Biosocial Pathogenesis

Ralph I. Horwitz^a Burton H. Singer^b Allison Hayes-Conroy^c Mark R. Cullen^d
McKayla Mawn^e Katharine Colella^e Ida Sim^f

^aDepartment of Medicine, Lewis Katz School of Medicine, Temple University, Philadelphia, PA, USA; ^bDepartment of Mathematics, University of Florida, Gainesville, FL, USA; ^cGeography and Urban Studies, Temple University, Philadelphia, PA, USA; ^dStanford Center for Population Health Sciences, Palo Alto, CA, USA; ^eLewis Katz School of Medicine, Temple University, Philadelphia, PA, USA; ^fDivision of General Internal Medicine, University of California, San Francisco, CA, USA

The headline was irresistibly provocative: “Lonely flies, like many humans, eat more and sleep less,” suggesting the proof of cause to a long-standing but unproven epidemiological association between loneliness and poor health [1]. Yet, pulling back the veil on the sensational implications in the headline reveals the limitations of our current approach to and the need for a new model that explains disease pathogenesis. In this paper, we propose a model, biosocial pathogenesis, that integrates both a person’s biology and their biography, or lived experience. To understand why this new approach is needed, and how it might help us to tailor treatment more effectively for patients, let’s begin by looking more closely at what happens to flies and humans who are socially isolated.

A rigorous science of social relationships and especially their health consequences developed as part of a broader consideration of the role of social determinants of health [2, 3]. Social isolation and loneliness have been a focus of research by social epidemiologists and geriatrics specialists for decades, culminating in a notable event with the appointment of a Minister of Loneliness in 2018 by then British Prime Minister Theresa May [4]. Her decision became prescient when the Coronavirus pandemic

made social isolation part of the therapeutic strategy to control and defeat the epidemic.

One of the challenges in carrying out research on social relationships is how easily terms can be misunderstood. Social isolation (the objective state of having few social relationships or infrequent social contact with others) is not the same as loneliness (a subjective feeling of being isolated). Social isolation and loneliness are different concepts and are measured differently. The National Academy of Medicine in its authoritative 2020 report on social isolation and loneliness in older adults stated, “While there is evidence that loneliness is associated with mortality, the existing evidence does not yet approach the cumulative weight of evidence for the association between social isolation and mortality.” Furthermore, as the report points out, some isolated persons are lonely, but many others are not. And it is also true that many lonely individuals are not isolated at all [3]. Which brings us back to the flies and a fresh conceptualization of disease pathogenesis.

Mark R. Cullen is retired.

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In an act of imaginative experimentation, Li et al. [5] used the exhaustively studied fruit fly, *Drosophila melanogaster*, as a model for studying the effects of social isolation. The investigators kept flies in groups or in isolation for either 1–3 (acute) or 5–7 days (chronic). Flies kept in acute isolation or in groups behaved normally, but flies kept in chronic isolation had disrupted sleep and ate twice as much food. Remarkably, the investigators succeeded in identifying 214 genes from whole fly heads whose expression was changed, and many of these genes are known to be associated with biological pathways that influence patterns of sleep. So far so good. What are we to make, however, of the conflation of isolation with loneliness, something that happens often in research on humans, or of the inference by commentators of the research that the change in behavior of the flies was attributable to feelings of loneliness, for which no fly-specific psychometric scale or index was reported?

Despite the leaps of inference by those who have commented on the research, it is thrilling to witness research that attempts to link so directly and so fundamentally the biology of the fly with its social context. It is this very linkage that now is required with equal imagination and rigor to understanding how individual human biological difference and individual human biographical difference affect each other to create the risk for disease and the response to treatment. The stage for this new research paradigm, that we refer to as biosocial pathogenesis, has been well set.

Nearly two decades ago, the neuroscientist Bruce McEwen argued that chronic stress could both damage health and accelerate disease [6]. His emphasis on stress was based on a series of novel conceptual and experimental advances that described the many ways in which adaptation to chronic stress impacts trajectories of health and disease [7]. In a landmark paper with Elliot Stellar they pointed out the hidden costs of chronic stress to the body over long periods of time, and how individual differences in the susceptibility to stress are tied to individual behavioral responses and environmental challenges all of which are coupled to physiological and pathological responses [8].

Modern Foundation for Biosocial Pathogenesis

McEwen and Stellar proposed a model in which the stress to disease relationship was linked to two factors that are unique to the individual, the way a person perceives a

situation, and a person's general health, determined by genetic and biological factors but also by life experience. Some isolated people may perceive their isolation as a source of stress and the adaptation that they will make to this chronic stress will require the participation of their physiological systems, an adaptation referred to as allostatic load [9–11]. This interaction of the perception of stress with the patient's unique biology is an example of biosocial pathogenesis. There are many more.

Consider as further example how the biological pathogenesis of type 2 diabetes mellitus is understood. Decreased peripheral glucose uptake, primarily by muscle, combined with increased endogenous glucose production are characteristic features of insulin resistance. Compensatory insulin secretion by the pancreatic beta cells at first maintain normal range plasma glucose levels, but beta cell function worsens over time.

The biological story sounds compelling and complete until you start to ask what is happening in the patient sitting across from you in the office. It turns out that there is enormous inter-individual variation in diabetes and that biography plays a critical role. In a study of 800 people without diabetes that included diverse data such as sleep, physical activity, weight and diet, gut microbiome inhabitants were assessed and the participants' blood glucose was measured weekly [12]. The research demonstrated that postprandial glucose response is highly variable across individuals even when individuals ate the same standardized meals, and that clinical features and microbiome composition accurately predicted each person's postprandial glucose response. Previous studies have documented how social relationships and stress strongly influence the composition of a person's microbiome [13]. It is also well documented that stress and anxiety are influences on glucose regulation, both through the hypothalamic pituitary adrenal (HPA) axis and the sympatho-medullary pathways.

Epigenetics is another biological process that is influenced by biography, as we learned in a series of tragic natural experiments, such as the Dutch Famine Study in which an enforced food blockade by the Nazis resulted in famine causing some genes to be silenced for the fetus in utero with health effects that are experienced later in life [14]. Other examples abound, including the effects of social and biological influences on circadian rhythms, immune system regulation, and sleep patterns and disruption [15].

There is also an enlarging scientific literature on how everyday experiences in life influence human gene expression. Living in dense urban areas, being poor or poor-

ly educated, experiencing discrimination or social threats have been associated with differential expression of gene transcripts in leukocytes and even diseased tissues such as metastatic cancer. Cole and his colleagues have demonstrated that social adversity elicits a conserved transcriptional response to adversity that is characterized by the enhanced expression of pro-inflammatory genes and the reduced expression of genes involved in innate antiviral responses and antibody formation [16].

The extensive research on stress and disease over the past 50 years, the groundbreaking work on social isolation, social networks and the broader life context, the emerging understanding of how social adversity broadly defined affects health (including discrimination, marital discord, job loss and many other life events), all point to the critical role of a person's unique biography in both the risk for disease and the response to treatment of disease [17]. What do we mean, then, by a patient's biography?

Biography is a description of a person's life that involves more than listing facts such as education, work, relationships, and death. Biography portrays a person's experience with and perception, or sense-making, of these events. Medical biography is the person's lived experience, their understanding of those experiences elicited as relevant information in the evaluation and management of disease [15]. Consider too that biographical factors can be positive or negative. The same "objective" social relationship, marriage for example, can be perceived as caring and supportive or a source of exploitation and abuse. Perceived social isolation (loneliness) increases attention to events and stimuli that are interpreted as negative, making the unique biography of the individual subject a critical element of any effort to understand the pathogenesis of disease associated with isolation.

The term "biosocial" is not new and has been referred to in previous work, perhaps most notably by George Engel [18]. The biopsychosocial model described by Engel was a revolutionary idea that strongly influenced the approach to care that was adopted by the specialty of family medicine. A recent commentary highlighted Engel's concern that the transition from a narrow biomedical challenge to the biopsychosocial model was a major challenge to medicine in the modern era [19]. New biosocial science builds on the Engel foundation while giving greater emphasis to social determinants and structural issues such as race and racism, inequality, poverty, and trauma [20].

Biosocial pathogenesis is distinctive in its efforts to understand the scientific basis of the intimate relationship between biology and biography [21]. Biosocial pathogenesis is a complex process requiring the interplay of extrin-

sic (outside the body) and intrinsic (inside the body physically or mentally) factors. Extrinsic factors include societal structural issues (such as health care access, but also racism, sexism, and ageism), environmental factors (including excessive heat or cold, floods, famine, and drought), life events (of marriage/divorce, trauma, immigration, and job loss or gain), personal behaviors (sleep, exercise, eating), and especially how individuals experience their life (acute or chronic stress, learning, love, trust, depression, etc.). And all of these extrinsic factors interact in complex ways with intrinsic conditions (personality traits, and inherent capacities such as self-efficacy, coping strategies, and resilience) and an individual's diverse biology (our microbiome, genomics, metabolomics, epigenetics, etc.). Although some biosocial pathogenesis pathways are the focus of considerable research, such as how stress causes disease, other pathways such as the influence of loneliness on health are still lightly researched and poorly understood.

Biosocial Pathogenesis Is Different than Current Model of Disease Pathogenesis

The current model of a strictly biological disease pathogenesis is wrong: it is insufficient to account for all of the factors that make individuals susceptible to disease, resilient when disease occurs, and variably responsive to treatment. For that reason, it misleads us when we develop therapeutic strategies to treat disease, and leaves physicians and patients frustrated by less benefit from treatments than expected.

If we treat adult-onset diabetes mellitus as a biological disease alone, and do not pay equal attention to the role of social and lifestyle factors such as stress, social adversity, and exercise [22], we will fail to achieve our treatment goals despite the extraordinary plethora of new anti-diabetic medications developed over the past two decades. If we continue to understand asthma as an inflammatory disease of the conducting airways, modified by newly described immunological pathways, and fail to account for the ways that life experience, physical environments, and social factors influence the expression of disease, even the newest biological agents targeting IgE and eosinophils will not adequately control the disease. Biosocial pathogenesis is a critical new way of thinking about disease origin and progression because we need biosocial approaches to disease prevention and treatment. The COVID-19 disease pandemic has tragically and powerfully made this point. Neither vaccines to prevent the dis-

ease or monoclonal antibodies to treat it are sufficient without the social and behavioral strategies of mask wearing, social distancing, and individual adherence to strategies that benefit the population as well as the person.

It is important to acknowledge the extensive research in humans that seeks to understand the mechanisms that underlie the adverse health effects of social isolation and loneliness. Human investigations of neuroendocrine stress mechanisms suggest both the activation of the HPA axis and, importantly, disruption of a social bond between a significant pair of individuals, are critical contextual elements in humans that are difficult to model in flies [23]. Key to this understanding is the central role of the human brain that does not simply react to stimuli but rather interprets and evaluates stimuli and activates physiological and pathological systems in light of current states, prior knowledge, and anticipatory options.

Approaches to Research and Practice of Biosocial Pathogenesis

The old methods of research for biological pathogenesis do not suffice for the new model of biosocial pathogenesis. Putting a fly alone in a test tube is not the same as a person choosing social isolation or having it imposed on her. While we may never know whether an isolated fly feels lonely, we can know whether the social isolation of a person is experienced as loneliness. Integrating this knowledge with broader elements of the person's biography, and the insights derived from the biological research on the brain and the physiological changes that occur under conditions of social isolation, will together give us a richer understanding of the biosocial pathogenesis of diseases influenced by isolation and loneliness.

Of course, no one will randomize subjects to be socially isolated, nor to loneliness. Because these are choices either made or imposed by circumstances, their study will require the use of "real-world" data in which both biological and biographical features are present. Occasionally, natural events will create circumstances in which we can study the interplay of biology and biography, as when the financial crisis of 2008 increased financial stress for many people, or the coronavirus pandemic, in which social isolation has been necessitated as a therapeutic approach to infection control.

Even these natural experiments, as valuable as they are, will need to be supplemented by studies that systematically collect data that is able to integrate pre-specified measures of biology and biography, especially

for disease-specific biosocial pathogenesis. What can we do now? A committee of the National Academy of Medicine (NAM) in 2015 defined a set of 12 social/psychological domains that should be added to all clinical research to enable biosocial research. These domains included financial resource strain, stress, depression, social isolation, and intimate partner violence, among others [24].

The NAM proposal for psychosocial domains suggests what might be measured, but does not suggest how it should be measured. Most currently available measurement tools are indexes and scales that are developed based on psychometric principles that do not always reflect the experience of the patient or the practice of medicine. For instance, quality of life scales and patient reported outcome measures were developed with psychometric criteria for validity and thus emphasize homogeneity of elements in the scale, even though in clinical medicine patients express a heterogeneous array of symptoms with varying levels of severity. Assessing the role of biography will require a "clinimetric" approach that acknowledges the distinctive context of the patient experience. Considerations will encompass diverse issues such as patterns, severity, and duration of symptoms and their rate of progression, psychological well-being and euthymia, and many other contextual features the patient denotes as important to their current ill health. Fortunately, an array of new clinimetric tools have been developed to measure allostatic load, lifestyle, and well-being, among others.

Health systems should collect biographical data using these tools routinely in their EMRs to monitor patient care and to carry out research on biosocial influences on clinical outcomes. Pharmaceutical companies testing new medicines and companies testing new devices for regulatory approval could design studies that include these and other apposite measures in the design of their studies. Clinical and translational scientists need to adopt these biopsychosocial measures and develop new ones as we broaden our understanding of the interplay of biology with life experience. In particular, it is time now to expand the important work on the measurement of clinical experience that can help to provide fresh insights into a patient's biography [25, 26]. Finally, journal editors should require investigators to expand the table 1 features of cohort composition to more broadly represent life experience and a subject's biography, and to use this expanded scope of features in the analysis of results [27].

Concluding Comments

Biosocial pathogenesis is a conceptual paradigm for understanding the origin and development of disease that integrates both a person's biology and biography (life experience). Biosocial pathogenesis is a complex process requiring the interplay of extrinsic (outside the body) and intrinsic (inside the body physically or mentally) factors. A strictly biological model of pathogenesis that ignores a person's life experience and social context is insufficient to account for all of the factors that make individuals susceptible to disease, resilient when disease occurs, and variably responsive to treatment. We may never know if isolated flies are lonely, but the time is past when our understanding of disease pathology can be limited to biology alone. Only by integrating biology with biography can we have a complete appreciation for disease pathogenesis, and a successful development of treatments that will create the maximum benefit for our patients [28].

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