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Capitalizing on Advances in Science to Reduce the Health Consequences of Early Childhood Adversity

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Advances in biology are providing deeper insights into how early experiences are built into the body with lasting effects on learning, behavior, and health. Numerous evaluations of interventions for young children facing adversity have demonstrated multiple, positive effects but they have been highly variable and difficult to sustain or scale. New research on plasticity and critical periods in development, increasing understanding of how gene-environment interaction affects variation in stress susceptibility and resilience, and the emerging availability of measures of toxic stress effects that are sensitive to intervention provide much-needed fuel for science-informed innovation in the early childhood arena. This growing knowledge base suggests 4 shifts in thinking about policy and practice: (1) early experiences affect lifelong health, not just learning; (2) healthy brain development requires protection from toxic stress, not just enrichment; (3) achieving breakthrough outcomes for young children facing adversity requires supporting the adults who care for them to transform their own lives; and (4) more effective interventions are needed in the prenatal period and first 3 years after birth for the most disadvantaged children and families. The time has come to leverage 21st-century science to catalyze the design, testing, and scaling of more powerful approaches for reducing lifelong disease by mitigating the effects of early adversity.

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Extensive research indicates that responsive relationships and health-promoting environments in the early years provide a strong foundation for a lifetime of effective learning, adaptive behavior, and good health.[1] In contrast, chronic stress without the buffering protection of supportive caregiving can produce patterns of adaptation and physiological disruptions that become embedded biologically and increase risk for multiple impairments, including cardiovascular disease, type 2 diabetes, addictions, and depression.[2] Abundant evidence also indicates that the longer we wait to intervene the more difficult it becomes to achieve healthy outcomes.[3]

Decades of evaluation research reveal that effective interventions for disadvantaged, young children can produce short-term developmental gains, higher rates of high school graduation, increased adult employment, and reduced incarceration. However, the average magnitude of effect is typically modest, and few studies have assessed health outcomes.[4] In this context, 21st-century biology offers an opportunity to gain greater understanding of why some interventions work better than others both inside the brain and throughout the body. Leveraging that knowledge could inform more effective strategies for reducing disease by mitigating the effects of adversity early in life.[5,6]

Mobilizing Diverse Frameworks and Converging Knowledge

Three complementary bodies of work have generated growing attention to stress-related illness. These include the reported association between adverse childhood experiences and adult disease, the concept of toxic stress, and the notion of trauma-informed care.

The Adverse Childhood Experiences Study[7] collected retrospective data on 10 types of childhood maltreatment or household dysfunction from more than 9000 middle-class respondents in 1995-1996 and found a linear correlation between the number of reported adversities and multiple health impairments in adulthood, including heart disease, obesity, cancer, alcoholism, and depression. Although retrospective data have limitations, more than 50 reports from the Adverse Childhood Experiences Study[8] over the past 20 years have confirmed this linkage.

In 2005, the National Scientific Council on the Developing Child, working in collaboration with the FrameWorks Institute, introduced the term *toxic stress* to describe excessive or prolonged activation of stress response systems in the absence of buffering protection from adult caregivers.[2,9] The precipitants in early childhood include extreme poverty, child maltreatment, maternal depression, parental substance abuse, and family violence. Potential consequences include the disruption of developing brain architecture, other maturing organs, and metabolic functions, as well as a lowered threshold for stress system activation that can lead to greater risk of chronic disease. This differentiates toxic from positive and tolerable stress responses, which do not produce lasting biological consequences.[9]

Although many questions remain about the pathogenic nature of stress, broad agreement exists on several key concepts. McEwen[10] conceptualized the consequences of excessive stress activation (including the effects on the hypothalamic-pituitary-adrenal axis and

autonomic, metabolic, and inflammatory systems) and the vulnerability of neural circuits that mediate cognitive, social, and emotional development as the dysregulation of mediators of adaptation (allostasis). These mediators operate interactively and nonlinearly. When persistently activated or dysregulated in association with risky behaviors precipitated by adversity, they lead to increased allostatic load or overload.[11,12] When disease follows, it reflects the physiological, epigenetic, and structural price that the brain and body pay for adapting to significant challenges.[13]

Excessive stress activation during early childhood shifts mental and physiological resources from long-term development to immediate survival, increases vigilance at the cost of focused attention, stimulates impulsivity at the cost of behavioral regulation, and limits long-term biological investment in the brain and other organ systems to the detriment of later health and capacity. Over time, chronic stress can alter biological functions associated with immunity, growth, cardiovascular function, metabolism, and sleep.[14]

Trauma-informed care is an approach to the design, organization, and delivery of behavioral health services based on an understanding of the distinctive nature of impairments that are caused (or exacerbated) by significant exposure to violence, loss, or other emotionally traumatic experiences. In 2014, the Substance Abuse and Mental Health Services Administration[15] published a report to advance the integration of trauma-focused research, practice-generated knowledge, and the perspectives of trauma survivors. That report presents the following 6 principles to guide effective practice: safety; trustworthiness and transparency; peer support; collaboration and mutuality; empowerment, voice, and choice; and cultural, historical, and gender issues.[15] Some treatment models (eg, cognitive behavioral therapy and child-parent psychotherapy) have been modified to incorporate these principles, and positive outcomes have been reported.[15-18] However, variability in definitions and gaps between research and practice have led some experts to question whether trauma-informed care produces greater benefits than conventional, evidence-based treatments.[19]

In summary, adverse childhood experience (ACE) scores quantify increased risk (but not a diagnosis) of later health problems, toxic stress focuses on causal mechanisms that link adversity to impairment, and trauma-informed care provides guidelines for treatment. Building on their diverse origins in epidemiology, biology, and clinical practice, these 3 bodies of work present an opportunity to construct an integrated approach to the prevention and management of stress-related disorders beginning in the earliest years.

Moving From Proof of Concept to Larger Effects at Scale

The diverse landscape of programs for young children and families facing adversity has produced many positive effects, but the variable quality of the data on services received and outcomes achieved makes it difficult to determine which interventions are effective for different populations in different contexts. This difficulty is particularly true for children who face threats to healthy development (eg, maltreatment and maternal depression) that require specialized services exceeding the capabilities of most community-based programs. The challenge is especially urgent during the prenatal period and first 3 years after birth, when neuroscience tells us that the stakes are high.

The most rigorous data from programs that begin before age 3 years are from the Carolina Abecedarian Project,[20] a 1970s intervention for children living in poverty that provided center-based services by trained staff from early infancy to age 5 years. Although its short- and long-term effects on multiple developmental outcomes have been well documented, its scalability has been limited. A report of treatment-control differences in blood pressure and metabolic syndrome 30 years after enrollment in the project provides a rare example of an adult health effect from an early childhood intervention, but the absence of a causal explanation limits its replicability.[21]

The largest system of services for infants and toddlers living in poverty—Early Head Start—offers a promising infrastructure for population-level effect, but the data on its implementation and effectiveness are problematic. The initial evaluation launched in 1996 (based on random assignment of 3001 families at 17 sites) showed small mean effects at age 3 years on multiple child outcomes (effect size range, 0.10-0.20) and some aspects of parenting.[22] Subgroup analyses focused on race/ethnicity, demographic risk, and nonspecific program features found differences in multiple child and family outcomes over time but no identified patterns to guide targeted replication. The variable types and amount of services received by both treatment and control groups also make it difficult to draw valid inferences about the program effects.[23]

The more systematized approach to service definition and implementation used by the Nurse-Family Partnership from the prenatal period to age 2 years provides an alternative example of program development and evaluation.[24] As this intervention is being scaled, challenges serving less responsive subgroups (eg, women experiencing depression or family violence) are being addressed through "model improvement research," which involves pilot testing, evaluation, and translation of promising findings into practice.[25]

Understanding variability in response to adversity is essential for prescribing effective interventions. This variation—often labeled vulnerability or resilience—can be influenced by differences in children, caregivers, families, or communities. This distinction is particularly important for children who exhibit increased biological sensitivity to context, resulting in high rates of psychiatric disorders under adverse conditions yet high levels of adaptive behavior in nurturing environments.[26,27] Greater focus on heterogeneity of needs and differential response to services calls for a more active role for parents in the development and evaluation of new interventions for young children facing adversity. This approach is aligned with the mission of the Patient-Centered Outcomes Research Institute,[28] which was established by the Patient Protection and Affordable Care Act of 2010 to fund clinical effectiveness research responsive to the concerns and outcomes that are most salient for patients.

Looking forward, population-level reductions in stress-related disease will depend on the formulation of science-based theories of change to drive the design of explicit strategies targeted toward identified subgroups focused on specific causal mechanisms to produce important outcomes. Statistically significant, average program effects without causal explanations have limited value because successful replication demands adaptations for different populations. Greater focus on mediating variables that are amenable to intervention (eg, self-regulation in children or interactional skills of parents) suggests a more promising strategy than subgrouping by maternal education. Services matched to key moderators (eg, family strengths

and cultural values) are likely to be more effective than categorical assignments based on race/ethnicity. Beyond the need for greater specificity in program design and impact evaluation, advances in implementation science are essential for producing greater effects at scale.[29,30] Demonstration projects that produce positive outcomes for small numbers of children illustrate what is possible, but population-level effects require expertise in implementation to assure model fidelity and adaptation to context.

Building a More Robust Science Engine to Catalyze Breakthrough Outcomes

Discoveries in neuroscience and epigenetics indicate that children must be protected from the biological disruptions of toxic stress and not just provided with enriched learning opportunities. Therefore, new policies to promote health and prevent disease must begin with more effective strategies for reducing poverty, maltreatment, community violence, racism, and other threats to child well-being, as well as strengthening neighborhood-level supports to reduce the precipitants of toxic stress.[31] However, addressing these challenges is far beyond the capacity of the health care system alone. Nevertheless, given the critical role of caregivers in protecting young children, pediatricians must move beyond simply providing information and focus greater attention on capacity building for parents raising young children under adverse conditions.

Evidence-based approaches to strengthening adult capabilities through mentoring and coaching offer a powerful strategy for supporting parents whose adaptive skills are constrained by the consequences of their own adverse childhood experiences. Interventions that strengthen executive functioning, self-regulation, and mental health increase caregivers' ability to buffer their children from stressors and scaffold the early development of resilience.[32] These core capabilities also enhance a parent's employability and the likelihood of greater family economic security, which further improves a child's life prospects. In short, if we want to achieve breakthrough outcomes for children facing adversity, we have to support the adults who care for them to transform their own lives.[5]

As new interventions are developed, valid and reliable measures of toxic stress effects will be essential for assessing their impacts. These measures (both biological and biobehavioral) must be sensitive to short-term changes in mediators of long-term health outcomes and feasible, affordable, and acceptable in practice settings. Assessing their predictive validity requires mining of extant longitudinal databases and new cohort studies using state-of-the-art measurement batteries. Equally important, given the ethical and political sensitivities of collecting biological information from disadvantaged children (particularly children of color), progress will require trusting collaboration among scientists, clinicians, community leaders, and parents.

The biological basis of heightened responsiveness to environmental influences (ie, plasticity) represents another fertile area of investigation. This work includes research on the role of excitatory-inhibitory circuit balance as triggers of critical periods in brain development, pruning of synaptic connections as mediators, and molecular "brakes" as stabilizers that limit adult brain plasticity but also provide potential mechanisms for reopening critical periods previously considered to be irreversible.[33] Sensitive periods in the developing circuitry of advanced executive function skills in early adulthood as well as evidence from animal studies that excessive stress can accelerate the opening and closing of some critical periods in infant brain development are 2 examples of findings with implications for optimal timing of both child- and parent-focused interventions.[34]

The biology of variation in vulnerability and resilience presents another rapidly moving research frontier that is ripe for application. Epigenetic discoveries could inform targeted interventions matched to differences in how children and families respond to different adversities and alternative services.[35] Drawing on lessons learned from the prevention and treatment of infectious disease, progress in combatting the consequences of toxic stress could be achieved by a multitiered strategy guided by insights about its underlying pathophysiology.

Beginning with the example of smallpox, which was eradicated by removing the causal agent, eliminating poverty, violence, and racial/ethnic discrimination in the lives of children would have massive, beneficial effects. While others address these social determinants of health at a societal level, pediatricians must devise more effective strategies for protecting developing brains and other biological systems from the socioeconomic pathogens that threaten child well-being.

The next tier of intervention includes strengthening the body's defenses in a comparable fashion to what is achieved by individual immunizations and community ("herd") immunity. To that end, resilience in the face of adversity can be enhanced by building social capital at the neighborhood level, stress-buffering capacities at the caregiver level, and coping skills in young children themselves, beginning as early as possible.

The final line of defense against infection uses effective drugs matched to specific microorganisms and alternative therapeutics for pathogens that are resistant to conventional treatment. In a comparable fashion, effective intervention for a child facing adversity cannot be determined by asking "what is the most effective program?" but rather "how can we match effective services to specific causal factors and differential responses to intervention?"

Implications for the Future of Clinical Practice, Training, and Policy

Most articles on this topic typically conclude with a call for increased funding for existing services, improved screening and referral, a broader perspective on health that extends beyond the medical system, and recognition of the complex causes of disparities in health outcomes. The scientific advances described in this article provide a platform for greater specificity and aiming higher.

In 2012, the American Academy of Pediatrics issued a technical report[36] and policy statement[37] endorsing a leadership role for the pediatric community "to catalyze fundamental change in early childhood policy and services"[37(pe224)] and "to inform the development of innovative strategies to reduce the precipitants of toxic stress in young children and to mitigate their negative effects on the course of development and health across the life span."[37(pe224)] The frontiers of the biological, behavioral, and clinical sciences offer opportunities to galvanize these new strategies, but success will require a more rigorous approach than conventional practice to designing, testing, evaluating, and scaling services.

Although the pathophysiology of many stress-related diseases is understood at a general level, existing knowledge could be mined far more productively to catalyze new approaches in clinical practice and public health.[2,5,38] Medical students, residents, trainees in related professions, and practicing clinicians should be learning about the biology of adversity and its application both for and beyond individual medical care. Innovative approaches to health promotion and disease prevention should be breaking down the walls that separate pediatrics, internal medicine, obstetrics, and public health.

The complementary lenses of adverse childhood experiences, toxic stress, and trauma-informed care underscore the potential power of a 3-pronged strategy. Increasing public awareness of the lifelong consequences of adversity in childhood builds broad-based support for addressing problems that affect all social classes. Greater understanding of toxic stress creates a sense of urgency by explaining how early hardship can cause lifelong illness. Expanding knowledge about developmental plasticity and variation in susceptibility to adversity offers new insights that can improve trauma-informed care.

Policy makers and practitioners often invoke science to generate support for existing programs, yet few are using that knowledge to develop new strategies. This missed opportunity is especially problematic for young children and families whose needs are not being met by existing efforts. While most leaders are focused on delivering state-of-the-art services today, a pioneering group should be developing breakthrough solutions for tomorrow. The value of a balance between advocating for best practices and driving a dynamic research and development agenda is illustrated by the comparative 50-year histories of early childhood intervention for children living in poverty and the treatment of children with acute lymphoblastic leukemia.

When Head Start was launched in 1965, the 5-year survival rate for acute lymphoblastic leukemia was less than 5%.[39] Ten years later, that number had increased to 57%, and it exceeded 90% some 4 decades afterward.[40] Today, the treatment of acute lymphoblastic leukemia begins with baseline data that determine the most effective treatment plan among alternative options while basic and clinical researchers are striving to push survival rates even higher and reduce the undesirable effects of existing therapies.[41]

During this same half century, the short-term effects of early childhood programs on cognitive and achievement scores have continued to average a small (approximately 0.2) effect size.[42] This contrast is not presented to equate the adverse effects of poverty with a diagnosis of cancer. It is designed to illustrate lessons that early childhood policy makers and practitioners could learn from the battle to cure acute lymphoblastic leukemia.

The first lesson is the need for simultaneous investment in both the provision of evidence-based care and a robust research and development effort to create more effective interventions. The second lesson is the role of basic science in elucidating causal mechanisms and informing the design and evaluation of targeted interventions for identified subgroups. The third lesson is the importance of continuous experimentation with informed consent, learning from failure and success, and an unwavering commitment to greater effects until the problem is fully solved.

The evolving concept of "precision medicine" reflects a similar approach to greater understanding of how environmental effects on gene expression influence disease risk, pathogenic mechanisms, and differential response to treatments. That same scientific thinking is waiting to be leveraged to drive a comparable transformation in how we address the biological consequences of significant adversity in the lives of young children—and how we determine what works best for whom and why.[43]

In an early childhood policy environment concerned primarily with school readiness and educational outcomes, equal attention must be directed to the prevention of lifelong disease. At a time when most investments in young children are directed toward preschool for 4-year-olds, there is a compelling need for more effective interventions during the prenatal period and first 3 years after birth for children and families experiencing significant adversity. In a field guided largely by competing interpretations of program evaluation data, advances in neuroscience and epigenetics offer promising catalysts for fresh thinking. The time has come to launch a new era in early childhood policy and pediatric practice driven by 21st-century science and a research and development platform that tests new ideas, learns from failure, and settles for nothing less than breakthrough outcomes at scale.[44]

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