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Conceptual Model of the Psychosocial Effects of Beryllium Sensitization and Chronic Beryllium Disease

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Abstract The objective of this research was to develop a theoretical model that describes the psychosocial effects of beryllium sensitization (BeS) and chronic beryllium disease (CBD). The medical, nursing, health education, and psychological literature was reviewed to identify theories that might support the development of a psychosocial model of BeS and CBD. A proposed model was synthesized based upon elements from multiple academic disciplines. The conceptual model is based on three prominent psychological theories: 1) health, stress, and coping, 2) uncertainty and illness, and 3) psychosocial adjustment to illness. The model hypothesizes that workers who are diagnosed with BeS or CBD experience a great deal of uncertainty that has a detrimental effect on their health quality of life. The focal relationship in this model is between the independent variable *uncertainty* and the dependent variable *health quality of life*. It is further hypothesized that the relationship between these two variables is affected by an intermediate variable, the ability to make *psychosocial adjustments to disease*. Creating this model is a step toward filling a void in our understanding of the natural history of CBD. Once validated it will establish a foundation for future research, interventions and program evaluations and may lead to changes in the psychological, social, financial, and disease management support provided to this population.

Keywords: *Beryllium, berylliosis, uncertainty in illness, psychosocial adjustment, stress and coping*

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1. Introduction

A research gap exists in the development and testing of theoretical models which might explain the psychosocial aspects of beryllium sensitization (BeS) and chronic beryllium disease (CBD). Such research would help clinicians understand the total experience of their patients and might suggest changes in the types of psychological, social, financial, and disease management support provided to workers with BeS or CBD. The purpose of this research was to develop such a model.

Beryllium is a strong, lightweight metal that is toxic when inhaled into the lungs. People who work in factories where beryllium is processed are sometimes exposed to beryllium particles and may develop an allergic reaction to the metal. In some, this reaction, called BeS, leads to a severe, incurable occupational lung disease known as CBD.

Beryllium is widely used in the aerospace, electronics, biomedical, defense, telecommunications and other industries [1,2,3,4]. The 2010 estimated consumption of beryllium in the U.S. was 320 metric tons and was valued at about $160 million [5]. Beryllium consumption is currently dominated by electronics applications [6]. The estimate for the number of U.S. workers ever exposed to beryllium ranges from 800,000 to 1,000,000 [7,8,9].

Most people who are exposed to beryllium will not experience health effects because there is a strong genetic susceptibility component to sensitization and subsequent disease. However, some develop BeS and some of them go on to develop CBD. Epidemiologic studies have shown that on average, 1-6 percent of exposed workers develop BeS, although the rates can be as high as 19 percent among workers with the highest exposures, such as beryllium machinists [10,11,12,13,14]. Most workers who are going to develop BeS tend to do so early on, but follow-up testing over the years continues to identify workers with BeS-up to 30 percent in one group of workers [15].

The percentage of people with BeS who go on to develop CBD is highly variable, ranging from 10-100 percent in different worker populations [16]. Individuals exposed to the highest levels of airborne beryllium dust are at greatest risk of sensitization, although skin exposure may also be important [17]. Recent research suggests that each year, 6-8 percent of people with BeS will develop CBD [18]. The latency for converting from BeS to CBD is highly variable, ranging from 1-12 years in one longitudinal study [19]. Factors such as particle size, type of beryllium used, amount and duration of exposure to beryllium, occupation, industry, and genetics all play a role in determining why some people develop CBD and others do not [14,16]. Once a person is exposed to beryllium, they carry a lifelong risk of developing

beryllium sensitization or CBD, even if the exposure amount was small or their exposure ceases. [16].

The National Research Council (NRC) [20] recognized that the diagnosis of BeS or CBD may be associated with psychosocial stress and/or loss of income and that there was an absence of published data on those phenomena. The NRC further suggested that implementation of a comprehensive beryllium-exposure and disease management program that includes appropriate worker education and counseling, medical-removal, and protection against lost wages can minimize such potential adverse consequences [20].

2. Materials and Methods

The medical, nursing, health education, and psychological literature was reviewed to identify theories that might support the development of a psychosocial model of BeS and CBD. Online searches were conducted to identify publications in the scientific literature and library searches were conducted to identify and obtain other scholarly works. Government publications were obtained from agency websites or through personal requests to contacts in the agencies.

The search was conducted in a sequential manner starting with the medical and epidemiologic literature related to chronic beryllium disease. This was followed by an analysis of the nursing literature related to the psychosocial effects of illness. The psychological literature related to health, stress, and coping was then evaluated. Models from the health education literature were then reviewed to determine how they might be applied to this project.

The literature was synthesized and a figure of the model was developed. Draft versions of the model were shared with subject matter experts from various academic and medical disciplines. Through repeated discussions with experts from multiple disciplines, the proposed model was further refined. The model was shared with key informants who had either BeS or CBD to get their feedback. A research plan was developed to identify how future qualitative and quantitative research projects might be used to validate the proposed model.

3. Results

3.1. The Natural History of CBD

Beryllium induced lung disease can usually be categorized as either an acute or chronic disease process [21]. Acute beryllium disease is of historical significance and was identified in the U.S. in the 1940s [22,23] and is considered an irritative chemical phenomenon related to high exposure levels [24]. With advances in industrial hygiene, acute beryllium disease has been virtually eliminated in the U.S. [21]. Despite these historical improvements in workplace exposure conditions, cases of CBD continue to occur [25].

According to Newman, Lloyd, and Daniloff [25] CBD is a systemic disorder that occurs when a sensitized (i.e., allergic) person's lungs react with beryllium that has been inhaled, producing inflammation in the lungs which leads to the formation of lung granulomas and scarring. They described CBD as a beryllium-specific, cell-mediated immune response gone awry. Based on their review of historical studies Newman, Lloyd & Daniloff [25] concluded that: 1) the disease varies in its clinical presentation, 2) the disease varies in its rate of progression, 3) while removal from exposure may be medically prudent, it is not known to what extent such restrictions will change the natural history for more than a minority of patients, and 4) earlier studies did not systematically review the risk factors for disease progression [25].

The symptoms that cause the patient to seek medical evaluation can include arthralgia, chest pain, cough, or most commonly dyspnea with relatively mild exertion [21]. While some persons with CBD die within a few years of diagnosis in respiratory failure and cor pulmonale, others experience a more insidious downhill course extending over decades [25]. Workers exposed to persistent (i.e., non-soluble) beryllium antigen are at lifelong risk of CBD [16,26].

The diagnosis of CBD is usually preceded by identification of BeS and those workers that become sensitized are at high risk for developing CBD [16]. Conversion from BeS to CBD is highly variable, ranging from 1-12 years in one longitudinal study [18]. The current diagnostic criteria for CBD include all of the following [27,28]:

1. History of or evidence of beryllium exposure
2. Evidence of an immune response to beryllium, that is, positive response in blood or bronchoalveolar lavage lymphocytes exposed to differing levels of beryllium in *in vitro* cultures (i.e., the beryllium lymphocyte proliferation test (BeLPT)) in two independent tests
3. Symptomatic disease with histological demonstration of noncaseating granulomas on lung biopsy

Current medical management of CBD involves cessation of beryllium exposure and use of immunosuppressive drugs [29,30] but there is limited literature regarding the effect of these interventions on the natural history of CBD. Published mortality rates range from 5.8 to 38% [31].

3.2. Beryllium Sensitization

The development of the BeLPT [11] created a fundamental change in our knowledge of CBD. According to Maier [32], it revolutionized our approach to the diagnosis, screening, and surveillance of beryllium health effects. BeS is not a disease in its own right and has no symptoms, but it is important because it identifies a subgroup of exposed workers who are at risk for developing CBD [20]. A positive BeLPT result differentiates CBD from other lung diseases such as sarcoidosis, chronic obstructive pulmonary disease, and hypersensitivity pneumonitis [20,27,33].

BeLPT results are not always consistent or stable, creating clinical uncertainty [34-38]. Because the test is difficult to perform and results are not always consistent, most physicians and researchers like to require two independent abnormal tests in order to categorize a worker as BeS. Greene and Smith [39] argued that the empirical uncertainty arising from the probabilistic nature of BeLPT

screening can be highly unsettling for workers who might expect clear guidance from medical testing. Despite its limitations in test consistency and repeatability, the BeLPT has been an invaluable tool in the identification of workplace risks in population studies and intervention effectiveness [16] and has led to the identification of clinically milder cases [20].

3.3. Lung Cancer

In addition to CBD, workers exposed to beryllium also have significantly elevated risks of lung cancer [40,41,42,43]. The National Toxicology Program [44] listed beryllium as a known carcinogen, as did the International Agency for Research on Cancer [45]. However, beryllium exposure is more commonly associated with CBD than lung cancer and according to the National Institute for Occupational Safety and Health [46], controlling beryllium exposure to prevent CBD should also reduce the risk for lung cancer. The reader is referred to the Agency for Toxic Substances and Disease Registry, Toxicological Profile of Beryllium [47] and Groth [48] for comprehensive reviews of the carcinogenic properties of beryllium.

3.4. Epidemiology of CBD

For the most comprehensive description of the epidemiology of CBD, the reader is referred to the literature review completed by the National Research Council, Committee on Toxicology [2]. This work, along with its companion report [20], were completed for the U.S. Air Force and represent the most current and complete compilation of the beryllium literature.

The population at risk for CBD is workers in industries where beryllium is processed in a manner that creates multiple pathways for inhalation and skin contact with beryllium particles [17]. The range of estimates for the number of U.S. workers exposed to beryllium is 20,000 to 1,000,000 [7,8,9]. Henneberger and others [49] relied on sampling data from the Occupational Safety and Health Administration (OSHA) to estimate that 134,000 U.S. workers were potentially exposed to beryllium. Kreiss, Day, and Schuler [16] believed that the number is far higher because OSHA had not sampled for beryllium in military and nuclear weapons complex workplaces. Other workplaces, such as those recycling electronics equipment, may also be a source of previously unsuspected exposure [20].

The prevalence of BeS and CBD in exposed workers ranges from 1 - 19% and from 0.1 - 7.8%, respectively [14,16]. Table 1 provides prevalence data of BeS and CBD from recent cross-sectional and longitudinal studies conducted in U.S. industry.

Table 1. Prevalence for Beryllium Sensitization and Chronic Beryllium Disease from Selected Epidemiologic Studies

Industry	n	BeS %	CBD %
Nuclear Workers [10]	895	2.0%	1.7%
Nuclear Workers [50]	5,173	4.5%	1.6%
Beryllium Production Workers [12]	627	9.4%	4.6%
Beryllium Machinists [51]	235	9.4%	5.5%
Beryllium Ceramics Production [52]	151	9.9%	5.3%

CBD is typically considered only when occupational exposure to beryllium is a certainty; however, CBD has occurred in occupational and environmental settings where exposure was unexpected [21]. Individuals who live near plants that process beryllium may be at greater risk than the general population [53,54]. The general population is exposed to beryllium through inhalation of air and consumption of food and drinking water but people who work in beryllium manufacturing, fabricating, and reclaiming industries are exposed to much higher levels of beryllium than the general population [47].

The nuclear weapons industry has received substantial attention because of worker exposure to beryllium. In fact, beryllium disease was recognized among workers involved in the early development of atomic energy in the World War II era [22,55]. As nuclear weapons proliferated during the Cold War, the number of workers in the U.S. Department of Energy (DOE) nuclear complex grew and the number of workers exposed to beryllium grew proportionately. Beginning in the late 1980s, clusters of CBD were recognized in workers from nuclear weapons plants across the U.S. [11]. A number of additional epidemiologic studies of nuclear workers have been completed over the past two decades helping us to understand the risk of CBD in this population [10,50,56-62]. These studies and others were chronicled in the DOE regulation (i.e., the Chronic Beryllium Disease Prevention Program) that was promulgated to prevent the continued occurrence of CBD [63].

Among other things, this rule created the DOE Beryllium-Associated Worker Registry for current workers who are exposed to beryllium in their current job, or may have been exposed to beryllium in the past from work conducted at a DOE site [64]. The goal of the registry is to determine the incidence and prevalence of BeS and CBD. The data are analyzed to better understand CBD and to identify those at risk. Another goal is to monitor and evaluate the effectiveness of the Chronic Beryllium Disease Prevention Program. Coupled with the DOE Former Worker Medical Screening Program [65], these surveillance programs provide a mechanism for collecting data about those at risk for BeS and CBD.

3.5. The Psychosocial Aspects of CBD

The National Research Council (NRC) recognized that the diagnosis of CBD or BeS may be associated with psychosocial stress and/or loss of income and that there was an absence of published data on those phenomena [2,20]. The NRC further suggested [20] that implementation of a comprehensive beryllium-exposure and disease management program that includes appropriate worker education and counseling, medical-removal, and protection against lost wages can minimize such potential adverse consequences.

At the 3rd Annual International Conference on Beryllium Disease, Newman [66] made a presentation identifying unanswered questions related to CBD. He argued that there was still much to be learned about the neuro-psychological and social effects of CBD on BeS and CBD patients. He reported that his patients asked how beryllium will affect their employment, finances, insurability, workers compensation, personal well-being, and social

lives. Later at the same conference, Cragle [67] encouraged researchers to consider the sensitized/CBD patient as a whole human being and asked, "where are the social scientists?"

In 1999, at the Conference on Beryllium Effects on Worker Health, Henneberger suggested that it was important to survey former employees to estimate the full extent of the problem and to understand the natural history of CBD [68]. In 2008, at the Third International Conference on Beryllium Particulates and Their Detection, McCawley [69] presented the results of a survey of members of the Beryllium Health and Safety Committee to identify the most important topics for future research. In the area of health effects, McCawley reported the second highest priority was to "identify opportunities for therapeutic interventions (pre-CBD) or specific therapies for CBD" and suggested that a research plan needed to be developed to help people with BeS and CBD.

3.6. Theoretical Perspectives and Relevant Studies

3.6.1. Stress and Coping Theory

Stress is a term that originated in the disciplines of physics and engineering. Early research on human stress was conducted by scientists in the fields of biology, physiology, and psychology. It was Cannon [70] who coined the enduring term "fight or flight" to describe the human response to stress. Endocrinologist Hans Selye [71] was the father of modern stress research and was the first to publish a paper on the biological syndrome of stress. Over the next twenty years he further explored the concept as it related to disease in man, eventually publishing *Stress and Life* [72]. In this seminal work, he defined three stages of stress: alarm reaction, stage of resistance, and stage of exhaustion. He described the alarm stage as a generalized call to arms of the defensive forces in the organism. Following this was a stage of biological adaptation of the organs to the stress. After prolonged exposure, the adaptation was eventually lost and the animal entered the stage of exhaustion. At the end of a life under stress, there was a premature aging due to wear and tear. To describe this progression, he used the term *general adaptation syndrome* [72]. Thus began the study of stress and illness.

While Selye initially focused on biological stress, others turned their attention to the concept of psychological stress. Lazarus [73] considered the field of stress a collective term that included physiological, sociological, and psychological phenomena and their respective concepts. He argued that these diverse terms could be combined in the same study. Lazarus extended the *general adaptation syndrome* [73] by incorporating the concepts of stress appraisal and coping. He suggested that for a psychosocial situation to be stressful, it must be appraised as such. That is, one must determine whether a situation is potentially threatening, constitutes a harm/loss, is challenging, or is benign. He theorized that this assessment occurred during primary and secondary appraisals. The primary appraisal includes the perception of how stressful the stimulus is and the secondary appraisal estimates whether one has adequate resources to deal with the problem. He defined coping as the strategies one employs for dealing with stress and that when the individual discovers some important motive or value is being threatened, coping activity is mobilized by this threat, by virtue of the cognition that "my life, health, wealth, or cherished social relationships are in danger." Lazarus [73] referred to these coping modes as direct action, vigilance, and avoidance.

Selye later published a new model [74] that divided stress into eustress and distress. This differentiated stress that enhanced physical or mental functioning (i.e., eustress) and persistent stress that was not resolved through coping and adaptation (i.e., distress). Eustress is positive adaptation to stress and is typified by activities such as exercise to build strength and cardiovascular capacity. Distress results in negative functioning and may lead to anxiety, depression and/or physical ailment. This model more accurately represented both the positive and negative potential associated with stress.

Holroyd and Lazarus [75] explored the linkage between stress, coping, and illness, describing three ways that stress might lead to somatic illness. The first was by the disruption of tissue function from neural and hormonal outpourings (e.g., pounding heart, sweating, trembling, etc.). The second was by engaging in coping activities that were damaging to health (e.g., tobacco use, alcohol consumption, poor diet). The third way that stress might lead to disease is by psychological and/or sociological factors which lead the person to minimize the significance of symptoms or to fail to comply with treatment programs (e.g., avoidance of doctors). They concluded that whether stress led to somatic illness via one of these mechanisms was influenced by a person's coping methods and skills.

Lazarus and Folkman [76] recognized that people exhibited different coping styles when confronted with stress. They suggested that coping styles are broad, pervasive, encompassing ways of relating to particular types of situations such as ambiguous or clear, imminent or distant, temporary or chronic, evaluative or nonevaluative. They also recognized that coping styles are dynamic and subject to the personality of the individual. These dynamics properties make for a diversity of strategies for those coping with illness. Stress can also have a distinct physiologic effect.

O'Leary [77] reviewed the empirical evidence linking emotional stress to immune function in humans. She reported that chronic stress has been associated with suppression of immune function, and that there is evidence that the immune system may not adapt over time [77]. There is evidence that psychosocial stress influences a variety of immune functions and on several disease processes. This presents some provocative questions about the interaction between psychosocial and physiological stress associated with immune mediated diseases, like CBD.

As the theory of stress and coping evolved and matured, key concepts became more defined. Folkman [78] recognized that the scope of coping had been broadened to include regulation of positive well-being in the face of stress. In addition, research is now being conducted on future-oriented coping, interpersonal coping, and religious and spiritual coping. Models have been developed to explain the concept of stress and coping in society. One such model that explains how stress and coping theory applies to health and well-being is the Transactional Model of Stress and Coping.

3.6.2. Transactional Model of Stress and Coping

Understanding stress and coping is essential to health education, health promotion, and disease prevention [79] and the Transactional Model of Stress and Coping is a framework for evaluating processes of coping with stressful events. Glanz and Schwartz articulated the constructs of the model which is rooted in the cognitive theory of psychological stress and coping developed by Lazarus and Folkman [80]. The theory is transactional in that the person and the environment are viewed as being in a dynamic, mutually reciprocal, bi-directional relationship. Stress is conceptualized as a relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and as endangering well-being [79]. The theory identifies two processes - cognitive appraisal (primary and secondary) and coping strategies (problem, emotion, and meaning-based) as critical mediators of stressful person-environment relationships and their immediate and long-term outcomes including emotional well-being, functional status, and health behaviors [79]. Because stress effects people differently, the ability to cope with stress influences decisions about seeking medical care and social support and whether one believes the advice of professionals. This model serves as the theoretical basis for many health education and disease prevention programs.

3.6.3. Psychosocial Adjustment to Illness Theory

The ability of humans to adjust to threatening events is a derivative of stress and coping theory. Taylor [81] observed that one of the most impressive qualities of the human psyche is its ability to successfully withstand severe personal tragedy. Based on her experience with cancer patients, cardiac patients, rape victims, and other individuals facing life-threatening events [81], she argued that when an individual has experienced a life-threatening event, the readjustment process focused around three themes: 1) a search for meaning in the experience, 2) an attempt to regain mastery over the event in particular and over one's life more generally, and 3) an effort to enhance one's self-esteem, to feel good about oneself again despite the personal setback.

How one adjusts to illness has been the subject of much research over the past thirty years [82,83]. Mechanic [84] noted that what interested behavioral scientists was the tremendous variability in response to what was presumably the same illness condition. While one person hardly acknowledged a condition and refused to allow it to alter his life, another with a milder form of the same condition would display profound social and psychological disabilities.

Psychosocial adaptation to chronic illness and disability has been the subject of more research as the prevalence of chronic disease increases in our society. Livneh and Antonak [85] suggested that the prolonged course of treatment, the uncertain prognosis, the constant and intense psychological stress, the gradually increasing interference with the performance of daily activities and life roles, and the associated impact on family and friends all combine to create a profound effect on the lives of persons with chronic illness and disabilities. Cassileth and others [86] compared the psychosocial status of five groups of patients with chronic illness (i.e., arthritis, diabetes, cancer, renal disease, and dermatologic disorders) and found them remarkably adaptive in comparison to patients with depression. They concluded that psychological status was independent of the specific diagnosis for these chronic diseases.

Derogatis was one of the early pioneers in this field and he, along with Abeloff and Melisaratos [87], reported on the psychological coping mechanisms in patients with metastatic breast cancer. They found that, in general, the long-term survivors had higher psychological distress levels than the short-term survivors. They also established that cancer patients whose coping styles facilitated external, conscious expression of negative emotions and psychological distress appeared to survive longer while patients whose coping styles involved suppression or denial of affect or psychological distress had a shorter length of survival. They [87] suggested that psychological interventions could be redesigned to put patients more in touch with their emotions and possibly promote a more successful psychological outcome. This early research led Derogatis to explore the development of psychometric scales that could be used to measure the ability to adjust to illness.

The Global Adjustment to Illness Scale (GAIS) was developed as an instrument to measure the prevalence of psychiatric disorders among cancer patients [88]. In this study the GAIS, along with two other instruments, were administered to a sample of 215 cancer patients. The results of the survey indicated that 47% had a psychiatric diagnosis and that approximately 68% of those diagnoses consisted of adjustment disorders. The authors further suggested that pervasive emotional distress and dysphoria often associated with cancer may not be an inherent part of the neoplastic disease, but rather a separate and potentially treatable condition. This study provided an epidemiologic benchmark for the prevalence of psychiatric disorders among cancer patients and has had far-reaching implications for treatment and therapy. It also motivated Derogatis to further refine his psychometric instrument.

In 1986, Derogatis introduced the interview-based Psychosocial Adjustment to Illness Scale (PAIS) and a self-reporting version (PAIS-SR) to assess the psychological and social adjustment of medical patients, or members of their immediate families, to the patient's illness. The PAIS and PAIS-SR were developed to reflect seven principal domains [89], all of which had been shown to have a high relevancy for adjustment to medical illness. The seven domains include:

1. health care orientation
2. vocational empowerment
3. domestic environment
4. sexual relationships
5. extended family relationships
6. social environment
7. psychological distress

The instruments were tested for factor structure, reliability, and validity and a library of six normative groups was developed (lung cancer patients, renal dialysis patients, acute burn patients, hypertensive patients, cardiac bypass patients, and heterogeneous cancer patients). Later, other researchers [90,91] conducted additional factor structure analyses on the PAIS-SR.

While Derogatis [89] noted that there were more than two dozen instruments available to assess psychiatric patients, he developed this instrument because there was a dearth of tools for measuring the psychosocial status of non-psychiatric patients. Others [92,93,94,95] began using the instrument to describe the psychosocial illness experience for patients with cancer and occasionally for other conditions like kidney disease [96,97] chronic lung disease [98], burns [99], and multiple sclerosis [100]. The PAIS and PAIS-SR were tools that helped fill the void in this field of research.

Folkman and Greer [101] provided an appraisal and coping framework that has helped tie adjustment to illness theory to the empirical data generated by research tools like the PAIS. They suggested a model therapeutic program aimed at improving the psychological well-being of patients facing serious illness. Since the 1990s, psychosocial interventions have become increasingly more relevant as evidenced by the meta analysis that Rehse and Pukrop [102] conducted on 37 controlled outcome studies. It is now widely recognized [103] that understanding the process by which most individuals adjust to illness offers important insights to enhance the efficacy of interventions that facilitate psychological adjustment. Helping individuals adjust to their illness has become a priority, especially for those with chronic diseases.

3.6.4. Uncertainty and Illness Theory

The uncertainty and illness theory is another attempt to explain the human illness experience. Spawned from stress and coping theory, uncertainty and illness has been of particular interest to clinicians and researchers trying to understand the challenges of patients coping with chronic illness.

According to Brashers [104] uncertainty exists when details of situations are ambiguous, complex, unpredictable, or probabilistic; when information is unavailable or inconsistent; and when people feel insecure in their own state of knowledge or the state of knowledge in general. Babrow, Hines, and Kasch [105] further postulated that because uncertainty is multilayered, interconnected, and temporal, people experience multiple sources of uncertainty at once, that manipulating one type of uncertainty can impact (e.g., increase or decrease) uncertainties of other types, and that experiences of uncertainty are ongoing and changing features of life.

After an exhaustive search of the psychological literature, Norton [106] concluded that no matter the source, when an event is judged to be uncertain, it will contain one or more of the following eight dimensions: 1) multiple meanings; 2) vagueness; 3) probability; 4) unstructured; 5) lack of information; 6) ambiguity; 7) inconsistencies and contradictions; and 8) unclear. This provided a framework for the concept of uncertainty that has been used in research across multiple disciplines.

Babrow, Kasch, and Ford [107] identified uncertainty as a central part of the experience of illness. They described multiple sources of variation within the concept of uncertainty including, complexity, qualities of information, probability, structure of information and lay epistemology. For example, clarity (e.g., the use of medical jargon), accuracy (e.g., laboratory analytical methods), and ambiguity (e.g., different interpretations of results) are all qualities of information that can vary greatly. They attempted to reconcile sources of variation in conceptions of uncertainty and synthesize more specific conceptions of uncertainty in illness. Recognizing what contributes to uncertainty in illness and how it can be managed remains a daunting assignment. One of the pioneers in this effort was Merle Mishel.

Mishel [108] investigated the role of uncertainty as a significant variable influencing patients' experiences in illness, treatment, and hospitalization. She proposed a model of perceived uncertainty in illness and developed an instrument (i.e., the Mishel Uncertainty in Illness Scale – MUIS) for measuring uncertainty in symptomatology, diagnosis, treatment, relationship with caregivers, and planning for the future. She continued to refine the structure of the model [109,110,111] and the MUIS was applied to a variety of populations [112,113]. In 1988 she published a seminal paper [114] on uncertainty in illness. In this paper she defined uncertainty as the inability to determine the meaning of illness-related events and stated the fundamental belief that uncertainty concerning what will happen, what the consequences of an event are, and what the event means, are important to a person with any illness. Furthermore, she argued that managing the uncertainty associated with an illness and its treatment may be an essential task in adaptation. She encouraged further research applying the model and MUIS in different patient populations and varied settings.

While the model had been previously applied to acute illnesses or those in a downward illness trajectory, little had been done to understand uncertainty in chronic diseases. Mishel [114] reconceptualized the uncertainty in illness theory to address the experience of living with continual, constant uncertainty in either a chronic illness or in an illness with a treatable acute phase and possible eventual recurrence. This was based in part on the qualitative observation that the longer chronically ill subjects lived with continual uncertainty, the more positively they evaluated the uncertainty. This supported the argument that uncertainty can be a positive experience but was contrary to the cultural value that uncertainty is an aversive experience and, except in an extreme situation, is definitely not preferable to certainty.

Drawing on chaos theory, Michel [115] postulated that uncertainty surrounding a chronic illness or life-threatening condition qualified as a sufficient fluctuation to threaten the preexisting organization of the person. Michel viewed uncertainty in illness as:

> "A fluctuation that begins in only one part of the human system and, according to chaos theory, can either regress and cause no particular disruption or spread to the whole system. As uncertain disease related factors, like severity of the illness, success of treatment, impact of illness on one's life, and ability to pursue life's dreams and ambitions, are introduced into the person's life the uncertainty competes with the person's previous mode of functioning. As the concentration of the uncertainty expands, it can exceed the person's level of tolerance, causing the personal system to become unstable. The uncertainty that early in the illness was the source of fluctuation, later in the illness becomes the foundation on which the person constructs a new sense of order." [[115], p. 259]

Thus, she postulated [115] that uncertainty is used by individuals to reformulate their view of life and that this new view of life allows one to view uncertainty as an opportunity rather than a danger or threat. Mishel [115] encouraged health care providers to adopt a probabilistic rather than a mechanistic paradigm. That is, accept uncertainty as a natural, inherent part of reality that is not determinable with precision and abandon the view that uncertainty is the enemy and must be eliminated.

Uncertainty and illness theory has matured over thirty years and become a cornerstone for understanding the psychosocial effects of chronic disease. In studies examining the adjustment to uncertainty in illness [115], the most common conclusion is that high uncertainty is related to high emotional distress, anxiety, depression, and fatigue. This progression has been supported by the work of others beside Mishel who have conducted research to clarify the concepts within the theory [108,116-123], understand how nursing interventions can be used to manage uncertainty [124], to illuminate processes of coping with uncertainty [125,126], and to conceptualize how adaptation to uncertainty effects health-related quality of life [127]. One chronic disease to which uncertainty and illness theory has been successfully applied is prostate cancer.

3.6.5. Psychosocial Effects of Prostate Cancer

According to the American Cancer Society [128], prostate cancer is the second most commonly diagnosed cancer among men in the U.S. and the second most common cause of cancer death among men. In 2010, an estimated 217,730 new cases of prostate cancer were diagnosed in the U.S. [128]. Changes in the incidence of prostate cancer over the past 20 years reflect the widespread use of the prostate specific antigen (PSA) screening tool [128]. According to Tombal [129], the PSA has led to a dramatic increase in the number of patients diagnosed with prostate cancer, a significant number of them being non-clinically significant. The diagnosis of prostate cancer has well-described psychosocial difficulties [130] that vary across stages of disease and types of treatment. Some men, who are asymptomatic and have low-risk, early stage cancer, are eligible for active surveillance which offers a means to monitor the cancer while delaying treatment [130,131]. This is in contrast to watchful waiting which is a conservative management strategy for men who are more likely to die from co-morbidities [131,132]. The result of this phenomenon is that there are now a large number of men living with localized prostate cancer and the uncertainty that it bestows.

Germino, Mishel and others [133] began applying uncertainty of illness theory to prostate cancer soon after the PSA-stimulated diagnosis boom. Since then, studies [134] have shown that prostate cancer is a disease fraught with uncertainty that often makes adjustment to the illness difficult. To gain a richer understanding of uncertainty in men undergoing watchful waiting or active surveillance, qualitative and quantitative studies [132,135,136,137,138] were conducted by number of researchers. Collectively, this body of knowledge has established a foundation from which researchers [139,140,141] can design and conduct randomized clinical trials to evaluate the efficacy of psychosocial interventions. Those experiments and a number of others were recently summarized [142] in the literature. With evidence on the efficacy of interventions in hand, researchers [143,144] are now reporting the results of longitudinal studies to measure the change in quality of life among prostate cancer patients and their partners.

4. Discussion

The example of prostate cancer suggests a possible path forward for the study of the psychosocial effects of CBD. In this example, researchers recognized that prostate cancer was unique from other types of cancers and studied both the physical and psychological aspects of the natural history of the disease. They conducted qualitative studies to gain an initial understanding of the psychosocial problems confronting patients and their partners. Then they developed a theory base (i.e., uncertainty of illness) and conducted quantitative studies to refine a model that accurately described the psychosocial component of prostate cancer. Following this, theory-based interventions were developed, implemented, and evaluated. Finally, longitudinal studies were conducted to determine the long-term effect of the intervention in the study population. Executing a similar systematic approach should be the goal for researchers and clinicians studying the psychosocial effects of BeS and CBD.

There are psychological theories described in the literature that help us understand stress, coping, and chronic illness. We know that the stress of chronic diseases, like CBD, affects people differently. Fortunately, humans have a remarkable ability to adapt to stress when faced with chronic disease. The Transactional Model of Stress and Coping was developed to help us understand the inter-relatedness of stress and coping concepts to health and well-being. This model is commonly used by health professionals who are developing interventions to help people cope with stress. There are valid and reliable instruments, like the MUIS and PAIS, which help us measure the psychosocial effects of stress and chronic disease. These instruments have been used in a variety of studies of chronic illnesses, like prostate cancer, but never to study individuals with CBD.

4.1. Conceptual Model

The conceptual model is based on three prominent psychological theories: 1) health, stress, and coping, 2) uncertainty and illness, and 3) psychosocial adjustment to illness. The model supports the hypothesis that workers who are diagnosed with BeS or CBD experience a great deal of uncertainty and that has a detrimental effect on their health status. The focal relationship in this model is between the independent variable *uncertainty* (i.e., the characteristic being observed) and the dependent variable *health status* (i.e., the outcome of interest). It is suspected that the relationship between these two variables may be partially mediated by an intermediate variable, the ability to make *psychosocial adjustments to disease*. Figure 1 illustrates the conceptual model.

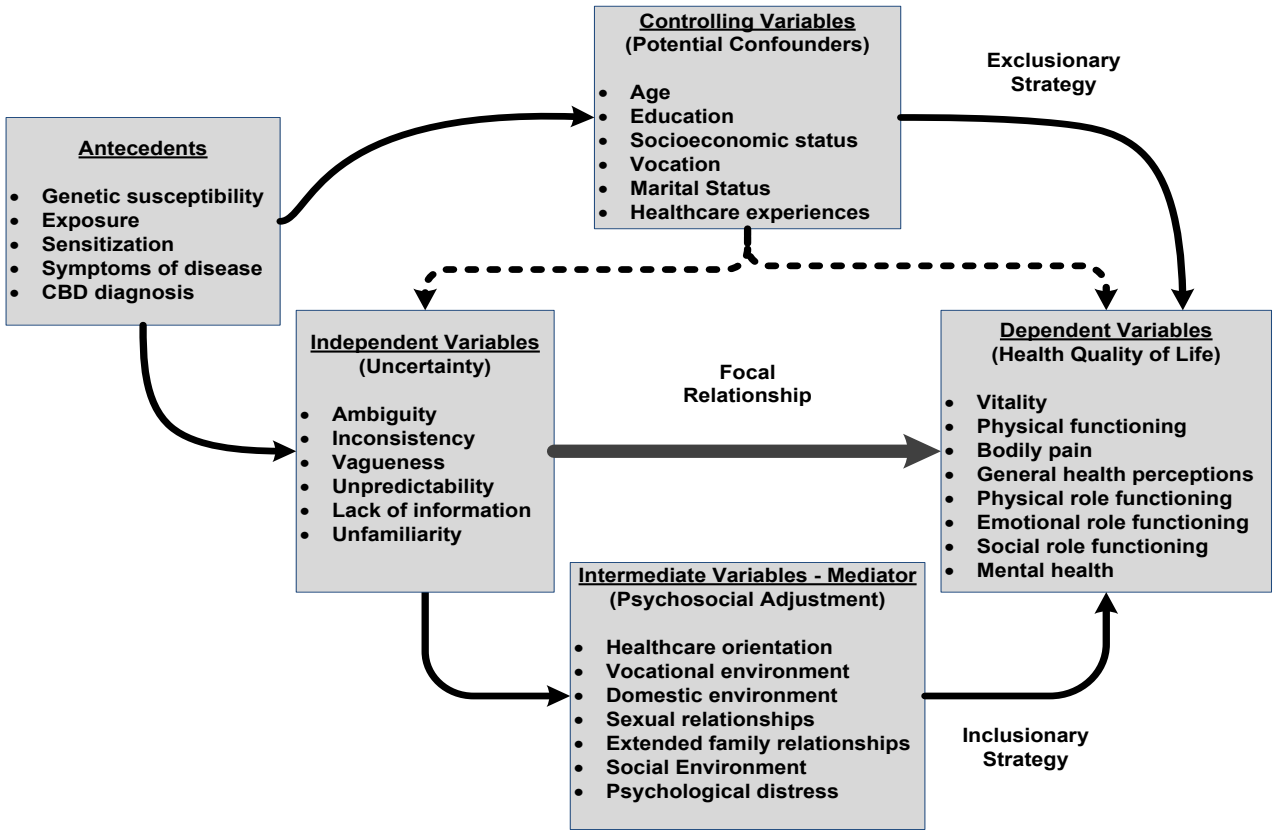

Figure 1. A conceptual model of the psychosocial effects of chronic beryllium disease

As depicted in Figure 1 there are five antecedents (i.e., preceding events) that influence the independent variable: 1) host (genetic) susceptibility to beryllium disease, 2) exposure to beryllium in the workplace, 3) sensitization (allergy) to beryllium, 4) symptoms of CBD, and 5) diagnosis of CBD. Exposure to beryllium in the workplace is the most critical antecedent. Exposure is necessary but not sufficient when acting alone (i.e., one cannot get CBD if he/she is never exposed to beryllium, but exposure does not guarantee that disease will occur). Exposure must be combined with host susceptibility, sensitization, symptoms of disease, and/or diagnosis of CBD to create a necessary and sufficient combination of factors to activate the model.

There are at least six potential confounding variables to be considered: 1) age, 2) education level, 3) socioeconomic status, 4) vocation, 5) marital status, and 6) history of involvement with the healthcare system. These variables may distort the truth because they may be associated with both uncertainty and health status. For example, individuals with a higher socioeconomic status may have less uncertainty (e.g., a more predictable life) because they own their home and have sufficient income so they do not live paycheck-to-paycheck. They also may have greater access to healthcare or seek and comply with medical recommendations better, which translates to regular physical exams and screenings that help prevent the development of chronic diseases (i.e., greater physical functioning).

In the model, uncertainty is proposed as an independent variable that influences health status. This proposition is based on the research conducted by Mishel [108] to determine how uncertainty influences patients' experiences in illness, treatment, and hospitalization. She developed a model of perceived uncertainty in illness and developed an instrument (i.e., the Mishel Uncertainty in Illness Scale – MUIS) for measuring uncertainty in symptoms, diagnosis, treatment, relationship with caregivers, and planning for the future. The MUIS has six primary domains: 1) ambiguity, 2) inconsistency, 3) vagueness, 4) unpredictability, 5) lack of information, and 6) unfamiliarity. In studies examining the adjustment to uncertainty in illness [115], the most common conclusion was that high uncertainty was related to high emotional distress, anxiety, depression, and fatigue.

A proposed intermediate variable is psychosocial adjustment to illness. This proposition is based on the research conducted by Derogatis [89]. He introduced the Psychosocial Adjustment to Illness Scale (PAIS) to assess the psychological and social adjustment of medical patients, or members of their immediate families, to the patient's illness. The PAIS was developed to reflect seven principal domains [89], all of which had been shown to have a high relevancy for adjustment to medical illness: 1) health care orientation, 2) vocational empowerment, 3) domestic environment, 4) sexual relationships, 5) extended family relationships, 6) social environment, and 7) psychological distress. An example of the mediating role this variable may play is illustrated as follows. The lag period between when a person becomes sensitized and develops symptoms of CBD is difficult to predict and may range from months to decades. This subclinical period may be tempered by the individual's healthcare orientation (e.g., their general approach to taking care of their health). That is, someone who is very attentive to their health needs and exhibits healthy behaviors, such as

regular exercising and maintaining a proportional weight, may postpone the onset of CBD symptoms.

In the model, the outcome of interest is health quality of life. This includes both the physical and mental domains. The Rand Corporation developed an instrument (SF-36v2, Quality Metric Incorporated) that measures eight health concepts: 1) vitality, 2) physical functioning, 3) bodily pain, 4) general health perceptions, 5) physical role functioning, 6) emotional role functioning, 7) social role functioning, and 8) mental health. This is a valid and reliable scale that is widely used to measure health quality of life among sick and well populations. Based on anecdotal reports, a hypothetical example has been constructed to illustrate how this model functions.

4.2. Example

A skilled machinist applied for a job at a metal machining and fabrication shop where various aircraft parts were manufactured from beryllium and other metals. Whether he was genetically susceptible to beryllium was unknown. Prior to his employment, he was given a pre-employment physical examination and screened for beryllium sensitization using the BeLPT. The BeLPT was normal, he was declared fit for duty, and hired.

He worked in the factory for 5 years and was promoted to journeyman machinist. Each year he had the BeLPT and the result was normal. Industrial hygiene samples were occasionally collected in the factory and 90% of the results showed that airborne beryllium concentrations were less than the limit of detection of 0.05 micrograms per cubic meter of air ($\mu g/m^3$) and all of the results were less than 0.1 $\mu g/m^3$. This was 20 times less than the Occupational Safety and Health Administration (OSHA) standard so management believed the exposure levels were safe. Several breathing zone samples were collected from various machinists but none were ever collected directly from the breathing zone of this Worker.

During the Worker's annual physical at the start of his sixth year, his BeLPT result was abnormal. The plant nurse told him not to worry as false positives were common with this test and that they always had to do a second BeLPT to confirm the first result. She drew blood for a second BeLPT and sent it to the laboratory for analysis. The results, received six-weeks later, were reported as "borderline." The plant nurse told the Worker that a third test was needed because a borderline test was neither positive nor negative. They repeated the test and waited six more weeks for results. This result was also abnormal. The Company Doctor told the Worker that he was sensitized to beryllium. The Worker had no symptoms and his pulmonary function tests were normal. The Doctor told him he could not say with certainty if or when he might develop CBD. He said some people went for 10-15 years and never developed symptoms and others developed symptoms within a few months; everybody was different. In the meantime, it was prudent that he no longer work with beryllium.

The Worker's supervisor told him that he would not be able to come back to his machinist position because it was company policy that a sensitized worker could not work around beryllium and they did not have any machinists positions where he would not be potentially exposed to beryllium. He said he could transfer to the grounds maintenance, however, if he chose to do that he would have to work at a 50% pay reduction.

The Worker went home and told his wife that he would have to take a 50% pay reduction and work on the grounds crew if he wanted to stay at the factory. She was concerned about that but was mostly worried about what would happen if he developed CBD. The Worker wondered if he was going to have to change careers. He had always been a machinist and did not know what else he could do and make an equivalent salary. He wondered if he could make an insurance claim for disability or workers compensation because he was sensitized to beryllium.

In this example, the reader may have recognized two of the antecedents (i.e., exposure and sensitization) along with several sources of uncertainty. Ambiguity was represented by the alternating normal and abnormal BeLPT results. Vagueness was represented by the industrial hygiene sampling results that were reported as less than the limit of detection. Unpredictability was present when the Doctor described the natural history of CBD. Lack of information was present when the Worker wondered about whether he was eligible for a workers compensation or disability insurance claim. Unfamiliarity was present when the Worker wondered about what other trade he could learn.

The effect of this uncertainty may be mediated (i.e., modified) by the Worker's individual situation and life experiences. For example, his wife had a job in the healthcare field that paid well and mediated some of the healthcare and financial uncertainty. He had two friends from the factory that also had become sensitized to beryllium and they had joined a local CBD support group. This may have mediated the social functioning. His brother owned a construction business and he talked to him about working for him, helping to mediate the vocational uncertainty. This hypothetical example is a composite of actual scenarios and demonstrates the potential for uncertainty with BeS and CBD.

Creating this model is a step toward filling a void in our understanding of the natural history of CBD. Once validated, it will establish a foundation for future research and program evaluations and may lead to changes in the psychological, social, financial, and disease management support provided to this population.

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Statement of Competing Interests

The authors have no competing interests.

Authors Declaration

This paper does not breach the copy right of other persons and has not been published or submitted for publication to any other journal or book.

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