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From Witch Hunts to Autoantibodies: Overcoming Psychogenic Stigma to Uncover the Molecular Cause of Autoimmunity

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FROM WITCH HUNTS TO AUTOANTIBODIES:
OVERCOMING PSYCHOGENIC STIGMA TO UNCOVER THE MOLECULAR CAUSE OF AUTOIMMUNITY

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Introduction

Struggle to Catch Up with the Autoimmune Epidemic

Susannah woke up one morning in a hospital bed. While this would be an alarming experience for anyone who can't remember the events prior to landing oneself in an unknown medical facility, it was all the worse for Susannah who's first groggy sight upon opening her eyes was a bracelet strapped to her own wrist labeled "flight risk." As the panic set in and she attempted to flail about in the bed, she was only met with the terrifying freeze of paralysis. She abruptly became aware of the straps restraining her to the bed, cutting into her arms, physically restricting her from gathering more information on where she was, how she got there, and why she was there. Seconds later she tried to cry out for help, only to realize she had no voice, her throat choking on thin air through attempted screams for even the slightest sign of familiarity. Little did she know, Savannah was under close guard by hospital staff who at the moment were combing through stacks of medical records detailing the hallucinations, delusions, memory loss, and violent outbursts Susannah had been experiencing over the last month, searching for any thread tying her bizarre set of symptoms together. Despite starting an exciting journalism career for the *New Yorker* and anxiously pursuing her first serious romantic relationship just weeks prior, Susannah Cahalan had suddenly woken up to her worst nightmare. Her recollection of her personal dissention into a month of madness described in her book "Brain on Fire" is truly haunting in its implications for all of us.

In 2009, Susannah Cahalan was the 217th patient to be diagnosed with anti-NMDA receptor encephalitis in the United States (Cahalan, 2012). While this disease was only just identified in 2007 as an autoimmune disease which causes acute brain inflammation, it doesn't mean it hasn't been wreaking havoc upon lives for decades before its official naming (Ahmad et al., 2017). After a month of personal hell, Susannah herself was prompted to ask the question we are all wondering, "how many people throughout history suffered from my disease and others like it but went untreated?" (Cahalan, 2012, p. 221). The answer is not optimistic as one would hope, as Cahalan explains, "even though the disease was discovered in 2007, some doctors I spoke to believe that it's been around at least as long as humanity has" (Cahalan, 2012, p. 221). Even more problematic is the fact that although anti-NMDA receptor encephalitis was identified as an autoimmune disease two whole years prior to the day Susannah encountered symptoms, its recognition and etiologic understanding throughout the medical community did not save her from a lengthy month of misdiagnoses. The grueling thirty one days consisted of countless doctors dismissing her symptoms, arguing that they were caused by psychological phenomenon, blaming it on psychosis, and completely ignoring the possibility that she may actually be suffering from a physiologic disease.

Although Susannah Cahalan's tragic story is becoming more widely known through its publication as a gripping autobiographic *New York Times* bestseller in 2012 entitled *Brain On Fire: My Month of Madness*, this does not translate into popular awareness of similar widespread injustices occurring in our healthcare system today. In fact, many of us would prefer to turn a blind eye toward the terrifying reality that science

and medicine may not be prepared to treat us when the inevitable moment comes that our bodies decide to rebel against us. I, like many other Americans who have an unwavering faith in our advanced medical system, considered Susannah's story to be a tragic, rare example of one unlucky patient whose complex symptoms fell through the miniscule cracks in our now approaching foolproof protocol to obtaining a medical diagnosis. As a scientist and aspiring medical researcher myself, I spent the majority of my life subscribing to the common belief that doctors are the omniscient beings with all of the answers that their patients seek. Sure, they make mistakes from time to time, as this, no matter how annoying, is an unavoidable truth of the human condition. However, even the most complex, mindboggling set of unexplained symptoms could never defeat 12+ years of secondary schooling, a plethora of biomedical research, and hierarchy of medical specialists that each doctor wields in their bulletproof arsenal. At least, that's what I used to think. Now, after personal experience and academic research, I have never in my life been so eagerly able to admit that I was wrong.

Susannah is just one of the thousands of women each year who wake up one morning trapped between a debilitating illness and a medical system polluted with a centuries long gender bias that is not only ill-equipped to treat them, but at times even unwilling to believe them. If you subscribe to the same blind faith in science and medicine that I so recently began to question and are doubtful of this preposterous statement that challenges the very discipline that saves countless lives every year, firstly, I don't blame you. Secondly, I strongly suggest you investigate the perplexing statistics and testimonials that begin to unravel the mystery behind the autoimmune epidemic in

the United States. While many would like to brush over the fact that our medical system may not be prepared to diagnose and treat every demographic of society with the same empathy, diligence, and success, we owe a deeper investigation to those who have experienced firsthand the wrath of medicine's engrained bias. For those of us who have had the privilege of escaping medicine's limitations, we may still be clinging to the assumption that whenever the inevitable moment strikes that our bodies decide to turn against us, doctors will undoubtedly be able to put us back together. For those among the 9.8 million women in the US diagnosed with a common autoimmune disease, the inequity and ill preparedness of healthcare may come as a severe slap in the face (Lahita & Yalof, 2005).

Autoimmune diseases are one of the most striking examples of the inequity of our healthcare system, as their incidences in women comprise 78% of the autoimmune patient population, but even more concerning, so do their misdiagnoses (Fairweather & Rose, 2004). To illustrate, it takes a female autoimmune patient to see an average of six doctors before obtaining the correct diagnosis, over the course of five years in half of all cases (Nakazawa, 2008). Additionally, before a correct diagnosis is finally within grasp, it is likely the patient may be labeled a "hypochondriac" or "chronic complainer" (Dusenbery, 2018). In fact, 45 percent of patients with autoimmune diseases have been labeled as hypochondriacs in the earliest stages of their illnesses, according to a survey by The American Autoimmune Related Diseases Association (AARDA, 2001). This can lead to unnecessary long-term patient suffering, and also severe psychological damage. Repeated dismissal can influence feelings of isolation, paranoia, and worst of all

hopelessness that there isn't a treatment that will ever work, all while patients' physical symptoms worsen. Moreover, it is a vicious cycle so to speak in that many autoimmune symptoms are worsened by stress. The increased stress of being repeatedly stripped of a diagnosis can induce the release of stress related hormones and other compounds such as cytokines, which in turn increase the detrimental inflammation that can compound autoimmune patients' symptoms (Stojanovich & Marisavljevich, 2008).

Antiphospholipid antibody syndrome (APS) and anti-NMDA receptor encephalitis (ANRE) are both diseases that exemplify the public health issue of misdiagnosis of autoimmune diseases. They are in a disease category along with nearly one hundred others that have only started being understood on a molecular level during the past twenty years (Nakazawa, 2008). However, this recent understanding is not due to the rarity in instances of contraction as one may first think. To illustrate, as many as a quarter of women with recurrent miscarriages end up being diagnosed with the autoimmune disease antiphospholipid antibody syndrome, making it more prevalent in women than leukemia and ovarian cancer combined (Nakazawa, 2008, p. 23). Our lack of previous knowledge regarding these two diseases can be attributed, however, to the fact that both disorders have historically been misdiagnosed by the medical community as either hysteria or demonic possession (Uszkalo, 2012). As diseases that are disproportionally suffered by women and ones that commonly cause complex neurologic symptoms such as hallucinations and memory loss, they both exhibit the main criteria previously affiliated with the hysteria diagnosis. As we have witnessed from the story of Susannah Cahalan who presented symptoms of anti-NMDA receptor encephalitis after its

official classification as an autoimmune disorder, yet still had to endure a month of excruciating pain prior to alleviation via correct diagnosis, other patients still experience the wrath of stereotypes affiliated with these diseases on their own quest to a cure (Cahalan, 2012).

Despite being extremely vulnerable to the current fad of psychogenic diagnosis, both antiphospholipid antibody syndrome and anti-NMDA receptor encephalitis have well understood molecular autoimmune pathologies. It is crucial to understand the basis of these conditions as they are epitomes of molecular biology combating the pseudoscience of hysteria and a medical system polluted with bias. Thus, I will explore antiphospholipid antibody syndrome and anti-NMDA receptor encephalitis's etiologic transition from psychologic to its correct physiologic explanation from a molecular biology perspective. I will then apply this research to another, more poorly understood condition, fibromyalgia, a disorder that is currently classified as "psychogenic," yet is hypothesized to be autoimmune. It still isn't well understood, partly due to the fact that patients still face the stigma of hysteria when seeking a diagnosis. The purpose of this thesis is to combine biological and historical perspectives of medicine to explore the dangerous implications of labeling diseases as psychogenic, as this term often is merely a resurrection of the gender-biased concept of hysteria that impedes the diagnosis process on a daily basis. The dismissal of these conditions' true etiology illuminates the resurgence of hysteria as an acceptable medical diagnosis, revealing the urgency to emphasize the molecular forces underlying previously misunderstood diseases of anti-phospholipid antibody syndrome and anti-NMDA receptor encephalitis. Perhaps this

return to an enriched understanding of the biological phenomenon of autoimmune diseases will refocus the medical communities' efforts in further investigating the molecular causes of unexplained symptoms of fibromyalgia, rather than categorizing it as a psychogenic condition.

History of Hysteria: Medicine Becoming a Profession

Although a primarily scientific inquiry into the background of two recently understood autoimmune diseases anti-phospholipid antibody syndrome (APS) and anti-NMDA receptor encephalitis, it would be a disservice to neglect the historical changes in attitudes toward women, toward medicine, and toward the understanding of disease itself that was influenced by the hysterical explanation of these diseases. Despite questionable scientific accuracy, the richness of history of surrounding hysteria throughout its 4,000 documented years of prevalence cannot be denied (Tasca et al., 2012). It was in fact, the first mental disorder described to afflict women in the second millennium BC, with Hippocrates being one of the first to document the term, taking inspiration from the Greek word for uterus, hystera (Gilman et al, 1993). Some even argue that the idea of hysteria dates far prior to the ancient Grecian Father of Medicine. Ilza Veith, in her published history of hysteria, noted that although not given an explicit name at the time, the Egyptian papyri describes medical disturbances resulting from the movement of the womb (Veith, 1965).

While our modern definition of this medical diagnosis does not specifically refer to afflictions of the uterus parallel to the ancient understanding, Western medical practice

did attribute symptoms of anxiety, dissociated sensory loss, shortness of breath, and insomnia to "a wandering uterus" through the nineteenth century (Freidman, 2010). It does not take much research however, to realize that the scientific validity of hysteria has been debunked on countless occasions since its heyday in nineteenth and early twentieth century modern medicine (Gilman et al., 1993). Now a diagnosis deemed unacceptable within the medical community, there have been multiple studies conducted whose aim is to retroactively explain the symptoms of patients previously diagnosed with hysteria.

It has been found that many previous hysterical diagnoses were in fact presentations of various autoimmune diseases. To illustrate, one 2010 study looked at a pool of females experiencing symptoms commonly associated with hysteria symptoms. It was found that a "large percentage [of hysteria diagnoses], varying from 30-50%, ultimately were explained as the result of organic lesions. Neurological patients were found to have [multiple sclerosis] or unusual, but clearly organic, forms of epilepsy. Gastrointestinal symptoms were explained by inflammatory bowel disease. Systemic lupus erythematosus and other autoimmune disorders became apparent. Metabolic derangements became identifiable, and these, in retrospect, explained the earlier symptoms" (Freidman, 2010, p. 2). Unfortunately, even as these corrective studies are made, women such as Susannah Cahalan still experience dismissal of unexplained neurologic symptoms as the ideology of hysteria lives on.

How is this possible? How can such an obvious gender gap still exist within our healthcare system in times of prolific twenty first century technological medical advances and bounds made toward gender equality? The answer is largely lies in the murky history

of medicine becoming a profession. There is a two-fold phenomenon in this history that contributes to the neglect of female dominated diseases such as autoimmune disorders. Firstly, it is widely acknowledged that there is a knowledge gap in female conditions. One reason for this is that the professional medical system was largely male-dominated until the late twentieth century. Despite women being the predominant healers of the colonial era, the prevention of women from attaining formal medical education restricted them from the professional market until 1847, when Elizabeth Blackwell became the first female to be admitted to medical school (More, 1987). The increase in females in professional medicine was not as steep as one would expect after this historic date. Due to educational reform in 1910 called for by the American Medical Association, a large majority of medical schools educating women and minorities were closed, resulting in a puny 2.9% of medical graduates being female in 1915 (Flexner, 1910). Growth remained relatively stagnant throughout the 50s, with only 6% of the physician workforce being comprised by women in 1949. Statistics slightly improved with the passing of Title IX of the Education Amendments, and by 1990, the number of females in the physician workforce reached 17% (Staff Care, 2015).

Even after this historic era, when the number of female doctors began to rise in medical schools and in practice alike, men still maintained the majority of positions of authority. These positions included directors of hospitals and research institutions, those who have the most power regarding where research funding is appointed. Bernadine Healy, a revolutionist in the study of women's health, was appointed as the first female director of the National Institutes of Health in 1991. Before her spearheading of The

Women's Health Initiative, a $625 million effort to study the causes, prevention, and cures of diseases that affect women at midlife and beyond, research funds were directed to the causes deemed most urgent by the white males in power at the time. Thus, studies were, even comically at times, exclusive of disease categories such as autoimmune diseases that are suffered by majority women. For example, a Rockefeller University study funded by the NIH in the sixties aimed to observe how breast and uterine cancers were affected by obesity. The comical aspect of this study is illuminated when looking at its pool of study subjects, which shows that not a single woman was enrolled (Dusenbery, 2018). In modern times, is easier to maintain a lighthearted mindset regarding this phenomenon of the history of medicine, as recent studies have shown efforts to close the knowledge gap in women's health have been extremely successful. However, one group of diseases not showing an improvement in the knowledge-gap have been autoimmune disorders. Why does this disease class lag behind the others in its biomedical research and understanding within the medical community? To answer, we must again turn to the history of medicine as a profession.

Despite the gender knowledge gap being a large contributor to the problem of misdiagnosis of autoimmune conditions, I would like to focus on a second phenomenon of the early days of medicine becoming a profession. This anomaly is that diseases with inexplicable symptoms experienced by majority women were commonly dismissed by the male-dominated medical community as "hysteria," leading to a distrust of female autoimmune patients ever since the concept's indoctrination in medicine. While hysteria eventually came to be known as an affliction of both sexes by Sigmund Freud, hysteria

clearly has a gender stereotype engrained within the very being of its name, as it is derived from the Greek word for uterus, *hystera* (Tasca et al., 2012). This diagnosis has carried a negative connotation since its first description in the second millennium BC, morphing by the end of the nineteenth century into one that attributes the source of women's symptoms as purely psychological (Tasca et al., 2012).

In our increasing age of technology, doctors can frequently give an accurate diagnosis to a patient after just a few objective tests. When symptoms are not as clear, and these objective tests and technological scans do not immediately reveal concrete results, doctors often take the easy way out which is to blame the symptoms on the mind. While the concept of "hysteria" has proven to be a pseudoscience, with no basis in physiological fact, it has not stopped the idea of the cause of illness being blamed on the mind. Essentially, the concept of hysteria, while a seemingly outdated and sexist concept of the past at first glance, still runs rampant in the medical community today, just renamed as the less overtly problematic terms "medically unexplained symptoms" and "psychogenic diseases." The jargon has changed, but the ideology remains apparent for diseases presenting with complex neurological symptoms not quickly explained with objective tests. Furthermore, the stereotype that women are more prone to these unexplainable diseases of the mind than men has carried on far past the use of the term hysteria. In fact, patients today still face challenges in seeking a diagnosis and treatment of certain autoimmune diseases especially, and they are the epitome of a medical system hindered by a sexist, pseudoscientific ideology far overdue.

I

Antiphospholipid Antibody Syndrome

Demons in the Womb

15th century Europe was a barbaric time in many respects of medicine, but it was especially so for women experiencing infertility. Stories of patients experiencing infertility or spontaneous miscarriage are described in horrifying detail in *The Malleus Maleficarum* by Heinrich Kramer and James Sprenger, discredited Catholic clergymen of the era. This book, which translates most commonly to "The Hammer of Witches," was published in 1487 in Speyer, Germany. Despite the fact that the unethical book was condemned by the top theologians of the Inquisition at the Faculty of Cologne because of its clear contradiction of the "true" Catholic doctrines of demonology, the book's attributions of infertility to witches and demonic possession became common household beliefs. To most people's astonishment today, *The Malleus Maleficarum* even became the second-bestselling book in 15th century Europe. It retained this popularity for 200 years after its publication, falling in sales only behind the Bible itself. Because of this popularity, *The Malleus Maleficarum* had one of the strongest influences on cultural views of infertility and spontaneous miscarriage that informed medical practices of the times (Sprenger, 1487).

Documentation in *The Malleus Maleficarum* of the treatment of women suspected of being infertile or those who had experienced spontaneous miscarriage are horrific. For

example, the text describes “a most notorious witch, who could at all times and by a mere touch bewitch women and cause an abortion” (Sprenger, 1487). One specific story was told about a pregnant wife of nobleman who was threatened not to leave the castle in case of coming across this fearful witch. However, she disobeyed recommendations and was tempted into attending a gathering among her friends. Upon entering this gathering, a woman approached the pregnant wife, and gently touched her stomach. Suddenly, the pregnant wife, “felt the child moving in pain.” This pain continued and increased to unbearable severity of cramping. At the alarm of all of her friends, a heavy flow of blood began to expel, and the pregnant woman was rushed home for treatment from the castle’s midwife. However, *The Malleus Maleficarum* graphically reads that any medical intervention would have been too late,

> “‘Alas! you have already lost your child.’ And so it proved when her time came; for she gave birth, not to an entire abortion, but little by little to separate fragments of its head and feet and hands. And the great affliction was permitted by God to punish her husband, whose duty it was to bring witches to justice and avenge their injuries to the Creator” (Sprenger, 1487).

This is just one of the many incidences of this popular ancient text attributing women’s’ afflictions of infertility and spontaneous miscarriage to witchcraft. More generally, it inspired a popular belief in the 15th century that women who were repeatedly unable to conceive were possessed by the devil. It contains lengthy passages referring to

the “Incubi,” a demon in male form who seduces sleeping women, perpetually making their reproductive organs “useless.” Throughout the entire lengthy document there is never a single attribution of infertility to a physiological cause, instead one finds repeated assertion of the devil’s intervention in “poisoning the seed, or cooling the ardor between man and wife” in all patients suffering from devastating infertility (Sprenger, 1487).

After the text explains the role of demons in matters of infertility, it goes on to place further blame on female patients themselves. For example, it asserts that women are more susceptible to demonic temptations through “manifold weaknesses of their gender.” Women unable to conceive even after devoted prayer to St. Anne, patron saint of the infertile, were almost lucky if they were accused of demonic possession (Gillman, 1993). At least these women were subjected to further religious purification, unlike those actually accused of being witches themselves. Being condemned for witchcraft was definitely less fortunate, as it was as equivalent to a death sentence as the diagnosis of stage four cancer is today. At the encouragement of the *Maleus Maleficarum*, witches were frequently burned at the stake or drowned, all because of underlying medical conditions preventing them from baring children.

While the *Maleus Maleficarum* promoted burning these shunned “witches” at the stake or subjecting them to lengthy exorcisms, those who avoided this fate were instead forced into torturous “cures” for their infertility by medieval physicians. The fact that these patients, already traumatized from the heartbreaking and physiologically taxing reality of losing their pregnancy, were willing to undergo such agonizing treatments in order to conceive speaks to just how dire the situation actually was for those suffering

from infertility (Gillman, 1993). These excruciating treatments are documented in a 12th century book called *The Trotula* which translates simply to “Gynecology.” This popular reference novel for medieval physicians recommend choking the necks of women suffering from “uterine suffocation.” This “treatment” was thought to return the womb its correct anatomical position in the body conducive for carrying a child (Nezhat, 2012). In addition to pain, women also went to unthinkable lengths of discomfort in order to be proved fertile. A common one was drinking the urine and blood of pregnant animals. According to a 15th century conglomeration of medical potions entitled *The Liber de Diversis Medicinis*, "If a man wishes that a woman will conceive a child soon, take catmint [catnip] and boil it with wine until it is reduced to a third of its original volume, and give it to them to drink on an empty stomach for three days” (Ogden, 1939). Obviously none of these methods were rooted in scientific fact, and those quietly suffering from yet-to-be-identified diseases often turned to these unfounded “cures” just in order to escape persecution for witchcraft.

Clots of Doom

Jan Pankey was no stranger to the extreme stress of medical emergencies. Although frequently faced with the stress of making life or death decisions on behalf of her heartbreakingly young patients, she handled even the most confounding of medical enigmas with calmness and ease. She has woken up every day for the past 20 years to continue her dream job at Oakland’s Children’s Hospital where she exuded confidence in

the operating room as a pediatric and neonatal anesthesiologist. Her experience in combating challenging medical situations with a calm, cool, and collected attitude did not stop there. Jan maintained in an even more high-stakes position as a proud member of a physician-run medical team who completed missions overseas in helping children in developing countries receive lifesaving operations unattainable from their local medical facilities. With this extensive of training in the most critical of emergencies, one could not think of single a medical scenario that could even begin to phase Jan Pankey. At least that's what she thought at the time. However, one summer night in 2003, Jan's entire world would be turned upside down, and for the first time in her entire life, she was completely stripped of her ingrained confidence that our medical system could do anything to save her (Nakazawa, 2016).

On that fateful night in 2003, Jan awoke just before midnight in an Idaho hotel room, a midway stop on her and her husband's road trip to Montana for vacation. She was suddenly thrust out of her sleep by an intense burning sensation that took over her entire body. Upon trying to stand up, Jan realized that she couldn't even feel the floor beneath her feet. Somewhere between the agonizing pain and her struggle to fill her lungs with the shallowest of breaths, she had passed out and woke up to her husband soundly sleeping in the hotel bed. Jan used every last drop of strength to crawl to the side of the bed to wake him up for help, meanwhile the sensation that she was being burned alive from the inside out was increasing with such rapidity that the thought that these could be her last moments on earth definitely crossed her mind. Jan's husband David woke up to the horror of seeing his wife writhing on the ground in pain, a complete shock to her

completely healthy state just hours prior. In fact, Jan lead such a healthy lifestyle that in her yearly physical she was above-average in most measures predictive of relative health compared to her female peers also in mid-life stages. After all, the reason for Jan and David's trek to Montana was to complete a hundred-plus mile bike ride through Glacier National Park. A doctor himself, David struggled to find any reason that his wife, the prosopopoeial of an active lifestyle, would be suddenly overcome with such debilitating pain.

As the light of the rising sun began to spill through the curtains of the hotel room, Jan's bewildering symptoms began to subside. Against her husband's wishes, they piled into their station wagon, strapped the bikes on top, and forged on to reach their final destination of Glacier National Park. As they crossed the border into Montana, black smoke from the approaching wild-fires began to spill into the car. They had been raging for days, but Jan and David had made the pact that this natural disaster would not ruin their trip which had required a whole year of planning. However, minutes after the smoke became so thick to impede visibility, Jan's symptoms returned with a vengeance. Despite much reluctance from Jan herself, David drove her to the nearest emergency room for evaluation.

X-rays, urinalysis, and sets of basic vitals could not reveal anything out of the ordinary despite some slight shading around the lungs above the left half of Jan's diaphragm. The ER doctor did not seem phased by the slight anomaly and chalked the whole episode up to a flare-up in Jan's gastroesophageal reflux disease which was causing muscle strain along her chest wall. A dose of Prilosec should do, he thought.

Once again, Jan's stubbornness combined with her experience as a medical professional imparting a tendency to be unphased even by severe symptoms, convinced her husband to continue on their journey. They started the first leg of their cycling loop the next morning. All was well until something broke Jan's attention from the breathtaking views of the national park. From the tiny, innocuous hole of the IV insertion point administered the day prior in the ER grew a sinister red line that crawled all the way up her arm and radiated heat to the touch. Not one to ignore the signs of something as serious as a blood clot, Jan and David prematurely ended their trip and rushed home to get to a medical center they trusted.

In the ER of their home city of Albuquerque, New Mexico, the Pankey's witnessed one of the most alarming X-rays either of them had ever seen in their combined 40 years in the medical field. Jan's lung scan revealed that over 50% of oxygen flow to her lungs had been cut off by pulmonary emboli. Further ultrasound revealed that her entire right leg was suffering from deep vein thrombosis, occluding blood flow from ankle to groin. Furthermore, small chunks of this enormous clot were breaking off at alarming rate and traveling straight to the lungs where they cut off more and more of Jan's blood supply. Finding no cause for the clots, after six days in the hospital, Jan was discharged with doses of blood thinners large enough that she began to develop deep purple bruises to the softest of touches. This high dose of blood thinners did Jan no favors, however, and within another week she was back in the hospital again. This time it was from a clot so large that as it dropped into her chest, it made the sound of the beat of a drum that reverberated through her lungs with an ominous thump.

After inserting a blood filter in the inferior vena cava of her right leg to prevent the emboli from traveling to her heart and lungs, Jan was once again cleared to leave the hospital. In addition to her life-threatening clots, after this stint in the hospital she had also began to experience a confusing set of symptoms that included extreme fatigue, shortness of breath at the most harmless activities such as walking up one flight of stairs, and finally, a mysterious "brain fog" that caused forgetfulness and haziness of the mind throughout the day. She went to see several different general physicians and internists who dismissed these troubling symptoms as side effects of her anticoagulants or just as Jan being too hyper-vigilant about her own condition stemming from her own experience as a doctor. However, despite this repeated dismissal, Jan Pankey knew something was deeply wrong inside her body, and she was not going to wait for the rest of her blood to gelatinize into sludge before anyone would take her seriously.

As karma would have it, Jan ended up at a conference for work held by a physician who studied rare clotting disorders. His name was Dr. Alex Spyropolous, and Jan immediately knew he could be the answer she had been waiting for. She became his patient shortly after the conference, and once her blood work hit Dr. Spyropolous' desk, Jan heard the words she had been so veraciously seeking,

"I think I know what you have, Jan. Your blood work shows the exact biomarkers indicative of antiphospholipid antibody syndrome" (Nakazawa, 2016).

From Demons to Antibodies

While seemingly disparate victims of unexplainable medical maladies of their times, Jan Pankey and our patient from the witch trials in the early 15th century share a startling multitude of commonalities. First, they could both be victims to one of the latest named autoimmune diseases to be sweeping our nation: Antiphospholipid Antibody Syndrome (APS). Secondly, despite living centuries apart, no one in their times could immediately pinpoint the cause of their baffling symptoms with any semblance of accuracy. Finally, they both share an additional similarity in the distressing way in which they were treated following the onset of their debilitating disease. They were both targeted, cursed, condemned, or told that they were psychologically crazy after accepted institutions of the times could not find answers to their condition. For example, our 15th century patient who experienced lifelong infertility and spontaneous miscarriage in multiple pregnancies was encouraged seek answers from religious figures. After countless hours of prayers were not answered, and this "cure" of religion deemed ineffective, she and her husband were shunned from the church, their relationship accused of being tainted by the devil's prowess. Jan Pankey, over 500 years later, was turned away by physicians and told that her condition was all in her head despite clearly apparent physiological symptoms. Her own institution of medicine had dismissed her as a hypochondriac. Clearly, something underlies the condition of antiphospholipid antibody syndrome that has lingered from its occurrence in medieval times to impede its diagnosis today. It would be years before this devastating condition would be understood on a molecular level, transformed from a stigma of demonic possession to its accepted reputation as one of the most common autoimmune diseases in today's society.

Antiphospholipid antibody syndrome is also known as Hughes Syndrome, named after the doctor who in 1983 noticed his patients experiencing an eerily similar pattern of symptoms as the more well-known autoimmune disease lupus erythematosus (Anderson et al., 1989). However, unlike lupus, this syndrome was characterized by phospholipid antibodies. At the impetus of this discovery by Hughes, the diagnosis of APS then split from lupus into its own category in the same year. Because it is a rarely discussed condition, many assume that its frequency of incidence in the US population is fairly low. Unfortunately, this assumption could not be more incorrect. In fact, one in five women who've "suffered blood clots in the legs or strokes in the prime of life test positive for APS, making it more prevalent in women than leukemia and ovarian cancer combined" (Nakazawa, 2016). It does not discriminate against pregnant women either. To illustrate, as many as a quarter of women with recurrent miscarriages end up being diagnosed with the autoimmune disease. It is plausible that our patient from the 15th century suffered undiagnosed from the same common condition. Despite its lack of publicity and fundraising for further research, antiphospholipid antibody syndrome is definitely a public health issue whose prevalence only increases as the years pass.

If this disease is so common, why did doctors blatantly miss this diagnosis for our two patients discussed? It comes as absolutely no surprise for our patient living in medieval Europe, as the lack of scientific knowledge and technology prevented the correct diagnosis of conditions as simple as the common cold. Because of this lack of knowledge and resources, they used other disciplines to attribute diagnoses to diseases, especially religion. Religion was so intricately woven into every detail of life in that

century that it was often used as an explanation for mysterious medical symptoms. That is why our patient's symptoms were blamed on everything from the demonic possession to witchcraft; medieval physicians used the very little information they had to do their best in diagnosis, most of which had been steeped in teachings of the Catholic Church for decades (Gillman, 1993). As we have seen, this became very problematic for patients experiencing infertility or repeated spontaneous miscarriage. Because infertility had such a strong religious affiliation, infertile women were passed off as being punished by God for their sins, or more problematically, shunned for being possessed by the Devil. We now know that many women with this medical problem, as many as a quarter in fact, could have been silently suffering from antiphospholipid antibody syndrome while being demonized by those very closest to them.

The same cannot be said about our modern patient, Jan Pankey. We have come so far in improving our medical knowledge and advancing technology since the 15th century that there is no excuse for how this diagnosis slipped through the fingers of six out of the seven doctors Jan Pankey saw. While it is relatively rare for extremely active, healthy, middle-aged women to develop pulmonary emboli, much less antiphospholipid antibody syndrome, the disease is still more common than rare cancers like leukemia. Thus, no excuses exist for patients to go months without proper diagnosis.

In reality, it was not the rarity of the disease impeding the diagnosis, but the fact that this disease, like many autoimmune conditions, has only been studied on a large scale in the last twenty years (Gezer, 2003). Unfortunately, the murky history of this disease rooted in sexism and witchcraft lingered far too long, preventing a scientific drive

to uncover a true physiologic cause. On the positive side, we now are able to debunk the pseudoscience that once served as the widely accepted explanation for antiphospholipid antibodies' common symptoms such as migraines, limb spasms, shortness of breath, and recurrent miscarriages. The scientific community has determined the molecular etiology of this syndrome to be autoimmune, and while this has overthrown previous attributions of demonic possession, a negative stigma still surrounds this disease. It is crucial to expand our knowledge of the physiological cause of poorly understood medical conditions in an effort to improve the suffering of those who cannot achieve an efficient diagnosis of antiphospholipid antibody syndrome.

What is APS?

Simply stated, autoimmune diseases occur when our bodies make the critical mistake of perceiving self-antigens as threatening foreign bodies. The result of this error is detrimental inflammation and self-destruction of our own body tissues. Which tissues and organs are affected, however, depends on the specific autoantibody that is created by our immune system contingent on the particular autoimmune disease the individual develops.

Specifically, anti-phospholipid antibody syndrome affects the clotting properties of blood through the presence of one or more of three distinct antibodies: cardiolipin, anti-β2glycoprotein 1, and lupus anticoagulant. While the primary form of this disease occurs without the presence of other autoimmune diseases, a secondary form is also

common which accompanies another disease in this same class of autoimmunity, most often lupus erythematosus. Secondary APS patients will often produce antibodies to both β2glycoprotein 1 and lupus anticoagulant. APS occurs most commonly in young to middle-aged adults; however, it also can occur in children and the elderly in rarer cases. Another demographic feature is that like many autoimmune diseases, it disproportionately affects women in the ratio of five women to every one male patient (Sangle & Smock, 2011).

The autoimmune nature of antiphospholipid antibody syndrome is caused by the presence of antibodies directed against phospholipid-binding plasma proteins, mainly β2 Glycoprotein I (β2GPI)-a plasma apolipoprotein and prothrombin. These antibodies attack two entities: clotting factors and platelets. Resistance to natural anticoagulants such as protein C, impaired fibrinolysis, activation of endothelial cells to a pro-coagulant phenotype and activation of platelets, are among the proposed mechanisms of how APLS causes thrombosis that are partially supported by experimental evidence (Vlachoyiannopoulos & Routsias, 2010). The clotting that results from this resistance to natural anticoagulants is what has given APS the common name of "sticky blood syndrome." But where exactly does this fearsome antibody, one that can turn blood into sludge at the drop of hat, come from? It turns out that the culprit behind the production of anti-β2 Glycoprotein I may be lurking in the immune system weeks, months, or possibly even years prior to the onset of APS, leaving researchers sifting through patients' medical history for the seemingly benign illness that triggered this life-threatening disease.

There isn't a clear reason why one's body begins to produce the antiphospholipid antibodies that result in APS, but there are theories supported by academic research. The latest of which explains that it is likely caused by an initial infection unrelated to the disease itself, in the form of a virus or bacterium. The mechanism by which this occurs involves the cell walls of certain bacterial cells and certain coatings of viruses are especially reactive with the antiphospholipid antibodies. This stealth mode of molecular self-destruction is termed molecular mimicry. Molecular mimicry occurs when a foreign antigen such as a virus or bacteria shares genomic sequence or structural similarities with antigens towards your own body tissues (Cusick, Libbey, Fujinami, 2013). APS is a disease especially vulnerable to molecular mimicry, partially because cell membranes of wide range of tissue cell types are made out of the same structural elements, phospholipids, that APS antibodies are fashioned to attack.

Viral and bacterial mechanisms of molecular mimicry by which the body begins to produce APS-causing autoantibodies differ in a few crucial ways. Viruses are designed to destroy specific T cell types, which can cause an imbalance in the host immune response and autoimmunity later down the line. The most common viral infections associated with APS include hepatitis C virus, human immunodeficiency virus (HIV), cytomegalovirus, varicella-zoster, Epstein–Barr virus, adenovirus, and parvovirus B19. Evidence suggesting microbial agents as APS triggers is less compelling; however, in rarer cases microbes have been found to induce "superantigens" that can selectively activate similar subsets of T cells as viruses (Shoenfeld et al., 2006). Additionally, recent

research has proposed the production of chemokines and cytokines by certain bacteria as modes from which amplify the inflammatory response of the immune system.

Shoenfeld et al. proved the molecular mimicry hypothesis as a probable mechanism for the development of APS antibodies through a study utilizing immunized mice with various microbial pathogens that share structural features with β2 Glycoprotein I (2006). The results were astounding. Infection with *Haemophilus influenza, Neisseria gonorrhoeae, and tetanus toxoid,* caused mice to produce antibodies that attacked their own β2 Glycoprotein I receptors. Increased fetal loss and thrombocytopenia, two key features of APS experienced by humans, were seen in this mouse model. For the first time, a study proved that microbial infection can induce molecular mimicry to cause APS in model organisms, suggesting that the same could be true in humans.

Although molecular mimicry as a mechanism for explaining the sudden production of anti-β2glycoprotein 1 and anti-cardiolipin antibodies is an attractive model for its simplicity, it may be too simple. Cusick et al. argues that molecular mimicry could have been misinterpreted as a different mechanism which more accurately underlies APS. This mechanism is the expression of dual T cell receptors (TCR) on a single T cell. Dual expression is not inherently dangerous, but when these two receptors become simultaneously reactive to both foreign and self-antigens, our bodies can suddenly mount an autoimmune response when faced with an onslaught of viral or bacterial pathogens.

However, there is also evidence showing that APS has a genetic component that could cause the development of this specific type of autoimmunity (Garcia et al., 2013). To illustrate, polymorphisms in a few genes have been found in people with

antiphospholipid syndrome and may predispose individuals to produce the specific antibodies known to contribute to the formation of thromboses. Rarely, the condition has been reported to run in families, but it does not have a clear pattern of inheritance as far as geneticist sleuths have uncovered thus far (Feldman & Levine, 1995).

We have already seen an illustration of some of the common symptoms of antiphospholipid antibody syndrome from the introduction of our two patients, but there is a well-recognized "trifecta" of components of antiphospholipid antibody syndrome that define its clinical manifestation. The trifecta consists of thrombosis, otherwise known as blood clotting, thrombocytopenia, (low platelet count leading which causes internal bleeding), and recurrent miscarriage in female patients. This last symptom, arguably one of the most mentally devastating experiences a woman can endure throughout her lifetime, has been a particularly troublesome mystery for the scientific community to unravel. It is still somewhat unclear why and or how the antibodies indicative of APS can be poisonous to the placenta. What we do know, however, is that this condition frequently leads to a mother rejecting her placenta (Gezer, 2010).

II

Anti-NMDA Receptor Encephalitis

Unraveling the Mystery of Betty and Abigail Parris

While the most widespread instances of accused witchcraft disseminated through Europe between the 14th and 17th centuries, causing the execution of tens of thousands of women over these centuries, the burgeoning American Colonies were not immune to the religious fad of demons and witches either (Blumberg, 2007). Despite this witchcraft mania not catching on in the colonies until the very tail end of the European era craze, witchcraft has a rich history on our own New England soil, one that has reignited the interest of modern historians and biomedical scientists alike.

In 1692 Colonial Massachusetts, the population of which would fit into Yankee Stadium today, would find itself amidst one of the most dangerous social climates they had ever faced (Schiff, 2015). In light of their dangerous journey from England to North America to flee the persecution for their religious faith, the Puritans did not initially find the solace they were seeking. No one was safe. Family members accused each other. Suspicious glances flew between fellow church members. Children were ripped from their parents to be thrust into interrogation. In 1692, the Massachusetts Bay Colony executed fourteen women, five men, and two dogs for witchcraft. The minds of scientists and historians have been enraptured with unraveling the mystery of what could have possibly caused the bizarre behavior seen during the infamous Salem Witch Trials ever since (Zandi & Tam, 2017).

In January 1662, the revered Salem Reverend Samuel Parris awoke to his worst nightmare. Knowing full well that witchcraft laid between idolatry and blasphemy as the second capital offense decided upon by the community in 1641, he was taken aback to see his own nine-year-old daughter, Betty, and eleven-year-old niece, Abagail, overcome by suspiciously "demonic" behavior (Blumberg, 2007). Their symptoms perfectly mimicked those described in a popular book, "Memorable Providences, Relating to Witchcraft and Possessions," describing the afflictions of a family convicted of witchcraft just four years prior (Schiff, 2015). He shuddered in fear to realize that the "agitations, writhings, tumblings, tossings, wallowings, foamings" experienced by Betty and Abagail were even more severe than described in this fateful book. Meanwhile, the girls writhed in a burning sensation that overtook their entire bodies. They cried out that they were being repeatedly stabbed by needles or being bitten by invisible creatures. They had spasms in which their bodies would twitch and then become perfectly rigid. As their conditions deteriorated, they both frequently went into catatonic trances for which the Reverend prayed through all hours of the night, hoping and begging God to break them out of their stupor. Shortly after the onset of their bizarre behavior, another child, Ann Putnam, age 11, fell victim to the same symptoms, symptoms that their local doctor would later blame on demonic possession (Blumberg, 2007).

The magistrates of Salem, Jonathan Corwin and John Hathorne, pressured the young children for information on who could have possibly forced the Devil to enter their previously innocent souls (Schiff, 2015). On February 29th, the girls broke under the immense pressure and blamed three women for practicing witchcraft against them:

Tituba, a Caribbean slave, Sarah Good, a homeless beggar, and Sarah Osborne, an elderly impoverished woman (Baker, 2015). The community did not waste a second in jailing these three women for witchcraft, with only the testimony of the three afflicted children as their compelling evidence. Shortly after this incident, an uncontrollable wildfire of witchcraft paranoia spread throughout Salem. Children as young as 4 years old were taken in for interrogation. Even more frightening was that once you were accused, there was nothing you could say, no defense plausible enough, to convince the Magistrates of your innocence. You were already a dead woman walking (Hall, 1999).

Under the advisement of Harvard's then president, Increase Mather, a staunch Puritan and the author of that infamous witchcraft book "Remarkable Providences," in May 1693, Governor William Phipps claimed that the Salem Witch Hunt had gone too far (Blumberg, 2007). Mather, after a dedicated lifelong battle hunting those converted by the devil, finally denounced the use of controversial "spectral evidence" in the trials by saying, "It were better that ten suspected witches should escape than one innocent person be condemned" (Schiff, 2015). Governor William Phipps, hearing this critique of the witch trials from Mather in combination with the fact that his own wife had been accused of witchcraft, banned the future arrest of any accused of witchcraft and released many of those previously convicted from jail (Baker, 2015).

However, it was far too late. 19 people were already hanged on Gallows Hill, a 71-year-old man was crushed with heavy stones, many convicted had already died in jail, and 185 witches had been exiled for their suspected allegiance to the devil (Schiff, 2015). Much has been left to the imagination regarding the fates of the little Betty and Abigail

Parris, the first to come down with symptoms of demonic possession. Any written record of Abigail disappears after 1692, leaving many questions about her life, or possibly lack-thereof, after the trials (Baker, 2015). What is certain, however, is that these two children were jailed for their conditions, and in addition to suffering the physical agony of their symptoms, at nine and eleven years old, they also suffered abrupt exile by everyone in their community (Blumberg, 2007).

In 1976, a scientist named Linnda Caporael was the first to suggest a biomedical cause for the seemingly unexplainable events that unfolded in Salem in 1692. She proposed that those who were accused of witchcraft had consumed grain contaminated with the fungus *Claviceps purpurea*, which caused convulsive ergotism, a condition marked by the clinical features of muscle twitching and spasms, changes in mental state, hallucinations, sweating, and fever (Caporael, 1976). This was the first attempt at explaining the confusing events of 17th century Salem with a physiological disease. Although this theory is not widely accepted by today's historians, it sparked numerous studies into possible medical explanations of historical witchcraft epidemics. For example, Carlson et al. proposed encephalitis lethargica as a condition afflicting those in Salem. However, the most recent, and possibly the most striking resemblance of symptoms to those experienced by Betty and Abigail Parris is anti-NMDA receptor encephalitis (Zandi & Tam, 2017). A 2012 study by historian KC Uszkalo, suggests that the European witchcraft craze was caused by this rare autoimmune condition. Due to the strong overlap of events between the witch trials in Europe and in Salem, this theory has

caught traction among scientists and historians to describe the events in Colonial Massachusetts as well (Uszkalo, 2012).

"Demonic Possession" in the Modern Age

"There likely was a pathogen of some sort that had invaded my body, a little germ that set everything in motion. Maybe it came from that businessman who had sneezed on me in the subway a few days before, releasing millions of virus particles onto the rest of us in that subway car? Or maybe it was in something I ate or something that slipped inside me through a tiny wound on my skin, maybe through one of those mysterious bug bites? There goes my mind again. The doctors don't actually know how it began for me. What's clear is that if that man had sneezed on you, you'd most likely just get a cold. For me, it flipped my universe upside down and very nearly sent me to an asylum for life" (Cahalan, 2012).

The life story of Susannah Cahalan, like many heartwarming news stories of miraculous patient recovery, can easily be forgotten because of its happy ending. As we saw earlier, Susannah Cahalan's story has made the popular press headlines for her eye-opening ordeal in seeking a diagnosis for her acute neurologic symptoms in 2007. We know from her best-selling book, *Brain on Fire, My Month of Madness*, that she would later be diagnosed as the 217th patient in the United States with Anti-NMDA encephalitis. However, despite the sigh of relief readers feel at the end of her novel upon the long-awaited diagnosis and subsequent recovery, her journey to this diagnosis cannot be

mistaken for anything other than a long and winding road filled with confusion and suffering.

Arguably the most important take-away from Susannah Cahalan's experience is the fact that anti-NMDA receptor encephalitis is not the only physiological condition masked by seemingly unexplainable psychiatric components. In fact, Cahalan's saving grace, Dr. Najjar, believes that there are many mental disorders that can be explained by physiologic and molecular mechanisms. His research takes the link between autoimmune diseases and mental illnesses one step further: "through his cutting-edge research, he posits that some forms of schizophrenia, bipolar disorder, obsessive-compulsive disorder, and depression are actually caused by inflammatory conditions in the brain" (Cahalan, 2012). What does this mean for patients? Eerily, echoes of autoimmunity may lie behind many more mental health conditions than we even know.

Dr. Najjar's latest publication explores the concept of "autoimmune psychosis" and potential clinical approaches to combat new onset psychosis associated with immune dysregulation (Najjar et al., 2018). This type of psychosis, Najjar and contributors argue, is one of the most difficult to diagnose because patients often lack structural abnormalities of the brain frequently seen through MRI as clear signs of physiologic disease. Because the root cause of autoimmune psychosis lies in various invisible autoantibodies towards synaptic and neuronal cell membrane proteins, the condition is often overlooked as psychiatric in origin rather than having a treatable organic cause. However, autoimmune psychosis does leave clear anatomical traces in the brain that can be detected through various tests including cerebrospinal fluid analysis, EEG testing, and

different types of neuroimaging; it is just up to physicians to notice these subtle abnormalities atypical of many neurologic diseases.

The first challenge in diagnosing autoimmune psychosis is identifying inflammatory abnormalities connected with psychiatric symptoms. Steiner et al., utilized CSF analysis in a postmortem study of patients with schizophrenia to identify the one of the main inflammatory abnormalities associated with autoimmune psychosis is microglial activation. Excessive microglial activation is indicative of changes in the CNS microenvironment, such as the inflammatory and neurodegenerative processes that could cause psychiatric symptoms. Additionally, an earlier study by Dr. Najjar found that inflammation caused by autoantibodies

"predominated in brain regions of functional relevance to psychosis (e.g., dorsolateral prefrontal, superior temporal, and anterior cingulate cortices)" (Najjar et al., 2013). This study also confirmed the excessive production of inflammatory mediators in some cases of psychosis, such as the upregulation of pro-inflammatory cytokines and matrix metalloproteinases.

What does this mean for patients? Well, like Susannah Cahalan, some patients' psychosis is drug resistant to many of the anti-psychotic drugs utilized by today's medical protocols. This seems rather logical because the psychosis is being caused by agents that anti-psychotic drugs are not intended to attack. Dr. Najjar argues that timely recognition of the autoimmune causes of psychosis is crucial to more effective treatment because anti-NMDA receptor encephalitis patients "frequently respond well to timely treatment with proper immune modulatory therapies" (Najjar et al., 2018). Perhaps if

there is a greater acceptance among the medical community of organic, autoimmune, and inflammatory causes of mental illness, patients could be treated in a much more efficient and effective manner.

Debunking the Pseudoscience: What is Anti-NMDA Receptor Encephalitis?

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a treatment-responsive encephalitis associated with anti-NMDA receptor antibodies, which bind to the NR1/NR2 heteromers of the NMDA receptors (Hughes et al., 2010). Despite its rarity and common misdiagnosis within the medical community, it has a well-defined set of clinical manifestations which patients begin to exhibit in phases. For example, the main set of symptoms lie in the category of psychiatric changes which include anxiety, agitation, “bizarre behavior,” and paranoia. Epileptic seizures and impaired cognitive abilities more severely follow the noticeable psychological difference. The final ubiquitous symptom common between most anti-NMDA receptor encephalitis patients is called orofacial dyskinesia, in which involuntary movements of the face and mouth take over the body with a vengeance (Garcia et al., 2013).

Physicians have categorized this progression of symptoms into three distinct phases: the prodromal phase, the psychotic phase, and the unresponsive phase. As their names imply, each phase marks the onset of a more startling set of symptoms than the last, representing the extent to which the encephalitis is increasing in severity. More worrisome is the fact that recent research has determined that as the disease progresses through to these late stages of unresponsiveness and hyperkinesis, the more likely it is

that patients will suffer from irreversible brain damage (Liu et al., 2017). The prodromal phase is marked by viral infection-like symptoms of fever, headache, and fatigue. The second phase, the psychotic phase, causes patients to experience schizophrenic-like symptoms of disorganized speech and behavior, or delusions and hallucinations. The final stage, the unresponsive phase, includes the most serious symptoms of decreased levels of consciousness and central hypoventilation, which could become severe enough to cause death by hypoxia (Maneta & Garcia, 2017).

From the story of Betty and Abigail Parris, the young children afflicted with symptoms diagnosed as the evil acts of witches, we can see that some of their symptoms perfectly parallel those within the well-defined set of clinical features including psychiatric changes (anxiety, agitation, bizarre behavior, delusional or paranoid thoughts), epileptic seizures and cognitive disturbance followed by movement disorders, alterations in the level of consciousness and dysautonomia. A recent 2017 study by Tam and Zandi, attempts to attribute the historical descriptions of these children's bizarre actions with a corresponding clinical feature of anti-NMDA receptor encephalitis. The results are astounding.

They found ten symptoms outlined in primary historical documents from 1692 that can be explained by physiologic responses of the body to anti-NMDA receptor encephalitis. For example, the documentation from the time stated that the girls experienced, "Uttering foolish, ridiculous speeches, which neither they themselves nor any others could make sense of" (Calef, 1700). This can likely be attributed to the orofacial diskinesia of the psychotic phase of anti-NMDA receptor encephalitis.

Additionally, it was described that “their limbs wracked and, tormented so…their arms, necks, and backs turned this way and that way, and returned back again” (Lawson, 1692). This could possibly be referring to the convulsions and body dyskinesia caused by inflammation of the CNS. One of the most frightening symptoms to Reverend Parris was that his typically well-behaved daughter was taken over by bursts of violence. “She hurryed with violence to and fro in the room… and begun to throw fire brands about the house” (Hale, 1697). Zandi and Tam attribute this violent behavior to the behavioral disinhibition that frequently accompanies the disease. Finally, in the later phases of their illnesses, when asked questions by doctors or their families, the girls were often unresponsive, staring blankly as if focusing on something far in the distance. Sometimes, when they did manage speech, their responses were completely uncorrelated to the question asked, leading some to ‘‘take them as dumb’’ (Hale, 1697). This state is eerily similar to the states of catatonia patients experience in the unresponsive phase of anti-NMDA receptor encephalitis (Zandi & Tam, 2017).

Because the true cause of the bizarre conditions documented in the Salem witch trials will forever remain somewhat of a mystery, it is important to note that skepticism over whether the Parish cousins suffered from any particular disease is valid. After all, historians and scientists have been debating the cause of their psychosis for centuries and are no closer to a definitive answer. The crucial take away from this ongoing debate is that many of these academics agree on one telling point: Abagail and Betty likely suffered from an undiagnosed physiologic medical condition with a clear organic cause, one that the era just wasn’t equipped to uncover. We may never know if anti-NMDA

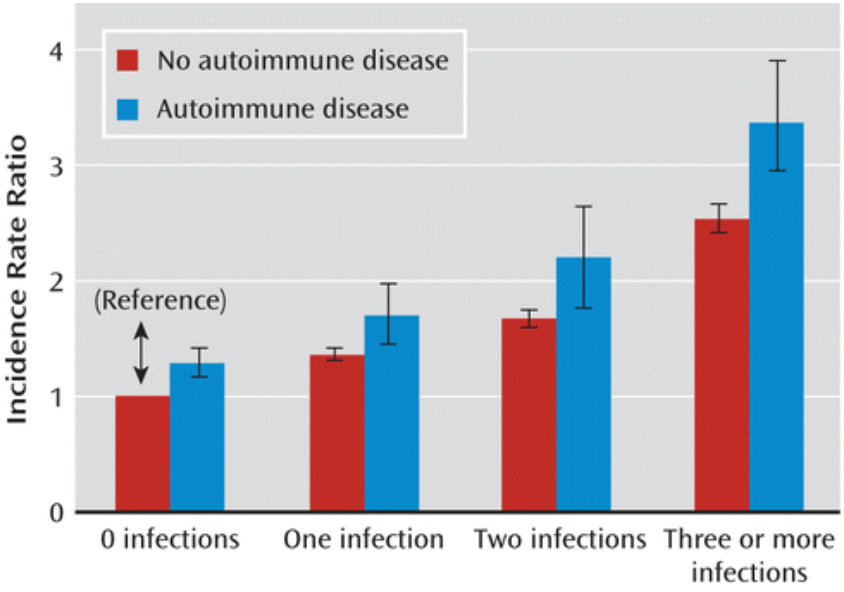
receptor encephalitis was the culprit, but pointing out historical inaccuracies and patient neglect is a step towards untying the study of psychosis from detrimental stigmas of the past.

Now that researchers are beginning to draw connections between probable historical instances of the disease and its known symptoms today, they are also studying the molecular components of the disease itself with the underlying goal of more effective treatments and prevention. It is known that NMDA receptors are a necessary molecular feature of the brain that consist of ligand-gated cation channels. These channels play crucial roles in our regular synaptic transmission and plasticity (Dalmau et al., 2008). Receptors are heteromers of NR1 subunits that bind glycine and NR2 subunits that bind glutamate (García-Carrasco et al., 2013). Reception of these amino acids is crucial for the normal functioning of the central nervous system, as the CNS relies on glutamate as its major excitatory transmitter. However, glutamate reception is also a frequent culprit in the abnormal functioning of the CNS because this amino acid is also an excitotoxin when excessively activated, destroying CNS neurons upon reception on dendritic and somal surfaces (Newcomer et al., 200). Even before the formal discovery of anti-NMDA receptor encephalitis as a disease, it was known that increased activity of NMDA receptors causes excitotoxicity and is a proposed underlying mechanism for many neurologic conditions such as epilepsy, dementia, and stroke. However, low activity produces symptoms of schizophrenia. This implicated possible repercussions in the form of neuropsychiatric symptoms for hypoactivity of NMDA receptors, and researchers began to search for possible inhibitors of these crucial channels (Liu et al., 2017).

It has been determined that one cause of hypoactivity of NMDA receptors is autoimmune in nature, giving rise to anti-NMDA receptor encephalitis. Anti-NMDA receptor antibodies bind to the NR1/NR2 heteromers of the NMDA receptors. Binding of antibodies prevents normal neuronal signaling and cause brain swelling of NMDA receptor Encephalitis (Hughes et al., 2010). Now that the synaptic and neuronal inflammatory reaction associated with psychosis in anti-NMDA receptor encephalitis is being connected, the question remains of how the NR1/NR2B autoantibodies are produced to ignite this autoimmune condition. It is not completely clear why the body starts producing these detrimental autoantibodies in the first place. The most recent research on the topic has noted a high frequency of anti-NMDA receptor encephalitis with ovarian teratomas has sparked study into whether malignant tumors could increase vulnerability to contracting the disease (Ahmad et al., 2017). Additionally, genomic studies have identified single-nucleotide polymorphisms in the HLA-II region of the genome. This suggests there may be specific mutations that lead to production of the NMDA receptor antibodies (Mueller et al., 2018).

Similar to anti-phospholipid antibody syndrome, previous viral and/or bacterial infection has also been connected to autoantibody production in the onset of autoimmune psychosis. In a study on the link between autoimmunity and acute onset of schizophrenia found that herpes simplex virus, *Toxoplasma gondii*, cytomegalovirus, and influenza during pregnancy increase the risk of developing schizophrenia significantly (Benros et al., 2011). Furthermore, Benros et al. found that any history of prior hospitalization due to an infection increased the risk of schizophrenia by 60%. The increased risk of

schizophrenic manifestations of autoimmune psychosis can likely be attributed to the infections that induce an inflammatory response through mechanisms like molecular mimicry (Rice et al., 2005). The figure below shows the significant linear trend in incident rate ratios of schizophrenia spectrum disorders associated with autoimmune disease and infection (Benros et al. 2011).



Overall, Benros and contributors have proven there is a significant link between autoimmunity and psychosis symptoms seen in diseases primarily classified as psychiatric, and they have identified a likely pathology of how these antibodies are developed: molecular mimicry from a previous infection. Antibodies produced in anti-NMDA receptor encephalitis could also be produced through a similar mechanism. Furthermore, it has been determined that autoantibodies are the cause of neurologic symptoms in more than just anti-NMDA receptor encephalitis. In fact, a wide array of autoantibodies can cause autoimmune psychosis in diseases not even primarily

neurologic. All that is required for psychotic disease manifestations is for autoantibodies to cross the blood-brain barrier. For example, in systemic lupus erythematosus, the crossing of antibodies over the blood-brain barrier can cause secondary neuropsychiatric symptoms in the affected individual (Benros et al., 2011).

Now that much more is known about the molecular physiology that underlies anti-NMDA autoimmune encephalitis, the current process of diagnosis is much clearer; however, like in Susannah Cahalan's case, much is left up to the doctor's intuition. The first step in the process is gathering a patient history. Because the disorder predominantly affects children and young adults, disproportionately female, symptoms resembling the disease progression that occur in young females should raise special alert of the possibility of anti-NMDA receptor encephalitis. Additionally, because many patients possess ovarian teratomas, a past medical history of a malignant tumors should also raise alarms, especially in women older than 18 years (Ahmad, et al., 2017).

The next step in the diagnosis process is a physical examination. Due to neurobehavioral changes that many patients experience, doctors will conduct a neuropsychological examination including multiple tests. The Buschke selective reminding test measures verbal memory, visuospatial memory, and logical memory. A Trail Making A and Trail Making B test examines executive functions of patients, while information processing speed is tested by the symbol digit modalities test. The clock drawing test targets visuoconstructive abilities. In fact, *Brain on Fire's* Susannah Cahalan was only properly diagnosed after Dr. Najjar administered the clock test, in which she failed to properly space out all twelve numbers over the entire clock circumference.

Instead, the numbers ended up jumbled and crammed into one side of the circle, indicating poor spatial awareness. The final neurobehavioral test is frequently a mini-mental state examination (Vahter et al., 2014).

A final diagnostic marker is laboratory tests. In a 2008 case study, blood tests showed the presence of antibodies to NR1/NR2B heteromers of the NMDA receptors were in the blood serum and CSF of all patients. However, MRIs, usually a scan that can diagnose a multitude of neurological disorders and what is usually the first diagnostic test ordered when doctors are presented with psychosis cases, show completely normal results. Likewise, single-photon emission computed tomography also shows normal results, but sometimes presents with focal enhancement in the medial temporal lobes. Electroencephalogram monitoring during the unresponsive and hyperkinetic phases showed diffuse delta activity without paroxysmal discharges (Dalmau et al., 2008). The combination of these three objective tests can confirm a diagnosis of anti-NMDA receptor encephalitis, but as previously said, much is left up to the doctor's intuition.

Dr. Najjar recommends combating the frequency of misdiagnosis of autoimmune psychosis in cases like anti-NMDA receptor encephalitis by encouraging doctors stay alert for abnormalities inconsistent with typical psychosis. These include finding elevated serum levels of antibodies that target synaptic and neuronal cell membrane proteins, cerebrospinal fluid samples that include the same neuronal antibodies, and MRI's showing certain structural abnormalities such as hippocampal inflammation consistent with autoimmune limbic encephalitis (Najjar et al., 2018). Finally, it is crucial that physicians take into account interviews of patient's family members including asking

questions such as if there is a strong prevalence of autoimmune disorders or mental illness that runs in their family history. Overall, utilizing a “multi-modal” diagnostic approach to psychosis with suspected organic pathologies can more quickly reveal an autoimmune causation of certain psychosis cases like anti-NMDA receptor encephalitis. Moreover, it can prevent situations of prolonged patient suffering like Susannah Cahalan’s, seen all too frequently in this era of advanced medical and technological practice.

III

Fibromyalgia- The Mystery Disease

Getting out of bed, cooking, and going to the gym. These are three activities I preform on a daily basis and whose ease of completion I, like many of us, often take for granted. Every morning my alarm clock goes off at seven for class and despite no obvious impediments to my daily routine, I admittedly have to stifle groans and overcome the occasional magnetic attraction between my hand and the snooze button in order to get through my morning routine. No matter how much unwarranted self-pity I may muster up in my day-to-day monotonies, I continue to live most of my days content, fulfilled, and optimistic, while each of these insignificant inconveniences float to the back of my mind faster than I can finish my first cup of coffee in the morning. These minor inconveniences and annoyances that we face in our everyday lives are of little consequence to our overall qualities of life. For the patients that will later be discussed, getting out of bed, cooking one's meals, and going to the gym all are momentous events that have at least at one time or another, caused them to spiral into health crises.

Almost everyone has experienced that sudden jolt of interrupted REM sleep that physically elevates you off the calm surface of the bed at the dreaded screech of an alarm clock. For Adrienne Dellwo, however, being jolted awake at 7:45 sends a shiver of pain down her spine from head to toe, leaving her paralyzed in bed for a few more minutes. Finally, she gains the strength to remove the CPAP breathing machine off of her head and

the splint that prevents her teeth from grinding and inflaming her TMJ. She goes through an elaborate stretching routine to assess which parts of her body need extra attention to loosen up before attempting to stand. She's crashed to the floor too many mornings before to forgo this mental assessment while still lying prone. Once sitting, she begins to beat herself up for making a crucial error in judgement the night prior: in her medically induced haze she forgot to place her slippers directly next to the bed. This will make her first steps of the day unbearable. Anticipating what's to come, Adrienne gently places one foot on the carpet only to be met with the feeling of sharp granules of sandpaper. She takes a couple steps forward and the friction radiates unbearable pain through the soles of her feet. At least she's awake now.

Susan Ingebretson describes a different struggle with an everyday task. A lot of us dread going to the gym, but unlike this patient we don't require a cane to steady ourselves while braving the terrain of the parking lot between our car and the grocery store. Upon entering her gym most days she has only one goal. She states, "Staggering on the treadmill like Captain Jack atop the Black Pearl, my simple goal was to stay upright. I gripped the weight machines for dear life and prayed for the room to stop spinning" (Ingebretson, 2013). Despite the pain, Susan would work out six days a week, and every night she would suffer excruciating leg cramps. She tried anything and everything to alleviate this pain. From over-the-counter anti-inflammatories to prescribed topical creams to endless soaks in boiling hot baths, the cramping never ceased. Regarding the countless combinations of potassium, magnesium, manganese, and calcium supplements she ingested in various cocktails, she jokes that she ate enough bananas "until I could

swing from trees and glugged enough chalky white concoctions to stripe a football field." Even these newly acquired superpowers did not decrease her pain. Nevertheless, Susan continues to drag herself to the gym every morning.

It is not waking up in the morning or going to the gym that Rachael Taylor finds is the most difficult task to complete on a daily basis, but instead the life-sustaining activity of cooking. Preparing meals is a comfort and calming pastime for many Americans living a healthy life; for Rachael on the other hand, it is her worst nightmare. There is the obvious debilitating pain, as expressed by Adrienne and Susan, but this time it is amplified by the need to lift, grip, and physically work heavy kitchen equipment. Additionally, there is the added challenge of standing for hours on end, putting immense strain on the back, legs, and feet. Finally, Rachael has a difficult time sifting through the thick brain fog long enough to see what ingredient comes next in a recipe. However, going without food just isn't an option, and nutritional demands of her medically prescribed diet could not be fulfilled from constant delivery and take-out meals. Thus, Rachael had to invest time and energy into building "a path of least resistance for [herself] throughout the whole kitchen" just to sustain herself on the worst days of her condition. One quick glance at her kitchen reveals hours of intentional planning including the heaviest items at the most convenient level while sitting,

Adrienne, Susan, and Rachael all have much more in common than just the inconvenience of having to alter their everyday tasks. They all suffer from debilitating pain from a mysterious illness that continues to stump the most experienced of medical professionals. This condition is called fibromyalgia syndrome (FMS) and as these three

women's stories can attest to, the ramifications of this disease spread far beyond the consequences for individual patients. As we have seen from our previous discussion of antiphospholipid antibody syndrome, and anti-NMDA receptor encephalitis, fibromyalgia is a condition whose modern diagnosis is impeded by its previous classification as a psychogenic. Patients frequently find themselves, judged, dismissed, and left with more questions than answers from the very physicians meant to alleviate their chronic pain.

What is Fibromyalgia?

While there have been many terms tossed around throughout the years to describe chronic muscular pain, the one that has seemed to stick was coined by British neurologist Sir William Gowers in the early twentieth century. He described the cause of widespread muscle pain to be "fibrositis," otherwise known as inflammation of the fibrous tissues of the muscle. Despite over eighty years passing without a single study finding any evidence of inflammation related to fibromyalgia, the name has stuck, even within the medical community. Similar to other chronic pain disorders, the inability of the medicine to pinpoint one specific organic pathology that could cause such pervasive pain has left the condition of fibromyalgia extremely vulnerable to the psychogenic explanations. Rommelfanger et al. describes a psychogenic condition as "a manifestation of symptoms that arise from a psychiatric origin, a confounding situation where an otherwise invisible illness becomes visible" (Rommelfanger et al., 2017). On the surface, fibromyalgia appears to be just that: simply a manifestation of pain with no obvious biological cause. It must be psychological, right?

As World War II came to a close, those who subscribed to the belief of the psychological cause of fibromyalgia felt vindicated by the increasing prevalence of "fibrositis" among returning soldiers. The unimaginable trauma of war must have flipped an internal psychological switch to cause the apparent "psychogenic rheumatism" experienced by so many of those veterans claiming to have unbearable widespread muscle pain. In 1943, almost forty years before post-traumatic stress disorder (PTSD) would be recognized by the American Psychiatric Association as a credible disorder, two U.S. military physicians offered credibility to this theory when they suggested "fibrositis" be renamed to "psychogenic rheumatism," a side effect of the psychological stresses frequently seen in shell shocked veterans. Perhaps this is historical phenomenon lurks at the heart of today's misunderstanding of fibromyalgia as having psychological origins.

About thirty years pass before the renowned Dr. Hughe Smythe, a venerated Canadian physician and cofounder/coeditor of the *Journal of Rheumatology*, would abandon the term "fibrositis" and replace it with the modernly recognized term, fibromyalgia. Considered the "grandfather of modern fibromyalgia," Smythe made much headway in specifically defining the previously ambiguous condition. He noted that fibromyalgia is a commonly encountered disorder characterized by chronic widespread musculoskeletal pain and related symptoms along with multiple painful "tender points," which consist of either the right or left sides of nine areas of the body. Although the idea of "tender points" has been abandoned by modern day physicians, much of Smythe's definition is still widely referred to in today's medical practice in the diagnosis of the life-altering disorder.

While the symptoms of fibromyalgia are consistent among patients and fairly easy to identify as fibromyalgia when viewed in aggregate, the underlying molecular cause of the disease is still up for much debate. It is clear that genetic and environmental factors may play a role in the etiopathology of FMS and other chronic pain syndromes, but the exact reason for the physiological pain and stiffness in identified tender points remains elusive. As with autoimmune diseases, infectious agents (viruses in particular), and vaccination have all been suggested as possible triggers of FMS, but these possible environmental agents tell us nothing about the biological mechanism from which pain floods the body.

One apparent truth about fibromyalgia is that it bears eerie similarity to autoimmune conditions, ringing alarm bells for many researchers who are investigating the possible link between autoimmunity and FMS. Autoimmune-like features of fibromyalgia include that it predominately affects females (90% of fibromyalgia patients are women) of childbearing age. However, it is more than just patient demographics that points to an autoimmune pathology of FMS. The connection between fibromyalgia and autoimmune disorders may even be so strong as to cause an increased likelihood of developing fibromyalgia if one already suffers from another autoimmune disease. To illustrate, fibromyalgia is reported in about 25 percent of patients suffering from lupus, 25 percent of patients with rheumatoid arthritis, and 50 percent of patients with Sjogren's syndrome. Likewise, recent studies have shown an overall predisposition for the development of FMS in patients with Hashimoto's thyroiditis. Moreover, the co-occurance of autoimmune diseases with FMS, especially thyroid disease, is known to

worsen fibromyalgia symptoms, increasing severity of pain in tender points and the frequency of full body fatigue (Bazzichi, Rossi, & Sarzi-Puttini, 2007).

Multiple studies corroborate this presently unfolding story starring autoimmune disease and fibromyalgia. For example, three studies have found thyroid autoantibodies to be in greater percentages in subjects with FMS compared with controls, in spite of the fact that most patients have normal thyroid hormone levels. One of these studies synthesized previous reports of autoantibody presence in FMS patients compared to control subjects and noted 34.4%- 41% of FMS patients tested positive for autoantibodies versus 15%- 18.8% of controls (Bazzichi, Rossi, & Sarzi-Puttini, 2007). It is not just autoimmune thyroid disease that is a potential culprit.

Autoantibodies to serotonin have also been found in higher than average levels in many patients with fibromyalgia. As a known regulator of our sleep cycle, serotonin has been of critical interest in the study of fibromyalgia because chronic fatigue is a common clinical manifestation of the disease. In a pool of 50 FMS patients, 74% showed elevated levels of autoantibodies to serotonin, whereas only 6% of 32 healthy (blood donor) controls showed the same level. Possessing high levels of autoantibodies to serotonin is not necessarily indicative of low serotonin blood hormone levels as one may think, speaking to the complicated and counterintuitive nature of autoimmunity itself. In fact, the same study showed that 90% of the FMS patients possessed normal levels of serotonin in their blood despite the elevated autoantibody concentration. This indicates serotonin receptor involvement, rather than a serotonin deficit, as the molecular

mechanism of the disease (Klein, Bansch, & Berg 1992). Then again, it is still unclear if serotonin is the main culprit at all in this mysterious autoimmune-like condition.

Perhaps the most eye-opening study regarding fibromyalgia and the immune system is a A 2012 study in the *British Journal of Medical Practitioners* which noted another key feature of fibromyalgia pathology that involves the immune system. Breeding et al. propose that it is a "chronic up-regulation of the immune system with subsequent hormonal, connective tissue and nervous system implications" that rewires FMS patients' pain circuitry to wreak havoc upon the entire body. In their rational albeit complex "integrated model" of FMS, an immune cascade which includes NF-[kappa]B be triggered by a chronic bacterial or viral infection (Breeding, Russel, & Nicholson, 2012). You may recall that this idea bears striking resemblance to the mechanism of APS antibody production previously discussed, in regards to molecular mimicry.

Why do diseases like Fibromyalgia continue to be dismissed as psychogenic?

Fibromyalgia is just one modern example of the concept of psychogenic diseases living on into the modern era. While antiphospholipid antibody syndrome and anti-NMDA receptor encephalitis have only recently broken out of their decades-long research sleep, FMS has only just begun its nap. Many biomedical researchers refuse to acknowledge the importance of increasing knowledge of this condition, simply based on the perceived credibility, or lack thereof, of FMS patients. There are countless articles

published in respected journals and magazines within the last ten years, spewing medical professionals' doubt over the existence of fibromyalgia as a legitimate medical condition.

For example, a 2008 article published in the *New Yorker* entitled, "Drug Approved. Is Disease Real?" exposes the opinions of practicing physicians who believe the diagnosis of fibromyalgia is a scam perpetuated by pharmaceutical companies trying to sell unnecessary drugs (such as the most widely used medicinal treatment for FMS, Lyrica). For example, Dr. George Elrich, a practicing rheumatologist and professor at the University of Pennsylvania, is in the camp that asserts that everyone experiences the aches and pains of a supposed "fibromyalgia," but most people are just stronger and better able to tolerate them. He states that people without chronic pain syndromes, "manage to get through life with some vicissitudes, but we adapt," while patients with fibromyalgia simply "do not adapt" to equally stressful and painful situations. Dr. Nortin Hadler, a rheumatologist and professor of medicine at the University of North Carolina, joins Elrich in this state of disbelieve over fibromyalgia. He even goes as far as to state that FMS patients, "live under a cloud, and the more they seem to be around the medical establishment, the sicker they get" (Berenson, 2008).

If fibromyalgia does show so many clinical features consistent with autoimmune disease, why is this disease still classified as psychogenic or questioned of its existence at all? For one, it is often associated with psychiatric symptoms of depression, anxiety, and insomnia even though there is no evidence supporting that the disease itself is causing these symptoms. Many believe these psychiatric symptoms are a result of the stress of living with this disease. In fact, recent studies have shown these negative psychological

symptoms to be more likely a result of the dismissal by the medical professionals, not a preexisting mental condition. Secondly, there are no serological markers that have been identified for the disease. No scan or previously developed blood tests reveal any specific signs of infection, autoimmunity, or inflammation. No blood test or imaging currently exists for FMS, so physicians have to rely on a detailed assessment of symptoms to make a diagnosis, and inexperienced ones unfamiliar with chronic pain often miss its confusing set of symptoms. This leaves FMS patients hopping from doctor to doctor, desperate for answers, but only accumulating doubt along the way.

Where do we go from here?

From our historic look at a few of medicine's most bewildering conditions, it is clear that there are a multitude of labels for clinical uncertainties. From "psychogenic disorders" to "medically unexplained symptoms" to "functional disorders," the medical community employs various jargon for the same frustration experienced by clinicians and patients alike. The definition, with slight variations, for all of these terms is "a manifestation of symptoms that arise from a psychiatric origin, a confounding situation where an otherwise invisible illness becomes visible" (Rommelfanger et al., 2017). Overall, the common thread tying APS, ANRE, and FMS together, is the fact that, at one point in time or another, the medical community could not identify a single biological cause or organic pathology that accounted for patients' physical symptoms. For the 10 million patients in the U.S. with fibromyalgia, the battle against the psychogenic

diagnosis seems never-ending, and if actions are not taken to prevent this ongoing struggle, the public health of our country is at stake.

While many argue for the necessary categorization and clinical diagnoses of these diseases as psychogenic until proven otherwise, there is inherent danger in clinically labeling poorly understood diseases with such speculative and detrimental diagnoses. As the stories of Betty and Abagail Parris, Jan Pankish, and Susannah Cahalan have illustrated so clearly, mistakes made as a result of lack of scientific knowledge in historical eras are undoubtedly carrying through to the present. Perhaps the way to tackle the increasingly relevant problem of misdiagnosis in medical practices, we must start by learning from our mistakes of the past.

The first step in preventing maltreatment and misdiagnosis of patients suffering from misunderstood diseases is acknowledgement of our historical bias against medically unexplained symptoms in dismissal as hysteria. Despite credible neurologists and psychiatrists diagnosing diseases as “psychogenic” or “functional” for decades, there are a few fallacies associated with psychogenic diseases that must be addressed.

There is countless historical evidence proving that previously labeled psychogenic diseases are now categorized under completely different disease categories after a molecular cause had been determined. For example, the first two diseases outlined in this thesis, anti-NMDA receptor encephalitis and anti-phospholipid antibody syndrome, have symptoms that initially present with psychogenic symptoms (neurologic symptoms with no immediately apparent origin). It was only the recent discovery of serologic markers of blood antibodies that shifted their categorization from psychogenic to autoimmune, in

1983 and 2008 respectively. With the vast uncertainty and ever-changing nature of science, it would be a complete delusion to believe that all symptoms that present in patients that can't be explained from an objective test are inherently a result of the patient's psyche. When it is clear that science has not yet developed tests to detect the physiologic cause for every single human disease, as new tests are being developed every day, jumping to the conclusion that some diseases have no physiologic cause is to naively rely on science's false omniscience.

Secondly, some would argue that there are certain innate pros that come with receiving a medical diagnosis of any kind, including those deemed psychogenic, when they often have the opposite effect. Under this train of thought, a patient who has struggled with painful symptoms for a lengthy period of time might find relief in the hope for enhancing treatment access, availability, and effectiveness that accompanies finally receiving a diagnosis, albeit one psychogenic in nature. However, what many don't realize is that the stigma that surrounds psychogenic patients often inhibits their access to treatment rather than expand it. To illustrate, psychogenic diseases are so frustrating for physicians, as it tests the credibility of their profession, that doctors often avoid patients with the label "psychogenic" at all costs, preferring to refer them to other doctors or dismiss their symptoms all together. Moreover, there is no specialty associated with psychogenic disease. Because these diseases are defined as not having a physiologic cause, it is easier for physicians to exclude them from their practice for not possessing a disease relevant to their scope of medicine. While we often associate the act of diagnosis with the empowering knowledge that comes with a disease label, the act of diagnosis by

exclusion in the case of psychogenic diseases limits treatment options and banishes patients as medical pariahs. It would be more beneficial for patients to remain undiagnosed while completing a more thorough investigation into their symptoms, rather than jump to the detrimental and likely false conclusion of a psychogenic diagnosis.

The second step that needs to be taken to prevent the neglect and misdiagnoses of patients suffering from misunderstood diseases is an increase in future studies conducted to expand our knowledge of etiopathologic causes of diseases with autoimmune features. While the National Institutes of Allergy and Infectious Diseases (NIAID) has estimated that the cost of treating autoimmune disease in the US is greater than $100 billion annually, the cost dedicated to autoimmune disease research is pitifully inadequate.

To illustrate, despite autoimmunity being the second most frequent cause of chronic illness in the U.S., the NIH dedicates less than three percent of its annual research budget to autoimmune diseases. This critical gap in base biomedical research must be bridged to compensate for the increasing number of cases of autoimmune nature seen in the last decades and continued lack of knowledge regarding their molecular pathologies. An increased dedication to identifying the molecular pathologies of fibromyalgia and other autoimmune-like conditions considered “medically unexplained” will be required to prevent widespread patient neglect.

References

Ahmad, J., Sohail, M. S., Khan, A., Qavi, A. H., Gaudel, P., Zahid, M., & Assad, S. (2017). Anti-n-Methyl-d-Aspartate-Receptor (NMDAR) Encephalitis in Association with Ovarian Teratoma. *Cureus*, *9*(7), e1425. https://doi.org/10.7759/cureus.1425

Asherson, R. A., Khamashta, M. A., Ordi-Ros, J., Derksen, R. H., Machin, S. J., Barquinero, J., … Hughes, G. R. (1989). Antiphospholipid syndrome: major clinical and serological features. *Medicine*, *68*(6), 366–374. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2509856

Baker, E. W. (2015). A Storm of Witchcraft: The Salem Trials and the American Experience. *Oxford University Press*, (234).

Bazzichi L, Rossi A, Giuliano T., (2001). Association between thyroid autoimmunity and fibromyalgic disease severity. Clinical Rheumatology. ; 26(12):2115-20.

Benros, M. E., Nielsen, P. R., Nordentoft, M., Eaton, W. W., Dalton, S. O., & Mortensen, P. B. (2011). Autoimmune Diseases and Severe Infections as Risk Factors for Schizophrenia: A 30-Year Population-Based Register Study. *American Journal of Psychiatry*, *168*(12), 1303–1310. https://doi.org/10.1176/appi.ajp.2011.11030516

Buskila, D., Atzeni, F., Sarzi-Puttini, P. (2008) Etiology of fibromyalgia: The possible role of infection and vaccination. *Autoimmunity Reviews*, 8(1), 41-43. https://doi.org/10.1016/j.autrev.2008.07.023.

Blumberg, J. (2007). A Brief History of the Salem Witch Trials: One Town's Strange Journey from Paranoia to Pardon. Retrieved December 7, 2018, from

https://www.smithsonianmag.com/history/a-brief-history-of-the-salem-witch-trials-175162489/

Cahalan, S. (2012). *Brain on fire : my month of madness*. Free Press. Retrieved from http://www.simonandschuster.com/books/Brain-on-Fire/Susannah-Cahalan/9781451621389

Calef, R. (1700). More wonders of the invisible world. http://name.umdl.umich.edu/A32160.0001.001. Accessed 3 Dec 2018

Caporael, L. R. (1976). Ergotism: the satan loosed in Salem? *Science (New York, N.Y.)*, *192*(4234), 21–26. https://doi.org/10.1126/SCIENCE.769159

Dalmau, J., Gleichman A.J., Hughes, E.G., Rossi, J.E., Peng, X., Lai M., Dessain, S.K., Rosenfeld, M.R., Balice-Gordon, R., Lynch, D.R. (2008). Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *The Lancet Neurology*, 7(12), 1091-1098. Retrieved from https://doi.org/10.1016/S1474-4422(08)70224-2.

Dusenbery, M. (2018). *Doing harm : the truth about how bad medicine and lazy science leave women dismissed, misdiagnosed, and sick*. Retrieved from https://www.barnesandnoble.com/w/doing-harm-maya-dusenbery/1123951266?ean=9780062470812#/

Fairweather, D., & Rose, N. R. (2004). Women and autoimmune diseases. *Emerging Infectious Diseases*, *10*(11), 2005–2011. https://doi.org/10.3201/eid1011.040367

Feldmann, E., & Levine, S. R. (1995). Cerebrovascular disease with antiphospholipid antibodies: immune mechanisms, significance, and therapeutic options. *Annals of*

Neurology, *37 Suppl 1*, S114-30. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8968222

Flexner, A. (2002). Medical education in the United States and Canada. From the Carnegie Foundation for the Advancement of Teaching, Bulletin Number Four, 1910. *Bulletin of the World Health Organization*, *80*(7), 594–602. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12163926

Friedman, J. H. (2010). Localizing the wandering uterus. *Medicine and Health, Rhode Island*, *93*(5), 130–131. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20533717

García-Carrasco, M., Pinto, C. M., Hernández, C. J., Poblano, J. C. S., Morales, I. E., & Martínez, S. M. (2013). Antiphospholipid syndrome. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK459442/

Gezer, S. (2003). Antiphospholipid syndrome. *Disease-a-Month*, *49*(12), 696–741. https://doi.org/10.1016/j.disamonth.2003.10.001

Gilman, Sander L., Helen King, Roy Porter, G. S. Rousseau, and Elaine Showalter *Hysteria Beyond Freud.* Berkeley: University of California Press, c1993 1993. http://ark.cdlib.org/ark:/13030/ft0p3003d3/

Gould, R., Miller, B. L., Goldberg, M. A., & Benson, D. F. (1986). The Validity of Hysterical Signs and Symptoms. *The Journal of Nervous and Mental Disease*, *174*(10), 593–597. https://doi.org/10.1097/00005053-198610000-00003

Hale J. (1697) A modest enquiry into the nature of witchcraft. http://name.umdl.umich.edu/N00872.0001.001. Accessed 2 Dec 2018

Hall, D. (1999) Witch-Hunting in Seventeenth-Century New England. Boston: *Northeastern University Press*, (280-81)

Hughes, E. G., Peng, X., Gleichman, A. J., Lai, M., Zhou, L., Tsou, R., … Balice-Gordon, R. J. (2010). Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*(17), 5866–5875. https://doi.org/10.1523/JNEUROSCI.0167-10.2010

Klein R, Bansch M, Berg PA. Clinical relevance of antibodies against serotonin and gangliosides in patients with primary fibromyalgia syndrome. Psychoneuroendocrinology. 1992;17(6):593-8.

Lahita, R. G., & Yalof, I. L. (2005). *Women and Autoimmune Disease: The Mysterious Ways Your Body Betrays Itself*. New York: HarperCollins.

Lawson D (1692) A brief and true narrative of some remarkable passages relating to sundry persons afflicted by witchcraft at Salem village. http://name.umdl.umich.edu/A49794.0001.001.Accessed 3 Dec 2018

Levine, S. R., Deegan, M. J., Futrell, N., & Welch, K. M. (1990). Cerebrovascular and neurologic disease associated with antiphospholipid antibodies: 48 cases. *Neurology*, *40*(8), 1181–1189. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2381525

Liu, C., Zhu, J., Zheng, X.-Y., Ma, C., & Wang, X. (2017). Anti-N-Methyl-D-aspartate Receptor Encephalitis: A Severe, Potentially Reversible Autoimmune Encephalitis. *Mediators of Inflammation*, *2017*, 1–14. https://doi.org/10.1155/2017/6361479

Maneta, E., & Garcia, G. (2014). Psychiatric Manifestations of Anti-NMDA Receptor Encephalitis: Neurobiological Underpinnings and Differential Diagnostic Implications. *Psychosomatics*, *55*(1), 37–44. https://doi.org/10.1016/J.PSYM.2013.06.002

More, E. (1987). The Blackwell Medical Society and the Professionalization of Women Physicians. *Bulletin of the History of Medicine*, *61*(4), 603–628. Retrieved from http://dml.regis.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=ahl&AN=45953978&site=ehost-live&scope=site

Mueller, S. H., Färber, A., Prüss, H., Melzer, N., Golombeck, K. S., Kümpfel, T., … German Network for Research on Autoimmune Encephalitis (GENERATE). (2018). Genetic predisposition in anti-LGI1 and anti-NMDA receptor encephalitis. *Annals of Neurology*, *83*(4), 863–869. https://doi.org/10.1002/ana.25216

Najjar, S., Pearlman, D. M., Alper, K., Najjar, A., & Devinsky, O. (2013). Neuroinflammation and psychiatric illness. *Journal of Neuroinflammation*, *10*, 43. https://doi.org/10.1186/1742-2094-10-43

Najjar, S., Steiner, J., Najjar, A., & Bechter, K. (2018). A clinical approach to new-onset psychosis associated with immune dysregulation: the concept of autoimmune psychosis. *Journal of Neuroinflammation*, *15*(1), 40. https://doi.org/10.1186/s12974-018-1067-y

Nakazawa, D. J. (2008). *The autoimmune epidemic : bodies gone haywire in a world out of balance-- and the cutting-edge science that promises hope*. Simon & Schuster.

Retrieved from https://www.amazon.com/Autoimmune-Epidemic-Balance-Cutting-Edge-Promises-ebook/dp/B0012ZKZM0

Neurobehavioral presentations of the antiphospholipid antibody syndrome. (1993). *The Journal of Neuropsychiatry and Clinical Neurosciences*, *5*(1), 37–42. https://doi.org/10.1176/jnp.5.1.37

Newcomer, J. W., Farber, N. B., & Olney, J. W. (2000). NMDA receptor function, memory, and brain aging. *Dialogues in Clinical Neuroscience*, *2*(3), 219–232. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22034391

Rice, JS., Kowal C., Volpe B.T., Degiorgio L.A., Diamond B. (2005) Molecular mimicry: anti-DNA antibodies bind microbial and nonnucleic acid self-antigens. Curr Top Microbiol Immunol 2005; 296:137–151 Medline, Google Scholar

Sangle, N. A., & Smock, K. J. (2011). Antiphospholipid Antibody Syndrome. *Archives of Pathology & Laboratory Medicine*, *135*(9), 1092–1096. https://doi.org/10.5858/2010-0325-RSR.1

Schiff, S. (2015). The Witches of Salem: Diabolical Doings in the Puritan Village. Retrieved December 7, 2018, from https://www.newyorker.com/magazine/2015/09/07/the-witches-of-salem

Steiner, J., Mawrin, C., Ziegeler, A., Bielau, H., Ullrich, O., Bernstein, H.-G., & Bogerts, B. (2006). Distribution of HLA-DR-positive microglia in schizophrenia reflects impaired cerebral lateralization. *Acta Neuropathologica*, *112*(3), 305–316. https://doi.org/10.1007/s00401-006-0090-8

Stojanovich, L., & Marisavljevich, D. (2008). Stress as a trigger of autoimmune disease. *Autoimmunity Reviews*, *7*(3), 209–213. https://doi.org/10.1016/J.AUTREV.2007.11.007

Tam, J., & Zandi, M. S. (2017). The witchcraft of encephalitis in Salem. *Journal of Neurology*, *264*(7), 1529–1531. https://doi.org/10.1007/s00415-017-8546-4

Tasca, C., Rapetti, M., Carta, M. G., & Fadda, B. (2012). Women and hysteria in the history of mental health. *Clinical Practice and Epidemiology in Mental Health : CP & EMH*, *8*, 110–119. https://doi.org/10.2174/1745017901208010110

Te-Yu Hung, Ning-Hui Foo, Ming-Chi Lai (2011). Anti-N-Methyl-d-Aspartate Receptor Encephalitis, *Pediatrics & Neonatology*, *52*(7), 361-364, https://doi.org/10.1016/j.pedneo.2011.08.012.

Uszkalo, K. C. (2012). Medical Theories on Malefic Possession: From Bewitchment to Anti-NMDAR Encephalitis. *Journal of Religion in Europe*, *5*, 323–348. https://doi.org/10.1163/18748929-00503001

Vahter, L., Kannel, K., Sorro, U., Jaakmees, H., Talvik, T., & Gross-Paju, K. (2014). Cognitive dysfunction during anti-NMDA-receptor encephalitis is present in early phase of the disease. *Oxford Medical Case Reports*, *2014*(4), 74–76. https://doi.org/10.1093/omcr/omu028

Vlachoyiannopoulos, P. G., & Routsias, J. G. (2010). A novel mechanism of thrombosis in antiphospholipid antibody syndrome. *Journal of Autoimmunity*, *35*(3), 248–255. https://doi.org/10.1016/j.jaut.2010.06.015