How Adversity Becomes Disease:

The Biological Embedding of Experience

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While it may come as no surprise that terrible life events lie at the root of many psychological problems, both for children and adults, it is not so well known that other less traumatic, yet psychologically damaging, life events have significant downstream effects on physical—as well as mental—health. Both traumatic early life experiences, such as sexual and physical abuse, and less severe adverse conditions, such as growing up in a home plagued by domestic violence in which family members may abuse substances or have a history of incarceration, may have profound and lasting consequences. In the landmark Adverse Childhood Experiences (ACE) Study, (Felitti, V, and Anda, R 2010), conducted on a sample of unselected adults attending a preventive medicine clinic in San Diego, the incidence of these types of experiences was recorded as part of their routine health assessment. The ACEs may be grouped in three categories: Abuse includes physical, sexual and emotional abuse; Neglect may be emotional or physical; Household Dysfunction includes the presence in the home of a substance abuser, parental separation or divorce, a household member having a mental illness, the mother being treated violently, or a household member having a history of incarceration.

To evaluate the cumulative effects of multiple ACEs, the researchers made the decision—revolutionary at the time—to assign a score of "One" to indicate the presence and "Zero" to indicate the absence of each type of adversity. In other words, for the purposes of this study one instance of sexual abuse counted the same as 10, and any type

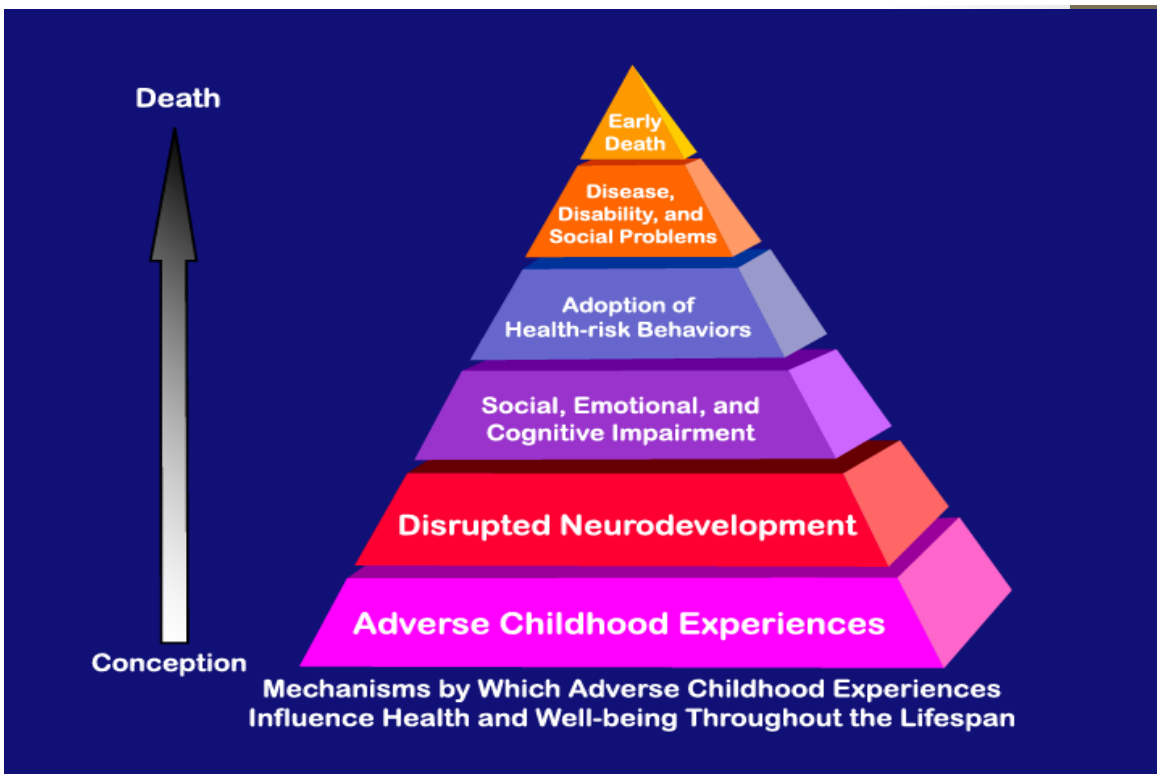
of adversity was given equal weighting. That is, living in a household, for example, in which the mother was treated violently or parents were separated counted the same as an instance of abuse or neglect. While few would argue that the impact of each of these kinds of adversity is equal, when these experiences are simply counted as present or not, and then the scores are summed, the results are remarkable and consistent. The first notable result of the initial study of 17,000 adults that now totals over 400,000, was that ACEs are extremely common: only one third of the original group had an ACE score of zero indicating no adverse experiences, while nearly a quarter of the group had three or more. Significantly, the presence of one ACE gives an almost 90% chance that at least one other ACE will be present. While these facts would be noteworthy on their own, they become a cause for alarm when we examine how the presence of increasing numbers of ACEs dramatically increases the prevalence of many serious mental and physical health consequences.

As ACE scores increased from 0 to 4 the prevalence of Chronic Depression went up from 10 to 35% in men and from 15 to 55% in women, while Suicide Attempts went from about 2% to nearly 20%. Even a symptom like Hallucinations, generally thought of as being biologically-based, increased from a prevalence of about 1% to 9% as the ACE score rose from zero to greater than seven, and at the highest ACE scores hallucinations were nearly as likely to be present whether or not the subject also abused drugs or alcohol. Similar, very steep increases in prevalence with increasing ACE scores were found for Smoking, Adult Alcoholism, and Injection Drug Use. Not surprisingly, the risk of becoming a perpetrator of domestic violence, the risk of having impaired work

performance, teen sexual behaviors that lead to early pregnancy, and, sadly, the risk of being raped later in life, all rise dramatically with increasing ACE scores.

Considering these profound behavioral effects, many of which, (such as alcohol, tobacco, and drug use), are themselves proximal risk factors for disease, it may not be so surprising to learn that high ACE scores also predict dramatic increases in the prevalence of liver disease, chronic obstructive pulmonary disease, and heart disease.

To help visualize the complex relationships between the Adverse Childhood Experiences and the severe deleterious effects on the development of disease, disability and social problems, all of which may lead to early death, the authors of the ACE study developed the following Adversity Pyramid.



In this graphic representation we can follow the proposed sequence: Adverse Childhood Experiences → Disrupted Neurodevelopment → Social, emotional, and Cognitive

Impairment → Adoption of Health-risk Behaviors → Disease, Disability, and Social Problems → Early Death. While this well-executed graphic presents an excellent broad overview of the problem and illustrates how far-reaching the effects of early adversity may be, it is slightly misleading. For it suggests that the layers of the pyramid exert their influence in a linear, causal manner, and that each layer is active only in a particular interval and time and that the interactions proceed from bottom-up. However, a closer examination of each of these layers of the pyramid will show a less linear, and perhaps even more far-reaching, set of relationships among these factors.

Before exploring some of the putative mechanisms through which these interactions occur, let us consider an illustrative example. Susie is a 22-year-old college student. Although she gets good grades, she is plagued by self-doubt. She has had a string of boyfriends, but none of her romantic relationships have been satisfying. Periodically, she will go to a local bar and pick up a stranger for a one-night stand. She has never been tested for HIV, because she doesn't want to know her status.

Susie was raised by her mother and her stepfather, after her biological father went to prison when Susie was two years old for fracturing her mother's jaw while he was high on crystal meth. When Susie was six, her mother began drinking heavily to cope with Susie's stepfather's increasingly aggressive outbursts. Shortly after Susie turned nine her stepfather began playing sexual games with her and threatened to beat her with his belt if she ever told anyone. When Susie finally did tell her mother that her stepfather had been raping her for the last nine months, just after she turned 13, her mother called her a whore and slapped her so hard that she left a palm print on Susie's face. A teacher saw Susie's bruised face, called children's services, and Susie was placed in emergency foster care.

Susie lived in a series of foster homes for the next two years, during which time her mother completed parenting classes and her stepfather moved out. When Susie was allowed to return home, her mother continued to use harsh corporal punishment, hitting her with belts and shoes. Susie never told anyone about this, because she was afraid she would be sent back to foster care.

When Susie saw a therapist for a few months after beginning college, she only wanted treatment for her depression and trouble falling asleep. She told the therapist that she could not remember anything before the age of 12. She didn't tell her therapist about her one-night stands, or that about once a week she would cut her forearms with a razor blade and watch herself bleed. This self-cutting helped Susie control overwhelming feelings of emptiness and shame. Susie's therapist referred her to a psychiatrist who put her on Prozac, but after two months Susie stopped the Prozac because it gave her headaches. Then she stopped therapy.

Although Susie appears to be physically healthy now at the age of 22, her exposure to at least seven categories of Adverse Childhood Experiences, giving her an ACE score of seven, places her at great risk for developing both physical and mental illness.

The neuroscientist Joseph Le Doux has described two parallel pathways for the processing of frightening information (Phelps, E. and LeDoux, J. 2005). The first of these, that Le Doux has dubbed, "the low road," is for split-second processing of a potential threat to life, when the smallest delays could lead to disastrous results. It is easy to see how such a mechanism could have evolved to protect our primordial ancestors: a caveman confronted at night by a large, dark shadow cannot afford to wait for close

inspection to determine whether this shadow is actually a rock or a large black bear. Therefore, in this case the visual information enters through the caveman's eyes, travels through the optic nerve, enters the visual part of a large, central structure within the brain called the thalamus, and without further processing goes directly to the amygdala, a part of the brain's limbic system critical to emotional responsiveness. From there the information flows out to the control center that prepares the body for fight or flight: the Sympathetic Nervous System. When activated, this system increases heart rate and respiration and shunts blood flow away from the skin and digestive system and toward the muscles to prepare for a flight from or a fight with a potential predator. At the same time that the low road is being activated, information also travels to the "high road:" this pathway begins similarly, with visual information entering through the eyes, and then through the optic nerve to the thalamus; but instead of going directly to the amygdala, information flows to the rear part of the outer shell of the brain called the occipital cortex, responsible for high-level processing of visual information, and only then does the information go on to the amygdala where it will elicit a behavioral response—this time only in the face of actual danger. This means that after our caveman has had another split-second to process the dark shadow he may conclude more definitively that it is, in fact, a bear and continue running, or he may decide that it was only a large boulder and continue a leisurely stroll, thereby conserving precious energy resources. While this mechanism is adaptive when one is faced with extreme danger, it also means that some threatening information is evaluated below the level of conscious (cortical) processing.

Now, let us return to Susie. As a child, Susie learned that her safest response to the threat posed by her sexually abusive stepfather was to avoid confrontation and to

comply with his demands. Over time, after what surely began as a series of frightening sexual encounters, Susie may have learned that her most adaptive response would not be to fight, but rather, to passively acquiesce to her stepfather's demands. While this behavior may have served her well in dealing with her stepfather, it is not hard to see how it might be related to her adopting a casual style in her adult sexual practices. In addition, because this frightening information was processed—at least in part—below the level of conscious awareness, Susie may not easily be able to connect her adult behavior to her earlier childhood experiences.

Whether she is aware of these connections or not, her childhood experiences interact with Susie's normal regulatory systems to confer greatly elevated risk for poor adult health outcomes. When a mammal experiences stress a whole cascade of physiologic responses follow. Although conventional wisdom has long suggested that prolonged exposure to stress can have deleterious health effects, it is only within the last decades that the emerging field of psychoneuroimmunology has elucidated some of the mechanisms through which specific life experiences may lead to severe downstream effects. In this conception, the term "experience" includes both the external stressors and the strong negative emotions these stressors may elicit. Stress may be defined as stimulation that activates the body's defensive response system: the hypothalamic – pituitary – adrenal (HPA) axis and/or the sympathetic nervous system (SNS) (Glaser, R. and Kiecolt-Glaser, J.K. 2005). Severe psychological stress may exceed an individual's ability to cope—that is, the ability of the individual to respond to the stressful event and then return to baseline. Just as a piece of metal will tolerate bending and return to its original shape only so long as it remains intact, when an individual's coping resources are

overwhelmed he or she may have great difficulty returning to baseline level of functioning.

Under normal circumstances a stressor will activate both the HPA axis and the sympathetic system. While the sympathetic system allows for an immediate response from the heart, lungs and blood vessels, activation of the HPA axis occurs over a longer time frame (Essex, M., Shirtcliff**,** E.**,** Burk, L. et al, 2011). In Susie's case the repeated and cumulative stress of seeing her mother being beaten, then being raped by her step-father and subjected to harsh corporal punishment would affect her physiological state as her sympathetic system would attempt to prepare her to respond quickly to these repeated threats to her own and her mother's bodily integrity, and her HPA system would attempt to provide her with the steroid hormones necessary to respond to prolonged stress. It is also likely that the stress experienced by Susie's mother who was herself living in a hostile, threatening environment, would have deleterious effects on her mother's ability to provide the necessary nurturing to ensure that Susie would feel securely attachment to her. The combination of poor attachment and later psychophysiological stress would have not just additive but multiplicative effects. This insecure attachment and unresponsive maternal care can then lead to further dysregulation of HPA reactivity.

The cumulative effect is that Susie lives in a heightened state of arousal in which she feels constantly overwhelmed and unable to protect herself. This state of fear produces an activation in the emotional parts of her brain that communicate with her hypothalamus, the brain center that connects directly to her pituitary gland, causing it to release hormones that stimulate the cortex, or outer shell, of her adrenal glands to secrete cortisol. The cortisol produced by her adrenal glands may help her deal with pain, but

will also reduce the responsiveness of her immune system, making her more susceptible to a variety of physical illnesses.

Susie's mother's lack of availability gives Susie the biological signal that she lives in a harsh, hostile world, one in which she needs to be always alert and ready to react. This is in contrast to a mother who is available, and by her soothing allows her child to develop an HPA system with less extreme sensitivity, that will then afford the child greater energy to be spent on activities like planning for the future.

In one study by Fisher and Gunnar, (2010), the higher the number of unique caregivers for children in foster care, the lower was their ability to engage in "executive functions," like planning, problem-solving, and initiating and monitoring actions. In animal models repeated small stressors may lead to better self-regulatory skills, while more severe stressors lead to significant impairment.

Of course, genetics, as well as environment and parental care, plays a role in response to adversity. In twin studies genes determine the response to low levels but not to high levels of adversity. In one intriguing study, Suomi (2013) has shown that monkeys who possess a genetically determined variant of the transporter for the neurotransmitter serotonin that would normally confer an intermediate risk for depression, *in a hostile environment* will perform better than their peers carrying the gene for the more robust serotonin transporter.

To understand the effects of adversity a quick review of a few genetic principles is in order. The human genome contains about 20 to 30,000 genes located on 23 chromosomes — but not every gene is expressed, even in the brain. DNA is a double helical molecule that directs cellular machinery to produce specific types of RNA that

then lead to the production of proteins that regulate virtually every chemical reaction within the body. Not very long ago as much is 97% of the DNA in the human genome was considered "junk," because it didn't appear to code for any particular protein. More recently, however, it has become apparent that this junk DNA is critical for regulating gene expression (Stahl 2013). Genes may become either silent or active under specific conditions. Changes in the expression of genes can lead to changes in brain connections, then to changes in the functions performed by these connections, and finally to changes in behavior. This process of gene regulation by DNA that is physically close to the genes themselves is called "epigenetics," and it is now believed that epigenetics may underlie both the mechanisms of psychiatric disorders and the actions of psychotropic medications. In a series of elegant animal studies researchers have shown that maternal nurturing behavior (for example, high licking and grooming of pups by mother rats) can alter the epigenetic profile of their offspring (Bagot and Meaney, 2010). Female rat pups exposed to a high degree of maternal nurturance, then, will mature to become mothers who provide good quality nurturing, while female pups exposed to poor mothering will themselves become poor mothers. However, pups born to mothers who are poor nurturers, but who are placed with or "fostered by" mothers who are good nurturers may grow up to be nurturing mothers.

So to return, finally, to Susie: her long chain of adverse experiences has left her with a hyper-reactive HPA axis and chronic feelings of emptiness. She attempts to regulate her poorly modulated emotions by cutting herself, taking drugs, and engaging in high-risk behaviors such as unprotected casual sex. Both her high-risk behaviors themselves and the negative emotional states that these behaviors often produce, lead

Susie to feel physically and emotionally drained. While it may certainly appear that the odds of her escaping from the downward cycle that her life has become seem to be poor, it remains possible that some of these effects are reversible. Even as genetics and early life experiences cannot be modified, through epigenetic control, gene expression *is* subject to modification, and although the effects of early life experiences are often long lasting, some of these effects may be reversible. Although Susie's history has shaped her present life, it does not necessarily determine her future.

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