Epigenomic Susceptibility to the Social World: Plausible Paths to a "Newest Morbidity"

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ABSTRACT

This article—presented on the celebratory occasion of Dr Robert Haggerty's 91st birthday—describes how a 1962 article by Dr Haggerty and his colleague Dr Roger Meyer launched a previously unexplored, pediatric research enterprise by asserting that: "There are little precise data to explain why one person becomes ill with an infecting agent and another not." Noting a prospective association between family stressors and the acquisition of β-hemolytic streptococcal infections, the article introduced a generation of young academic pediatricians—the author of the present article among them—to the possibility of causal linkages among children's adversity exposures, compromised immunological processes, and the development of immune-mediated, acute or chronic diseases of childhood. That research agenda has led, over the past 40 years, to the advent of psychoneuroimmunology as a field of study, to the recognition of childhood stress and adversity as potential etiologic agents among childhood morbidities, and to the discovery of differential susceptibility to social adversities within populations of children.

KEYWORDS: childhood adversity; differential susceptibility; psychoneuroimmunology

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I LEARNED EARLY in my professional career about 2 related, clinical phenomena about which Bob Haggerty taught and wrote extensively. First, it became apparent to me, as a pediatric resident, that children's medical charts were of 2 distinctive types, divided according to their bimodally distributed mass (this was the era in which charts were measurable in pounds and ounces, rather than in bytes and bits). Most patients had health care records of diminutive proportion: slim, succinct, virtually weightless. But there was a subgroup of our patients whose charts were ponderous, dog-eared tomes, filled with page after page of carefully and exhaustively rendered notes that recorded clinic visits, hospitalizations, disease complications and remissions, laboratory values, and medical procedures. Pediatric charts were either vanishingly small or massively large and usually delivered on wheeled carts.

Although I could not, at the time, have articulated the meaning or significance of this observation, I had stumbled upon the single most well replicated finding in all of previous child health services research: ie, that, as shown in Figure 1, a modest subsample of 15%–20% of children, within any given childhood population, sustains well over half of the physical and mental morbidities within that population and utilizes the major portion of the available health services. In an enormous variety of populations of children around the world—of varying ethnicities and strikingly disparate socioeconomic conditions—approximately 1 child in 5 has a radically disproportionate share of the illnesses, injuries, and psychological or behavioral disorders borne by the larger childhood population.

It is easy to understand the public health significance of this phenomenon: if we could identify the provenance of the morbidities endured by that small subgroup of children, we might effectively address and potentially prevent more than half of the entire population's collective afflictions and disabilities. What I could not have been aware of at the time was this phenomenon's position as the health instantiation of a more general principle first enunciated by a nineteenth century, Italian economist, Vilfredo Pareto. Pareto observed that approximately 80% of Italy's wealth belonged to 20% of its people and, more generally, that approximately 80% of effects come from 20% of causes.[1] So it also is in the distribution of human disease.

The second of my 2 early revelations emanated from having discovered a 1962 article by Roger Meyer and pediatrician Robert Haggerty, whose birthday and work this collection of articles commemorates. The article, entitled "Streptococcal infection in families: factors altering individual susceptibility,"[2] began with the observation that "There are little precise data to explain why one person becomes ill with an infecting agent and another not." It described an intensive, year-long study of 16 young, lower middle class families, comprised of 100 persons, each of whom underwent regular throat cultures for β-hemolytic streptococci, periodic measures of antistreptolysin O titers, and clinical evaluations of all illnesses. Acute and chronic

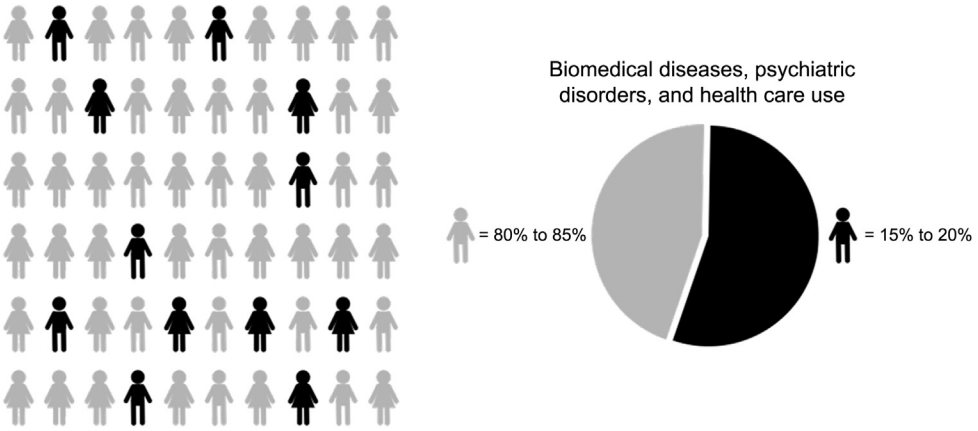

Figure 1. *The nonrandom distribution of childhood morbidities: 15% to 20% of children (approximately 1 in 5) sustain most of a childhood population's overall morbidities.*

family stressors were identified as one determinant of whether a given individual acquired infection, developed an antistreptolysin O response, or became ill, and this early Haggerty article became a pivotal, direction-setting signal in the research agenda of academic pediatrics.

Further, it seemed possible that the nonrandom occurrence of illnesses in children and the apparent role of family stressors in undermining disease resistance were plausibly linkable phenomena. Perhaps one of the determinants of exceptional disease vulnerability in a subgroup of children could be their disproportionate exposures to adversity within the family context. I thus became interested in, and eventually preoccupied with, the question of whether early psychological stress might function as a predisposing factor in the causation of childhood illnesses, infectious as well as noninfectious. My discovery, as a postdoctoral fellow, of the work of John Cassel, a South African epidemiologist who described the role of the social environment in disease etiology,[3] served only to reinforce and further augment that preoccupation. Haggerty went on to later describe these stress-related forms of childhood illness as "the new morbidity," demanding novel pediatric skills in managing the psychosocial origins of childhood disorders.[4]

INDIVIDUAL DIFFERENCES IN THE HEALTH EFFECTS OF ADVERSITY

Early studies of stress and illness, however, proved frustratingly inconclusive. A number of investigators—myself among them—were reporting reliable associations between childhood stressors and the incidence, duration, and/or severity of subsequent disease, associations highly unlikely to be attributable to the operation of chance alone. My colleagues and I found, for example, in one early project, that stressful life events among preschool-age children significantly predisposed them to longer, more persistent respiratory illnesses.[5] And social epidemiology, more broadly, began to document how children growing up in disadvantaged, often stressful conditions were liable to the acquisition of acute and chronic morbidities. Such adversity-exposed children appeared disproportionately susceptible to acute biomedical illnesses, chronic health conditions, minor and severe injuries, and disorders of mental health. The credibility of this emerging literature was even further bolstered by evidence—some of it truly experimental in design (eg, Cohen et al[6])—that immunologic processes often serve as mediating mechanisms in the linkage between adversity and disease.[7]

However, all was not well and universally promising within nascent research on social environmental determinants of health and illness. Among the difficulties confronting the research were those represented in Figure 2. Although strong, statistically significant, linear associations were quite regularly found between exposures to stressful, disadvantaged early environments and developmental or health outcomes, there was also an ubiquitous and striking individual variation in the consequences of such exposures.[8] Although highly reliable relations were found—for example, between family stressors and child behavior problems or between socioeconomic status and literacy scores—they never accounted for much more than 10% of the variance in outcomes, because of the extreme individual variation in effects. My research group spent some early years attempting to remove this "noise" from the adversity signal by developing more valid and reliable measures of exposure, by examining more proximal outcomes, and by moving from retrospective to prospective study designs. Eventually, however, we began to conclude that the noise was actually not noise, but rather the "music," ie, the variation in individual response was in fact the very issue to which we should be more closely attending.

With this change in perspective, we began to develop methods for measuring individual differences between children in their biological responses to a set of highly standardized, age-appropriate, laboratory challenges. Taking our lead from the adult literature on cardiovascular reactivity to stress, my colleagues and I conceived a highly scripted, standardized child reactivity paradigm, focused on the 2 principal human stress response systems in the brain: the corticotrophin-releasing hormone/hypothalamic-pituitary-adrenocortical system and the locus coeruleus-norepinephrine system. The former system regulates the expression of the glucocorticoid hormone cortisol, with its widespread, profound effects on