The Psychology of a Genetic Curse: Nancy Wexler and the Impact of Huntington's Disease

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There are countless amounts of people facing hardships in everyday life, and it can lead to the belief that life is simply unfair. However, for many, this thought is retracted and an overwhelming sense of gratitude is achieved when they discover the life that Nancy Wexler, and several others, are forced to endure. Nancy Wexler, and a multitude of other individuals, have a neurodegenerative disorder called, "Huntington's disease" (WETA National Productions, 2020). The disease is hereditary, as the gene responsible is autosomally dominant (Ciriegio et al., 2020). This means that individuals with affected parents, have a 50/50 chance of inheriting Huntington's disease as well, which became the reality of a geneticist named, Nancy Wexler. Unfortunately, many of Nancy's family members, including her mother, were affected by the disease and passed away because of it (Grady, 2020). Since no known treatment or cure to offset the symptoms existed, she dedicated her life to discovering one, for her family members and ironically one day, herself. Although much of her findings contributed profoundly

to Huntington's disease research, Nancy was unable to establish an effective treatment, and there is currently no known method of entirely diminishing the effects of the disease (National Institute of Neurological Disorders and Stroke, 2024). Today, she suffers with the symptoms of the disease, awaiting a cure to save her from her poorly dealt hand in life (WETA National Productions, 2020). Research for Huntington's disease is crucial, and many areas can be explored in an attempt to understand the impact of this neurodegenerative disorder on the psychological domains of emotion, sensation, cognition and behaviour. An understanding of the physiological effects of living with Huntington's disease, and the adverse psychological repercussions, as well as research on different kinds of treatment, will be investigated in an attempt to analyze this disorder in which thousands of people endure in today's society.

Nancy Wexler is a well established geneticist who devoted her life to researching Huntington's disease, which entailed indagating the gene associated and experimenting with treatments to the affected gene (Grady, 2020). She spent approximately 40 years researching the gene, which included visiting remote villages of Venezuela where a large number of affected individuals resided. With desires to use the genetic information of these individuals, she raised millions of dollars, created a clinic, and eventually discovered the gene associated

with Huntington's disease in 1993, *HTT*. This led to being able to begin creating a drug which could have an effect on the gene that may possibly cure the disease, as well as creating a test so individuals could confirm whether or not they were living with the gene. Growing up, she was exposed to multiple different family members living with Huntington's disease, which inevitably put her at risk for having inherited it. Her mother, uncles, and grandfather all died due to the disease, and her brothers were diagnosed. She chose her career path in an attempt to one day find the cure and destigmatize the degenerative disease, to save her brothers. For much of her life, she was in denial that she would ever fall victim to the oppressive disease as well. Throughout her career, she chose to keep her probable diagnosis quiet, and never discussed the possibility with her colleagues. It wasn't until she was 74 that, she acknowledged she too had inherited Huntington's disease, but she was then too old to qualify for a clinical trial for the drug she had created. Being surrounded by people close to her having Huntington's disease, as well as the possibility of having it herself, influenced Nancy tremendously. She dedicated the entirety of her professional career to researching Huntington's disease, and attempted to promote further research, educating others about how it works and affects people.

Huntington's disease is present in individuals who have a mutation on their *HTT* gene, a protein called "huntingtin", which resides on chromosome 4 (National Institute of Neurological Disorders and Stroke, 2024). Specifically, these individuals have an excess of the cytosine, adenine, and guanine trinucleotide repeat on this gene. Normal DNA repeats of these nucleotides exist around 27 times, individuals who likely won't develop the disease, but could pass on the gene have around 27 – 35 repeats, and affected individuals typically are found to have 36 or more repeats. When an individual experiences this genetic abnormality, areas of the brain responsible for motor activity control is compromised. Nerve cells in these areas break down and die, reflecting the neurodegenerative nature of Huntington's disease. The neurotypical role of these cells is to coordinate and maintain voluntary movements, as well as other similar areas. Since these brain cells undergo reduction over time, it makes Huntington's disease characterized by a gradual decline in motor ability, and a slow increase in corresponding symptomatology. The disease is not sex-linked, so it is not limited to one gender, and no gender has a greater risk of development than the other. However, certain studies have found links to individuals of European descent being more greatly affected than those of other races (Ciriegio, 2020). For many, Huntington's disease is inevitable and lifestyle choices cannot change the outcome of

the mutated gene living within them. Inheriting the disease is nothing more than an unfortunate hand in life, and it reflects why Nancy Wexler was so passionate about creating a cure and reducing stigma surrounding Huntington's disease. Especially, considering the corresponding symptoms that a diagnosed individual has to live with.

The neurodegenerative essence of Huntington's disease is represented by the corresponding symptoms a diagnosed individual experiences or is likely to eventually experience after onset. In the beginning, symptoms are minor and could potentially even go unnoticed, which was the case for Nancy Wexler (Grady, 2020). It was apparent to her peers and colleagues that she was living with the mutated huntingtin protein long before she realized the reality of the situation herself. Until she reflected on videos and recordings of herself, she was clueless to the related symptoms her body was displaying. After the review of video clips, Nancy saw that she was moving in involuntary ways, and each time she watched a new video, the movements worsened. Her first symptoms included having an unsteady gait, slurred speech, uncontrollable movements in her head and limbs, a short temper, and she required a walker to get around. Her associates began to see aspects of Nancy changing, such as spilling drinks more, strange body movements, and dishevelled handwriting. Prior to onset,

Nancy never experienced these things, making it clear to others what was going on inside her brain. Progressively, her health declined as the motor neurons continually broke down, creating a lack of motor ability among other symptoms. Presently, she struggles to talk and muscle spasms are prevalent, along with the other symptoms that have worsened as well (WETA National Productions, 2020).

Not specific to Nancy, other general and related symptoms of Huntington's disease include chorea, which is a term describing the involuntary movements an individual will typically undergo, difficulty walking, and muscle tremors (National Institute of Neurological Disorders and Stroke, 2024). Furthermore, they may experience issues with swallowing and speaking, seizures, and a loss of energy. On a more psychological level, patients often fall into a depressive state, or are anxiety ridden, and they could possibly deal with experiences of hallucinations, delusions, and other confusions. Areas of the brain responsible for organizational skills and planning have also been impaired by the disease. Another finding details that people experiencing the side effects of Huntington's disease will endure more extreme and noticeable symptoms when they are nervous or stressed. The onset of symptoms typically occurs around middle adulthood, ages 30 – 50 years old (Tillerås et al., 2020). The symptoms of

Huntington's disease are debilitating and take a great toll on an affected person's quality of life, let alone lifespan. Eventually, they lose the ability to work, drive or generally care for themselves independently (National Institute of Neurological Disorders and Stroke, 2024). Nancy Wexler, among others, are forced to deal with the aversive effects of Huntington's disease, since there is no known cure to rid them of their demons, evoked by the abnormal gene they inherited.

Living with the condition of Huntington's disease is evidently burdensome, so a desire to find out whether or not you may be living with the mutation, may be a more complex decision than expected. Tillerås et al. (2020) investigated the psychological needs of individuals at risk of being diagnosed with Huntington's disease as well as those both positively and negatively diagnosed. The researchers hypothesized that there would be a range of reactions and emotions towards diagnosis, and they sought to draw conclusions about understanding the depth of mental health effects regarding Huntington's disease (Tillerås et al., 2020). To do so, 33 participants consented to genetic testing to see if they carried the repeat in the *HTT* gene. The participants underwent semi-structured interviews before and after genetic testing was performed, allowing researchers to thoroughly evaluate the emotional states and feelings of the individuals. Reactions and emotional contexts were

documented, and then understood through a thematic analysis. The study found that many individuals made decisions with the possibility of being diagnosed in mind, some irreversible, prior to getting genetic testing and truly knowing if they one day would develop the effects of Huntington's disease. There were both negative and positive reactions to a person finding out they had the mutated gene, as well as finding out they did not. Since many people anticipated having Huntington's disease, for reasons such as their parents having it or maybe even early symptoms but did not end up being diagnosed, a feeling of regret for certain choices consumed them. Although it could be assumed that primarily feelings of optimism would be elicited from the knowledge of healthy genes, having made irreversible decisions under the assumption the test would be positive may bring upon unpleasant feelings. Similarly, survivors' guilt was found in individuals who did not have it, but realized their sibling could or did have it. This type of research is important for mental health practitioners who are dealing with an individual in any of these situations, as well as for general awareness regarding the mental health impacts of Huntington's disease.

As mentioned, the assumption that a person carries the mutated *HTT* gene prevails in individuals who are at risk, which inevitably creates an anxiety ridden mindset towards the future.

Offspring of diagnosed individuals are at a relatively high risk for also one day facing the hardships of the disease. Ciriegio et al. (2020) sought to gain a better understanding of the stress faced by the offspring of parents with Huntington's disease. Prior to this research study, it was found that stress can impair both executive function skills and secondary control coping skills, such as positive thinking and dealing with adversity at general ease (Ciriegio et al., 2020). The researchers hypothesized different correlations between the factors of stress and levels of anxiety and depression. All of which were pointing towards the general expectation that stress would significantly impact offspring of diagnosed individuals, comorbidly with anxiety and depression. Ciriegio et al. (2020) used a study population of adolescent and young adult offspring, whose parents' ages ranged between 32 – 58, generally when onset would have begun. To test their hypothesis, the researchers had the participants complete a questionnaire on a secure online database, called REDCAP (Ciriegio et al., 2020). This revealed demographics and coping strategies, then two more assessments were completed, one in which was to analyze stressors and strategies, RSQ-HD, and one for the symptoms of anxiety and depression, YSR and ASR. Finally, the "List Sorting Working Memory Task" was used to assess working memory. The data was collected through the self-report tests, and the findings

proved the initial hypotheses. Understanding the mental health risks that pertain to individuals at risk for developing the disease is arguably just as important as the mental health of a diagnosed individual. Nancy Wexler experienced similar stress towards the anticipation of developing the disease, which is reflected in her devotedness to find a cure. Although unprovable without knowing Nancy personally, if she was not worried at all about how the disease may possibly affect her one day, why was she so hesitant to take predictive testing?

Diagnosed individuals face stress regarding their health, perhaps in different ways than a person in anticipation would. Once diagnosis has been completed, stressors would turn to a reduction in lifespan and the future inability to live their everyday lives how they are used to living them. Ciriegio et al. (2022) conducted a study that intended to draw conclusions about the coping mechanisms of stress in diagnosed individuals, along with the associated symptoms of anxiety and depression. It was hypothesized again that there would be associations between control and attention, working memory, secondary coping skills, and anxiety and depression, all pointing towards stress and similar symptoms of anxiety and depression prevailing in individuals with Huntington's disease. The participants included adults aged 31 – 69 who were diagnosed with the disorder (Ciriegio et al., 2022). To understand the stress

associated with these participants, assessments were done using an anxiety self-report scale, GAD-7, and a depression self-report scale, PHQ-9. Results of these tests were analyzed and significant effects were found between inhibitory control and attention skills and symptomatology of anxiety and depression. Along with, between secondary control coping skills and anxious and depressive symptoms. The findings of these tests signify the impact that having Huntington's disease has on an individual relating to stress symptoms, such as control and attention skills, secondary control coping, as well as the effect it has on anxiety and depression. The importance of these findings again provides informative insight into what diagnosed individuals deal with, like Nancy Wexler.

Anxious and depressive feelings are common factors found to be seen in individuals either diagnosed with Huntington's disease, or even having a probable diagnosis, such as being an offspring (Ciriegio et al., 2020). So, it wouldn't be shocking to also understand that suicide in Huntington's disease is not uncommon. Lipe et al. (1993) explored the risk factors for suicide in diagnosed individuals, in a retrospective research style. Prior evidence suggests an increased frequency of suicide in Huntington's disease patients, with it being most prevalent in the earlier stages of the condition. The researchers hypothesized that consistent themes would be found between the diagnosed

individuals who had died by suicide, along with individuals at risk and individuals close to those affected (Lipe et al., 1993). Participants included eight males and one female diagnosed with Huntington's disease, one female with a probable diagnosis, and one unaffected female spouse, with ages ranging between 24 – 65. The study population was compared against a control population of similar diagnosed people who did not commit suicide. Through the revision of medical, genetic counselling, and social work records, the researchers made comparisons between the obtained data and the matched data of the living individuals. Several findings were discovered, which included common risk factors found among the deceased individuals. The highest found risk was having little family support and no contact with children. Other predictors were being male, having no offspring, other suicides in the family, living alone, being unmarried, depressed, and having little contact with other people. Figuring out the prevailing factors that contribute to an individual with Huntington's disease dying by suicide are substantial for many reasons. The value of a diagnosed individual's life does not decrease because of the condition taking over their mind and body. Family and friends close to them likely don't see them differently and are devastated by such news, not to mention the life lost that still had so much potential, regardless of ability. Although these individuals may lose hope

and see no reason to live anymore, they must have a support system that understands their feelings and can support their mental health journey, which is frankly exactly why this type of research is so vital.

As discussed, research regarding Huntington's disease is crucial for a variety of reasons, made even more apparent when reviewing the research surrounding the aversive mental health effects of the disease. Nancy Wexler being so closely associated with individuals suffering from a diagnosis understood this all too well, and was a part of imperative research exploring the causes and genetic makeup of Huntington's disease. Lee et al. (2020) researched the mutant gene, *HTT*, analyzing how the disease progresses and ways in which this progression could be reduced. Nancy Wexler was one of the geneticists involved in this study, where they hypothesized that the huntingtin protein responsible for Huntington's disease would undergo seeding, or proliferation, effectively progressing the disease. Once understanding the proliferation process, the goal of the study was to develop a way to decrease the seeding activity, through the targeting of specific parts of the mutated gene (Lee et al., 2020). Mice were the study population of choice, used to understand how the mutant *HTT* gene worked in humans as well. A cell line was produced to detect seeding activity, then characteristics of the disease were able to be analyzed, serving

as a cell-based tool. Specifically, an increased expression of the DNAJB6 molecule and the anti-polyP antibody were used to inhibit proliferation, leading to insights regarding mechanisms to cure Huntington's disease. Undoubtedly, Nancy Wexler was a part of contributing to Huntington's disease research, and this study specifically had a large impact on the advancements of the sought out cure for affected individuals.

Despite a successful medical treatment of sorts that would ideally slow down the progression of the impact of the mutated Huntington's disease gene being the primary goal of researchers, other treatments aimed at reducing symptoms are also functional for suffering patients. Research into alternatives serves as important, especially until a medical treatment targeting the gene is successful in the future. For example, cognitive behavioural therapy was proposed by Meyer et al. (2022) to treat post-traumatic stress disorder (PTSD) and obsessive-compulsive (OCD) in a Huntington's disease patient. Existing research reported significant findings of individuals diagnosed with Huntington's disease comorbidly dealing with obsessive-compulsive symptoms (Meyer et al., 2022). As well, research has been done on treating these symptoms with pharmaceuticals, which have been primarily ineffective at eluding the symptoms altogether. Thus, other treatment methods, such as cognitive-behavioural therapy, hold a need to

be studied. The researchers hypothesized that this type of therapy would be a better approach to treating OCD-related symptomatology, and they chose a single participant to perform the case study on. Prior to this case study, it was predicted that a Huntington's disease individual would not be receptive to this type of therapy, but this did not affect the researchers' decision to pursue this treatment. The Huntington's disease diagnosed individual chosen was a 43-year-old male experiencing both OCD and PTSD, where pharmaceutical treatments in the past merely relieved symptoms temporarily, but proved ineffective long term. To study the effects of cognitive behavioural therapy, the participant underwent exposure to his past trauma, as well as exposure therapy for his obsessive-compulsive tendencies toward cleanliness. He was evaluated using the Problem Behaviours Assessment, the Montgomery and Asberg Depression Scale, Yale-Brown Obsessive-Compulsive Scale, and DSM-5 Criteria for PTSD. Evaluations were completed both before and after ten, one hour cognitive-behavioural guided therapy sessions, over the course of ten weeks. PTSD and OCD symptoms completely resided, proving this treatment method effective in the reduction of comorbid Huntington's disease effects. This is substantial for individuals with Huntington's disease also struggling with similar outcomes. Additionally, these results proved that Huntington's disease affected

individuals do hold the capacity to be treated by cognitive behavioural therapy.

Not only has cognitive-behavioural therapy been proven to yield as effective in reducing symptoms relating to Huntington's disease, but so have rehabilitation programs catered to the needs of these individuals. Piira et al. (2013) reviewed prior research by Zinzi et al. (2007) and aimed to conduct a rehabilitation program that filled the gaps of this study, showing improvement and maintenance of physical and cognitive functioning in Huntington's disease individuals. The researchers hypothesized that through a one-year program consisting of three in patient stays of three weeks, that their improved plan would yield decreased side effects of Huntington's disease, more so than the prior study mentioned. Their rehabilitation program contained more assessments including quality of life, function in daily activities (ADL), motor and cognitive function, and improved follow up tactics to increase sustainability. 37 patients were enrolled in the centres providing the program, who all had early to middle stage Huntington's disease. Evaluations such as the Mini Mental State Examination, a cognitive assessment (UHDRS), an anxiety/depression symptoms assessment (HADS), and an assessment of quality of life (SF-12) were used to compare baseline levels to results after treatment (Piira et al., 2013).

Symptoms that improved due to the program included gait, balance, mental state, anxiety and depression, and physical quality of life. This shows that anyone dealing with these symptoms because of Huntington's disease would benefit from this type of program aimed at treating the effects of the disease. A shortcoming in the results was that the mental component of quality of life did not significantly improve, but with all the other advancements the rehabilitation program is objectively worthwhile. Nancy Wexler, and others, may be after a pharmaceutical cure but other types of treatment may aid in improving symptoms, at least enough to increase the standard of living in Huntington's disease patients to some degree.

Huntington's disease is associated with its unfavourable outcomes, greatly decreasing an individual's overall wellbeing through many different areas of life. Nancy Wexler committed herself to finding a cure, but now lives with symptoms inhibiting her motor control abilities that negatively affect her everyday life. As stated, Huntington's disease has been proven to break down areas of the brain associated with motor ability and control at a neurological level (National Institute of Neurological Disorders and Stroke, 2024). The result can be seen in the various behavioural side effects discussed, such as chorea and other motor inabilities. To go along with this, the area of the brain deteriorating lacks proprioception sensation abilities,

related to difficulties in motion and positioning of the body. Furthermore, individuals are affected emotionally, often experiencing depressive and stressful symptoms, both seen in the diagnosed population and their offsprings or close family members (Ciriegio et al., 2020). Cognitive abilities are also proven to be disturbed when a diagnosed patient begins to lack organizational abilities (National Institute of Neurological Disorders and Stroke, 2024). Nancy Wexler is a prime example of the effects Huntington's disease has on a person, as well as the participants involved in the research studies utilized in the investigation of the genetic disorder. The survey of the literature evidently proved that the neurological condition, Huntington's disease, impacts the psychological domains of emotion, sensation, cognition, and behaviour, to varying degrees depending on the stage of the disease.

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