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Review

Paradise Lost: The Neurobiological and Clinical Consequences of Child Abuse and Neglect

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In the past two decades, much evidence has accumulated unequivocally demonstrating that child abuse and neglect is associated with a marked increase in risk for major psychiatric disorders (major depression, bipolar disorder, post-traumatic stress disorder [PTSD], substance and alcohol abuse, and others) and medical disorders (cardiovascular disease, diabetes, irritable bowel syndrome, asthma, and others). Moreover, the course of psychiatric disorders in individuals exposed to childhood maltreatment is more severe. Recently, the biological substrates underlying this diathesis to medical and psychiatric morbidity have been studied. This Review summarizes many of the persistent biological alterations associated with childhood maltreatment including changes in neuroendocrine and neurotransmitter systems and pro-inflammatory cytokines in addition to specific alterations in brain areas associated with mood regulation. Finally, I discuss several candidate gene polymorphisms that interact with childhood maltreatment to modulate vulnerability to major depression and PTSD and epigenetic mechanisms thought to transduce environmental stressors into disease vulnerability.

> "Safety and security don't just happen, they are the result of collective consensus and public investment. We owe our children, the most vulnerable citizens in our society, a life free of violence and fear."—Nelson Mandela

> "The world is a dangerous place, not because of those who do evil, but because of those who look on and do nothing." —Albert Einstein

Introduction

In the last decade, a remarkable concatenation of research findings has accumulated supporting the hypothesis that exposure to early untoward life events (early life stress [ELS]) in the form of child abuse and/or neglect is associated with a marked increase in vulnerability to major psychiatric and other medical disorders including major depression, bipolar disorder, post-traumatic stress disorder (PTSD), alcohol and drug abuse, and perhaps even schizophrenia, as well as obesity, migraines, cardiovascular disease (CVD), diabetes, and others. More recently, the biological and neurobiological consequences of ELS have been scrutinized in order to determine the molecular and cellular mechanisms that mediate the effects of ELS on the aforementioned disease vulnerability. The present Review seeks to succinctly summarize a now vast literature encompassing the epidemiology and clinical course following exposure to ELS, findings utilizing laboratory animal models of ELS, the neuroendocrine and immunological consequences of ELS, and the interaction between ELS and genetic factors in disease vulnerability. In addition, the emerging role of epigenetics is also described. The persistent neurobiological effects of child abuse and neglect, as demonstrated by structural and functional brain imaging, are also summarized. Finally, there is now a burgeoning database concerning the treatment response of patients with mood and anxiety disorders with a history of child abuse and neglect. There is virtually universal agreement that this sizeable subpopulation of patients has a more severe clinical course in terms of symptom severity and age of onset and responds more poorly to pharmacotherapy and/or psychotherapy. A discussion of future research directions concludes this monograph.

A few caveats should be mentioned. First, this is now a vast and rapidly burgeoning field and because of space constraints and the limitations in the number of citations permitted, all of the original research publications could not be included in either the text or the reference list. Second, because our research group has been focused on this area for more than 30 years, there is naturally an over-representation of our own contributions. This is not, in any way, meant to minimize the contributions of other groups. Third, a number of other reviews, many quite comprehensive and lengthy, have appeared and are highly recommended. This includes a recent Institute of Medicine (IOM) report on new directions in child abuse and neglect research (http://www.nap.edu/catalog/18331/new-directions-in-child-abuse-and-neglect-research), as well as reviews from our group, (i.e., Newport et al., 2002; Heim et al., 2008a, 2010; Neigh et al., 2009; Nemeroff and Seligman, 2013; and other leaders in the field, including Bale et al., 2010; Baram et al., 2012; Danese and McEwen, 2012; Teicher and Samson, 2013; Rilling and Young, 2014; Veenstra-VanderWeele and Warren, 2015).

Finally, I wish the reader to appreciate the sea change that has occurred in this area over the last three decades. When we and others first began this work, largely derived from clinical observations and psychoanalytically based principles first promulgated by Freud, there was strong and widespread opposition to the hypothesis that ELS was capable of producing persistent CNS and other long-term biological alterations. Many initial grant

proposals and manuscript submissions were met with great skepticism and disbelief, analogous to the remarkably long time the field came to accept the findings of neurogenesis in the adult mammalian brain. As will be described below, the extant database on the adverse consequences of ELS is now very robust and many of the findings have been widely replicated.

Epidemiology and Clinical Course

As is not unusual in medicine, clinical observations over several decades served as an impetus for well-powered epidemiological and longitudinal cohort studies that have now led to one inexorable conclusion—namely that sexual, physical, and emotional abuse, as well as emotional neglect, leads to a very significant increase in risk in adulthood for mood and anxiety disorders, substance and alcohol abuse, and certain other medical disorders. For the reader who might not recognize the magnitude of this public health problem, it is worthwhile to briefly summarize the latest data on prevalence rates of childhood maltreatment. In 2012, the U.S. Department of Health and Human Services documented 3.4 million referrals to child protective services, representing 686,000 children. Approximately 80% of the maltreatment was perpetuated by one or both parents. In this report, ELS was comprised of neglect (78.3%), physical abuse (18.3%), and sexual abuse (9.3%). Neglect is frequently defined as the failure of a parent or another person with responsibility for the child to provide needed food, clothing, shelter, medical care, or supervision to the degree that the child's health, safety, and well-being are threatened with harm. All authorities agree, however, that the vast majority of cases of child abuse and neglect go unreported. It is also important to note that certain forms of abuse, most notably sexual abuse, occur primarily in the youngest age group. In 2000, 70% of all sexual assaults in the U.S. were committed against children. There are both global regional differences and gender differences in childhood sexual abuse with the highest rates overall in Australia, Africa, and the U.S., with the lowest rates in Asia. Girls exhibited the highest rates of sexual abuse in all regions studied except Africa and South America, where the rates between boys and girls were equal.

In summarizing the large literature on the effects of ELS on risk for adult psychopathology and other medical disorders, the landmark CDC-funded Adverse Childhood Experiences (ACE) epidemiological study provided the findings that, it is not an overstatement to suggest, launched the field (see Anda et al., 2006 for review). This study was comprised of 17,337 adult members of a health maintenance organization (HMO) in San Diego. Assessing eight ELS events including abuse, domestic violence, household substance abuse, parental loss (by incarceration, divorce, and others), the investigators calculated an ACE score as a measure of cumulative ELS to determine the "dose-response" relationship between ELS and adult pathology. The results were striking and conclusive; 64% of the respondents had, at least, one ACE. For those with $\geq$4 ACE events, there was a very significant increase in risk for depression, anxiety, panic attacks, suicide attempts, substance and alcohol abuse, sleep disturbances, obesity, smoking, chronic obstructive pulmonary disease (COPD), and heart disease. A large number of subsequent studies have confirmed and extended these findings. Scott et al. (2010) studied 2,144 individuals ages 16–27 years in New Zealand. ELS was associated with clear increases in PTSD, mood disorders, anxiety disorders, and substance use disorders. Results from the National Comorbidity Study of 9,282 adults were concordant with the ACE study in revealing a dose-response relationship between individual childhood adversities and risk for DSM IV mood, anxiety, disruptive behavior, and substance abuse diagnoses (Green et al., 2010). A prospective cohort study of 676 children with documented physical and sexual abuse or neglect were compared to a matched sample of 520 non-abused and non-neglected children showed a clear increased risk in the ELS cohort for major depression. Moreover, those who developed MDD exhibited higher rates of comorbid disorders including PTSD and substance/alcohol abuse (Widom et al., 2007). These findings are consistent with the findings of Putnam and colleagues (2013), who, further analyzing the National Comorbidity Survey Replication Sample of 9,282 individuals, found that multiple ACEs resulted in complex adult psychopathology, as defined by higher rates of comorbidity and a greater number of symptoms. The Mexican National Comorbidity Survey of 5,826 individuals supported all of the aforementioned findings, namely an increase in mood, anxiety, substance abuse, and externalizing disorders (attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorders) after exposure to family dysfunction and abuse (Benjet et al., 2010).

Several studies have sought to determine the consequences of a single type of ELS on adult psychopathology. A recent meta-analysis by Chen et al. (2010) of 37 studies (17 case-control and 20 cohort) of 3,162,318 participants sought to determine the effects of sexual abuse on lifetime risk for psychiatric disorders. There was a significant association between sexual abuse in both men and women and lifetime diagnosis of an anxiety disorder, depression, eating disorder, PTSD, sleep disorders, and suicide attempts, but not schizophrenia. Maniglio (2010) conducted a systematic review of the effects of sexual abuse in childhood on risk for depression, which was comprised of 60,000 subjects in 160 studies. Their findings indicated that sexual abuse is a significant risk factor for depression.

Bullying has been the focus of recent research, particularly important because this form of ELS has not been included in the vast majority of studies previously conducted. Teicher and Samson (2013) studied parental "verbal aggression" in 554 subjects 18–22 years of age. The untoward effects of this form of ELS was equal to that of those exposed to witnessing domestic violence and non-familial sexual abuse on depression and anxiety and, again, multiple forms of abuse was associated with very large effect sizes. Copeland et al. (2013) reported on 1,420 study participants who were either bullied or engaged in bullying between the ages of 9 and 16 years. In young adulthood, bully victims exhibited increased rates of agoraphobia, generalized anxiety disorder (GAD), and panic disorder, and those who were both bully victims and bulliers exhibited increased rates of MDD, panic disorder, and agoraphobia in women and suicidality in men.

Considerable research has been conducted in seeking to determine whether ELS is associated with increased vulnerability for PTSD. In a study of 4,529 male soldiers,