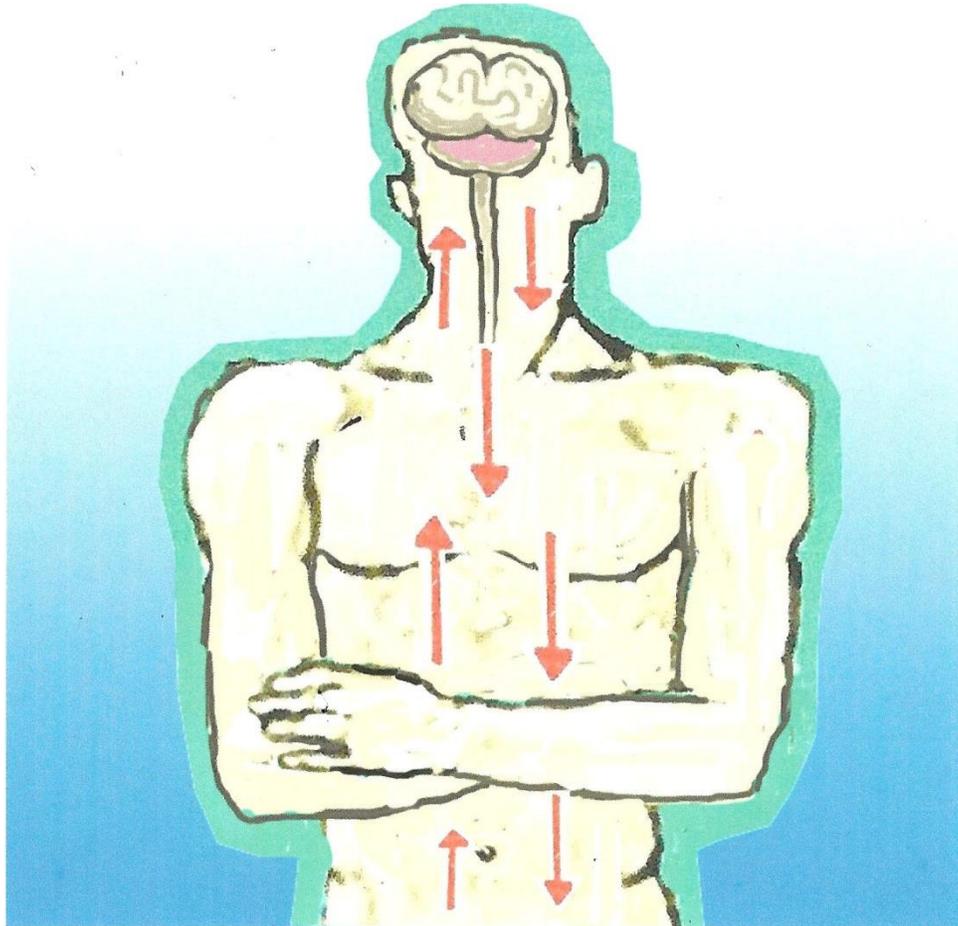


Illustration by William Hogan

*Editor's Note: Purpose in Life (PIL) is a research area that focuses on the interactions between mind and body and the powerful ways in which emotional, mental, social, and spiritual factors can directly affect health. It links the belief that your life has meaning and purpose to a robust and persistently improved physiological health outcome—particularly as a way to treat dementia, spinal cord injuries, stroke, and immunological and cardiovascular issues that include but extend beyond the brain. While it has inspired significant research, the authors contend that PIL is underappreciated, given its potential importance and interest to both the clinical and lay communities.*

*"He who has a Why to live for can bear almost any How." – Friedrich Nietzsche*

**W**hy are we here? What is the meaning of life? Existential questions such as these are captivating and considered fundamental to the human condition. Religions, philosophers, and scientists alike have sought answers for the human race as a whole, but the search for meaning also can be personal. People's perception of their own purpose may have profound consequences not only for the legacy they leave behind for others, but for the quality and quantity of their own life. We've all heard anecdotes of people who have suffered tragedies only to persevere with newfound purpose and zest for life.

These stories are certainly inspirational, but what if meaning also could soothe inflammation or protect neurons? What if finding purpose in your life could reduce your risk of dementia or stroke? That's the focus of research into what is now called Purpose in Life (PIL).

Interest in PIL, or the "mind-body axis," has ancient roots, but the study of it in individuals has attracted medical researchers' attention only recently. Current research reveals exciting correlations between PIL and positive health outcomes in a multitude of body systems. In the 1940s Viktor Frankl introduced PIL to psychiatry. That Frankl was able to share his theory at all is nothing short of miraculous. He was a Jewish physician trained in both psychiatry and neurology who practiced in Austria when it came to be occupied by Nazi Germany. He survived three brutal years in various concentration camps, among them Auschwitz. He writes about his experiences in his magnum opus, *A Man's Search for Meaning*, where he also summarizes "logotherapy," a set of ideas that sustained him during the Holocaust and crowned his professional career.

As Frankl writes, "Man's main concern is not to gain pleasure or to avoid pain but rather to see a meaning in his life. That is why man is even ready to suffer, on the condition, to be sure, that his suffering has meaning."<sup>1</sup> Frankl emphasizes that this meaning is individual rather than general—people have to determine for themselves their mission in life. Compared to other psychologic doctrines that focus on looking back to the impact of past events, or inwardly through introspection, logotherapy looks to the future and to a person's will to do something meaningful with it.

As modern psychiatry began to evolve, the application of logotherapy to the treatment of psychiatric disorders, particularly those stemming from an “existential vacuum,” was met by some with skepticism. The main criticism was that a person’s perception of purpose had not yet been operationalized, measured quantitatively, or studied systematically. In an attempt to address this, two early investigators, James Crumbaugh and Leonard Maholick, created a psychometric scale in 1964 to assess PIL.<sup>2</sup> After scouring literature related to existentialism and logotherapy, they developed a twenty-question PIL scale. Their scale and its derivatives have since been used in various populations and studies as a metric for PIL.

Other researchers have sought to characterize the nuances of PIL. The general consensus is that PIL includes dimensions such as (1) believing that life has meaning or purpose, (2) upholding a personal value system, and (3) having the motivation and ability to achieve future goals and overcome future challenges. PIL is a philosophical concept, but that has not stopped scientists from exploring its practical, biological impact. In particular, it seems that having a sense that one’s life has purpose significantly supports the health of the central nervous system (CNS).

### **Protecting Cognitive Reserve**

“Dementia” describes a global constellation of symptoms: memory, cognition, and communication problems. It commonly affects older people (most often age 60 and up), but it is not a normal part of aging. Dementia occurs when brain cells, or neurons, are damaged and no longer network properly. Different types of dementia are characterized by how and where the cell damage occurs.

The most common form of dementia, Alzheimer’s disease, accounts for 60 to 80 percent of cases,<sup>3</sup> and is the focus of much PIL research. Among the neurons most affected in Alzheimer’s are those found in the hippocampus, a seahorse-shaped region of the brain associated with short-term memory. Through mechanisms still being elucidated, proteins called beta-amyloid and tau accumulate in neurons and lead to cell death and improper functioning. The damage in Alzheimer’s primarily manifests as memory loss, starting with recent events and then more remote experiences.

The huge personal and public health implications of Alzheimer’s have generated significant interest into ways to halt or prevent this illness. Other than generic advice to eat healthy, exercise, and

engage in intellectually stimulating activities, researchers cannot yet tout strategies to reduce Alzheimer's risk significantly. However, new work by Patricia Boyle and colleagues at the Rush Alzheimer's Disease Center suggests that PIL could be neuroprotective (brain-preserving). After following more than nine hundred older people at risk for dementia for seven years, they found that those with a high PIL were only half as likely to develop Alzheimer's disease than those with a low PIL,<sup>4</sup> even after controlling for demographics, depressive symptoms, personality vulnerabilities, social network size, and number of chronic medical conditions. Those studied were also 30 percent less likely to develop mild cognitive impairment, a condition characterized by minor cognitive deficits that could (but doesn't always) progress to Alzheimer's.<sup>4</sup>

Boyle's group further explored the relationship between PIL and cognitive change over time. For people without Alzheimer's disease, a high sense of purpose was associated with slower rates of age-related cognitive decline.<sup>4,5</sup> In another experiment, they looked at autopsy specimens of people who had been diagnosed with Alzheimer's and examined the amount of beta-amyloid and tau deposits in their brains. People who had a high PIL before death demonstrated better cognitive function, even in the presence of higher burdens of Alzheimer's-related protein accumulation.<sup>5</sup>

These studies suggest that PIL may have a protective effect on what is known as cognitive reserve. Researchers believe that people with more cognitive resilience ("cognitive reserve") at baseline are able to withstand more brain injury before developing neurologic symptoms. While the biological mechanism of this relationship is uncertain, it warrants more research.

### **The Heart of the Matter**

Although the heart and blood vessels are not technically components of the nervous system, the brain and the CNS are inextricably linked to cardiovascular function. The heart's activity is intimately monitored and regulated by the brain, such as when your heart races when you are anxious or excited. When you experience these emotions, the brain initiates a series of events that lead to the secretion of adrenaline, causing the heart to beat faster. As William Harvey, the great pathophysiological and father of investigations into the cardiovascular system, once said, "Every affectation of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart."<sup>6</sup>

Nor can the brain function without the heart delivering a reliable and timely supply of oxygen-rich blood. This delivery depends on vascular health. A stroke occurs when blood vessels fail to oxygenate brain tissue, whether because of hemorrhage or obstruction. Strokes may range from brief, reversible transient ischemic attacks to massive, deadly infarcts (brain tissue death stemming from a prolonged lack of oxygen and blood). Survivors can experience physical disability such as paralysis, stiffness, dizziness, and fatigue, and/or higher cognitive disability, such as changes in mood, judgment, personality, or speech. Strokes are the fifth leading cause of death across the lifespan and a major cause of disability in the United States.<sup>7</sup>

While a healthy diet and regular physical activity are ways to reduce the risk of stroke, research suggests that having a sense of purpose also may play a role in prevention and prognosis. In one study, Eric Kim and his team assessed the level of PIL at baseline in almost seven thousand older adults who had never had a stroke and followed them over a four-year period to determine stroke incidence.<sup>8</sup> They found that for each standard-deviation increase in PIL score, these adults reduced their stroke risk by 22 percent.<sup>8</sup> The association held even after they controlled for behavioral, biological, psychological, and sociodemographic factors.

Other studies have looked at PIL and the risk of heart attacks. After following 1,500 individuals with cardiovascular disease for two years, researchers found that a higher baseline PIL was linked to a lower risk of heart attack. Each unit increase of baseline PIL (on a six-point scale) was associated with a 27 percent decreased risk of having a heart attack within two years.<sup>9</sup> Once again, these findings were still statistically significant after the researchers controlled for behavioral, biological, psychologic, and sociodemographic factors.

Researchers also have looked at the association between PIL and mortality, particularly from cerebrovascular causes. One study found that a strong sense of purpose was associated with a 72 percent lower rate of death from stroke, a 44 percent lower rate of death from cardiovascular disease, and a 48 percent lower rate of death from any cause in a population of men after an average of thirteen years of follow-up.<sup>10</sup> This relationship held even after researchers controlled for perceived stress and cerebrovascular risk factors.

## Reducing Inflammation

Inflammation has been implicated in many diseases that afflict the brain and nerves: from autoimmune CNS diseases (such as multiple sclerosis) to neurodegenerative diseases that share high rates of cognitive impairment and depression (such as Alzheimer's and Parkinson's).

Inflammation is caused by activity of the immune system, which is made up of many cells and chemical mediators (called cytokines) that allow for communication between immune cells.

Although inflammation is critical for clearing infection and healing wounds, excessive or persistent inflammation can lead to tissue damage and disease. Inappropriate immune system activity is thought to contribute to serious CNS maladies such as stroke, epilepsy, traumatic brain injury, Parkinson's disease, multiple sclerosis, and Alzheimer's disease.<sup>11</sup>

A less obvious contributor to inappropriate immune system activity is psychosocial stress. Our body's response to stress is controlled, in part, by what is called the hypothalamus-pituitary-adrenal (HPA) axis. Psychosocial distress is communicated by the brain (specifically the hypothalamus and pituitary) to the adrenal glands, which are located on top of the kidneys. The adrenal glands respond by secreting a stress hormone called cortisol. In the short term, cortisol actually depresses the immune system. However, when we experience stress for prolonged periods of time, the immune system stops responding as sensitively to cortisol. The result: more immune system activity instead of less. Although the evolutionary basis for this phenomenon remains to be fully elucidated, scientists believe that it is the body's way of gearing up for potential injury or infection related to the stressor.<sup>12</sup> This leads to sustained low-grade inflammation and higher levels of pro-inflammatory cytokines, which paradoxically can aggravate or cause disease.

One example of PIL and a link to positive, objective changes in inflammatory response is interleukin-6 (IL-6), a cytokine that is important in the proinflammatory initial response of the immune system to a host of general stimuli, including bacterial and viral exposure. IL-6 is one of the mediators that lead to the activation of the HPA axis and subsequent cortisol release. Dysregulation of IL-6 has been implicated in multiple CNS diseases, including cerebrovascular and Alzheimer's diseases. In an experiment that looked at the blood levels of IL-6 and its receptor in a population of women, researchers found that higher PIL scores were associated with lower levels of the IL-6 receptor, which implies less IL-6 activity.<sup>13</sup> This relationship held when researchers controlled for

sociodemographic and health factors, and it suggests that PIL may be associated with a chronic calming effect on immune system activity.

Other studies have examined the impact of PIL on the inflammatory stress response. Lower levels of PIL are associated with increased sensitivity of the immune system, specifically IL-6, with repeated stress.<sup>12</sup> In other words, higher levels of IL-6 were detected in the bloodstream of participants with low PIL scores in each subsequent stressful exposure. Another study looked more generally at stress-related “transcriptomes.” A transcriptome is essentially a collection of all of the genes that are expressed in a specific system. In this case, the researchers explored which genes were active in immune cells in people with hedonic or eudaimonic well-being. As defined by philosophers, “hedonic” well-being represents the sum of the positive emotional experiences that an individual has experienced, and “eudaimonic” well-being results from an individual’s striving toward meaning and a purpose beyond self-gratification. Immune cells in people with hedonic well-being expressed more pro-inflammatory genes than did those in people with eudaimonic well-being.<sup>14</sup> This correlation implies that seeking purpose helps avoid a pro-inflammatory state, a positive step in fighting neurological diseases.

### **The Pursuit of Happiness**

It’s much easier to understand something tangible like a physical disease or medical treatment than something conceptual like purpose in life, and only in the past decade have researchers explored the connection between PIL and neurologic disease. Indeed, the pursuit of happiness receives a lot more attention in our culture than the pursuit of meaning or purpose. People strive for happiness, which is even considered a fundamental, inalienable human right according to the Declaration of Independence, and who could blame them? We feel happy when things go our way, and lower levels of stress and worry often accompany that feeling, at least briefly. It’s a feeling rooted in nature: Even animals experience a sort of happiness when their needs are satisfied.<sup>15</sup>

But to derive meaning and thus identify a purpose in life is uniquely human and requires self-reflection and evaluation. Although both happiness and meaning play into overall life satisfaction, it may be possible to have a happy life without meaning or a meaningful life without happiness. A purely happy person is primarily concerned with the present and instant gratification of their own

needs.<sup>15</sup> A person who pursues a chiefly meaningful life is more likely to contemplate the past or future and be concerned about others' well-being.<sup>15</sup> Meaningfulness is more enduring than happiness and can sustain people through periods of stress and suffering, as Frankl observed in the concentration camps.<sup>15</sup> Man's desire to find a purpose in life may even have played a crucial role in our development as a species, when we needed to band together against predators and the elements to survive.

The antithesis of happiness is depression. Depression is a disorder of mood characterized by persistent feelings of sadness, hopelessness, guilt, and apathy. Even Crumbaugh and Maholick's original paper commented on the apparent overlap between PIL and depression: "The tendency of highly depressed patients to show a loss of life purpose and meaning is clearly observable in the clinic."<sup>2</sup> People who are depressed have transiently lower PIL scores than people who are not, though it may be difficult to untangle whether depression decreases PIL or low PIL leads to depression.<sup>16</sup> But this difficulty does not muddy the correlation between PIL and health outcomes, as all of the studies that controlled for depressive symptoms still saw significant relationships. Depression is not the reason that people with low PIL have worse outcomes compared to those with high PIL.

What do we know about the relationship between high PIL and depression? Unfortunately, it seems that a strong PIL does not protect the very old from developing depression over a five-year period.<sup>16</sup> However, another group of researchers looked at teenagers, who, like the very old, are prone to depression. Instead of specifically looking at PIL, this research group explored the impact of hedonic vs. eudaimonic well-being on the development of depression. Research has shown that teens who were more eudaimonic (striving toward meaning and a purpose beyond self-gratification) had lower rates of depression one year later compared to those with hedonic well-being.<sup>17</sup> So in addition to improving nervous system disease outcomes in older people, meaningful and purposeful activities may improve the mental health of younger populations.

Additionally, we can draw some parallels between meaningfulness and peaceful feelings that religion can bring. Many people experiencing a tragedy or crisis turn to faith to find comfort, support, and answers. It is possible to endure almost anything as long as we can identify a greater purpose, and for some, religious doctrines and beliefs provide reasons and reassurances for

suffering. However, research suggests a complicated relationship between one's religious beliefs and PIL, one that differs depending on how clearly and confidently an individual holds to their self-concepts of the world and their place in it. Researchers have shown that if a person has a low self-concept (for example, "My beliefs about myself often conflict with one another"), religion can return their PIL to baseline.<sup>18</sup> For those with a relatively high level of self-concept (for example, who endorse statements such as "I have a clear sense of who I am and what I am"), their level of PIL was unaffected by their degree of religiosity, demonstrating that PIL and religion are separate and independent phenomena.<sup>18</sup> This is consistent with the fact that PIL is self-defined and therefore subjective, and that the PIL metrics do not ask any specific questions about religiosity.

### **The Millennial Generation and Beyond**

Our current societal climate is particularly primed to embrace PIL. The Millennial generation is just coming into its own, and its members may not be as entitled and narcissistic as they are commonly portrayed. A study by the career advisory board at DeVry University looked at Millennials' attitudes about employment issues, based on input from hiring managers. The study found that 71 percent of Millennials ranked finding work that is meaningful as one of the top three factors determining their career success, and 30 percent of Millennials ranked it as the most important factor.<sup>19</sup> Millennials are willing to make less money and work longer, nontraditional hours, as long as their work is personally meaningful.

This newfound cultural emphasis on meaning should revitalize research into PIL. While research has suggested significant relationships between PIL and positive health outcomes, we cannot yet make any sweeping declarations about PIL being responsible for those outcomes. This is primarily because PIL studies that prove causation are difficult to design. But scientists can explore other aspects of PIL, such as its natural history. Is PIL a constantly shifting quality that changes throughout life? On what time scale? One recent study in a very old population demonstrated that PIL decreases over a five-year period, especially in women and/or people with depression.<sup>16</sup> But the researchers looked at PIL only at the beginning and the end of the study period. It could be insightful to see how PIL changes on a more regular basis and how that relates to health outcomes.

Another interesting avenue is to identify specific interventions to increase someone's purpose in life. A high PIL has been linked to the pursuit of community-oriented goals, as well as to higher levels of physical activity.<sup>20,21</sup> Although the directionality of these relationships cannot be determined from studies thus far, they are important jumping off points for future research.

Pharmaceutical treatments for any ailment that affects our minds and bodies absolutely have their place in healing, but they also can include significant potential side effects. Physicians should consider whether they are too quick to be pill pushers when they could be PIL promoters. Identifying a purpose to life can have profound implications in overall life satisfaction and health, as it motivates and drives us even in the face of difficulties and hardships. PIL appears to be biologically wired into our thinking and necessary for optimal health, a feature of our brain that defines each of us individually and simultaneously is a unique characteristic of the human condition.

## **Bios**

**Adam Kaplin**, M.D., Ph.D. is the chief psychiatric consultant to the Johns Hopkins Multiple Sclerosis and Transverse Myelitis centers and has a joint appointment as a clinician-researcher in the departments of psychiatry and neurology at Johns Hopkins, where his research focuses on immune-mediated mechanisms of depression and cognitive impairment in CNS autoimmune diseases. Kaplin is on the board of medical advisors to the Montel Williams MS Foundation and is a medical advisor to the Cody Unser First Step Foundation, the Transverse Myelitis Association, Johns Hopkins Project RESTORE, and Race to Erase MS (formerly the Nancy Davis Foundation for MS). He is the inventor and co-developer of [Mood 24/7](#), a site that employs mood-tracking technology, and also the CEO and president of Altimmune, a startup biotechnology company specializing in developing aggressive new therapies to put autoimmune diseases into long-term remission. Kaplin graduated from Yale University before receiving his M.D. and Ph.D. from the Johns Hopkins University School of Medicine.

**Laura Anzaldi** is a rising third-year medical student at the Johns Hopkins University School of Medicine. She graduated as the salutatorian from the University of Maryland, Baltimore County, in 2013, majoring in computer science, biology, and bioinformatics. She has not yet decided on a

medical specialty, but her research interests focus on the intersection of technology and medicine. Anzaldi is particularly interested in developing software applications to enhance clinical workflow, facilitate research, and improve patient care and education.

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