Childhood Violence Exposure and Effects on Long-term Health: Causal Theory Development
By Greg Miller

The social psychologist Kurt Lewin once said that "nothing is so practical as a good theory." And he was right. Even in research on applied topics, good theories help us to organize knowledge in an area and recognize where it is deficient. Theories also suggest hypotheses to be tested, competing ideas to consider, and boundary conditions that might be important. Perhaps most importantly good theories help us situate research findings in a broader epistemologic context. In short, theories help us see where we've been and where we're going with a particular research endeavor, which is especially important with complicated multidisciplinary problems. With that in mind, I'll devote this paper to a critical analysis of theory relevant to our topic, the long-term health consequences of childhood victimization. My hope is that the paper will catalyze a productive discussion in Switzerland about we might (a) build, test, and refine theory in this budding research domain, and (b) use this conceptual knowledge to inform prevention and treatment efforts.

What Does Our Theory Need To Explain?

To explain how childhood victimization contributes to medical problems across the lifespan, we need a theory that offers testable and plausible answers to a handful of questions. The first question has to do with the nature of the exposure itself. Do we hypothesize that all forms of victimization – bullying, maltreatment, domestic violence, etc - have the same consequences for health? If so, our theory would need to specify a psychobiological common denominator these exposures share, e.g., a generic appraisal of threat, with downstream behavioral and biological consequences of relevance to disease susceptibility. Alternatively, some of us may be inclined towards splitting - rather than lumping - and posit distinct effects of/pathways for various forms of victimization. In that case, our theory would need to specify what, mechanistically, allows different exposures to produce different effects. For example, one could argue that what's especially damaging for children is the kind of profound violation of trust that occurs with parental maltreatment and some, but not all, other kinds of victimization. To that end, Kendler's work shows that depression risks in sexually abused children rise dramatically if they've disclosed the situation to a parent, and that person has failed to intervene. One could also postulate other psychobiological mechanisms as critical junctures along the pathway to medical problems, e.g., the implicit social rejection that comes with parental neglect and school bullying, or the persistent fears about safety for those residing in violent areas. There are plausible arguments as to why these states could have distinct physiologies (1-4), but no real convincing data. Regardless, the bottom line here is that a good theory should take a stand, and specify what the toxic part of the exposure is and for whom it applies.

The second question has to do with mind-body mechanisms. How does violence get under the skin, at the level of tissues and organs, to push forward the pathogenesis of disease? Thanks to decades of research on the physiology of stress, we already have some plausible answers to this question (5). To be sure, there is heated debate about the utility of some concepts, like allostatic load and telomere erosion. But the mechanistic basis of mind-body effects is firmly established in most tissues that are relevant to our discussion. We know, in some detail, how threats that emanate in the social world activate the neural circuitry regulating the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenocortical (HPA) axis, and what effects changes in the outflow of these system have for the cardiac, vascular, immune, metabolic systems. A much thornier issue arises when we consider the temporal features of the phenomenon. Most of our mechanistic knowledge of stress pertains to its immediate biological consequences. We have fairly deep insights about what happens to various bodily systems when people are facing common real-life stressors. From work on PTSD, we also have a shallow sense of how these systems look in situations where the precipitating stimulus has dissipated but a sense of threat lingers in the individual. However, it

remains unclear how germane these insights are to the problem at hand, because the exposure and outcome being considered are so temporally distal. For example, if we're thinking about maltreatment that's confined to childhood, and later susceptibility to coronary heart disease, the period of incubation would be something like 50-70 years. Also, the PTSD literature deals with the durability of trauma's impact on the brain and hormonal processes it regulates. It's unclear how much this applies – or cascades out - to the organ systems where disease actually unfolds. To be successful, a theory will need to bridge that gap in a manner that's temporally, biologically, and mechanistically plausible. That's a significant challenge given our current state of knowledge

What Do Existing Theories Say?

To date, nobody has articulated a model explicating the health consequences of victimization. But scientists in other fields have struggled with similar problems, and generated some conceptual insights likely to be relevance to our discussion. These accounts are often loosely invoked in the discussion sections of papers on victimization, as authors try to explain why they've observed some lingering biological residue of previous exposure to violence. My goal here is to introduce the basic tenets of these models, and then candidly discuss what they do – and don't – offer us by way of answers to the overarching mechanistic and temporal questions outlined above.

The Fetal-Origins Hypothesis

The "fetal-origins" hypothesis grows out of research showing that children of low birth weight are at risk for various metabolic and coronary diseases in adulthood (6, 7). Barker and others have argued that low birth weight reflects nutritional deprivation *in utero*, which arises because of poor maternal diet and/or insufficient nutrient transfer across the placenta (6, 8). These ideas have spawned a voluminous literature on mechanisms, in which animals are exposed to nutritional imbalance *in utero* through manipulation of maternal diet or administration of glucocorticoids. The fetus responds to these manipulations with alterations in metabolic processes that regulate nutrient absorption and growth patterns. These alterations spare critical organs like the kidneys, heart, and brain, by favoring the emergence of a phenotype with small body size, low skeletal muscle, and high visceral fat (9). Because the adaptations occur during sensitive periods of fetal development, they get programmed into physiology in what appears to be a permanent, irreversible manner. From a theoretical perspective, it's believed that programmed adaptations are metabolically advantageous across the organism's lifespan, endowing it with a phenotype well suited to a nutritionally imbalanced environment, similar to the one it endured *in utero*.

The fetal-origins work provides some valuable insights for our purposes. To begin with, the studies are often conducted in model systems, allowing for a degree of methodologic rigor and mechanistic depth we can't achieve in human studies. As a result of these features we get convincing proof that, in principle, prenatal experience can exert lasting influences on physiology. This literature also provides us with a useful conceptual heuristic – programming - for conceiving of how experiences might acquire biological durability. Lately, researchers in this area have made strides identifying mechanisms that support programming at the molecular level, such as DNA methylation and histone modification (10). This kind of work is valuable for our purposes, too, as it helps address the incubation problem raised earlier, and does so in a manner that seems temporally and biologically plausible.

With all that said, the fetal-origins hypothesis has some important limitations in explaining the phenomenon we're concerned with here. First, the exposures in this literature are inadequate nutrition or excessive glucocorticoids, both of which are manipulated to fairly extreme degrees. As a result, it's difficult to know to what degree these exposures – either in kind or in dose – parallel the way that children's bodies would respond to violence. Along the same lines, there are reasons to

wonder how applicable the phenomenon of programming is to humans (11). Programming can been viewed as a shortcut organisms use to maximize their chances of reproductive success. It allows them to make an educated guess, based on cues from their mother, about the challenges they'll face in life, and adjust certain physiological thresholds in manner that optimizes fit with the predicted ecology. That kind of "bet" makes sense for animals with short lifespans and limited mobility. But humans and other primates species are different. Before reproducing, we live for a long time and often move around, which means that we're exposed to varying ecologies, and the disparate challenges they present. In short, we can't make educated guesses about what the future entails. So it's not clear that it'd be advantageous to lock certain physiological systems at functional setpoints from which they can't deviate, especially on the basis of signals registered during a relatively brief perinatal existence. A better strategy might entail setting the bounds of how these systems operate going forwards, but allowing for environmentally dependent plasticity in how the phenotype gets expressed. The level of plasticity might decline with age, as the organism gets more "data" upon which to base its predictions.

Finally, programming hypotheses often depict people as relatively passive victims of their perinatal environment. But we know that the experiences that people have in childhood shape the kinds of environments they create for themselves as development progresses, and the manner in which they respond to challenges in those environments. This would seem particularly true for children who've been victimized. Indeed, the literature is replete with examples of violence shaping the manner in which youngsters come to perceive, engage, and respond to their social worlds (12, 13). These tendencies cascade across domains and decades to structure key outcomes, like marital stability, educational attainment, and mental health (14). Across the lifespan these outcomes would seem to have continuing influences on many of the behavioral and biological processes that we're considering as mechanisms of pathogenesis (5). What does this mean for our theory? That victimized children can't simply be viewed as passive objects whose physiology has been irreversibly programmed. Instead, we need to consider how victimization puts them on trajectories of personhood, which have their own ramifications for downstream processes relevant to disease.

Lifecourse Approaches

Another class of models relevant to our discussion comes from lifecourse sociology (15). These models emphasize the pathways that childhood experience sets people upon, and the cumulative effects the subsequent exposures have on risk for later health problems (16). In some regards these models are a mirror image of those in the programming literature. They explicitly recognize that childhood experiences can set up lifecourse trajectories. In these "chains of risk", adversity begets adversity (17). For example, a child exposed to domestic violence might develop poor emotion regulation skills, which impair his ability to form close relationships and navigate challenging tasks. Over the long-term these tendencies might contribute to him being unmarried, having low academic achievement, etc, with downstream effects on behavioral and biological processes relevant to disease. Cascades like this are featured prominently in the Risky Families Model (18), which is essentially a lifecourse framework with a psychosocial emphasis.

The lifecourse models are instructive in highlighting the dependencies between experiences at different stages of the lifespan. This is an intuitively appealing notion. However, it hasn't been subjected to much in the way of rigorous empirical scrutiny. Much of the lifecourse research has focused on endpoints that are soft, like self reports of health, or modeled chains of interest with cross-sectional data, which can't speak to the temporal dynamics implicit in the theory (19, 20). The lifecourse models are also helpful in drawing our attention to the idea of continuity in exposures. Most of the medical outcomes that we're considering – cancer, heart attacks, strokes – are clinical manifestations of lengthy underlying disease processes, which in some cases unfold in a gradual

manner over multiple decades. By emphasizing the continuity of adversity these models help bridge the temporal gap, and explain how an early victimization event might continue resonating in the body over lengthy periods.

There are a handful of potential downsides of these models from our perspective. The most prominent is that many of them (but not all) see the timing of exposure as irrelevant. What matters for health risks is the degree of cumulative exposure, and whether it occurs in childhood or adulthood is unimportant. This seems like a difficult assumption to maintain. From decades of rigorous studies done in model systems, we know the perinatal months are a sensitive period, during which stress has especially potent and lasting influences on the HPA axis, as well as other downstream tissues with relevance for the diseases we're considering (21, 22). To me, this evidence suggests that our models must accord some unique effects to victimization that occurs during childhood, and strive to explain how and why that creates an especially potent form of vulnerability.

Another weakness of lifecourse models is the relative absence of details on pathogenic mechanisms. For the most part they don't specify how, pathogenically, a person gets from exposure to outcome. In more recent formulations authors have introduced mediating processes like allostatic load (23), but exactly how, where, and why they manifest in tissue isn't specified. Even if they did, the concept of allostatic load is problematic conceptually, and a boondoggle methodologically, at least in the manner it's been operationalized so far. In sum, we need a more complete account of disease pathogenesis, which postulates dysfunctions at the cellular and molecular levels, to make progress.

Is There A Middle Ground?

As this discussion suggests the strengths and weaknesses of these models are complementary. So is there a conceptual middle ground at which the attractive features of each can be joined? I'd say the answer is yes. In a recent paper we introduced a framework that tries to do just that in depicting how stress in childhood might play a role in shaping disease risks in adulthood. Its far from a perfect theory, but might be instructive here as an example of a hybrid. Its basic premise is that when stress occurs during sensitive periods of development, it calibrates how cells of the immune system operate going forward. We focus specifically on cells of the monocyte/macrophage lineage, which play a key role in initiating and maintaining inflammation, a process that is central to a number of chronic diseases of aging. The model highlights three mechanisms – epigenetic markings, post-translational modifications, and tissue remodeling – that might underlie this programming. As a result of these processes, stress gets programmed into macrophages, causing them to mount excessive inflammatory responses to microbial challenges, and be insensitive to inhibitory hormonal signals. This contributes to a chronic inflammatory state in the body.

The model goes on to propose that over the lifecourse, these pro-inflammatory tendencies are exacerbated through behavioral proclivities and hormonal dysregulation, themselves brought about through exposure to childhood adversity. Behaviorally, early stress leads people to become vigilant for threat and mistrusting of others. These traits shape the manner in which people engage their social worlds, making them more likely to elicit conflict and rejection, and less likely to garner warmth and support. They have persistent difficulties forming and keeping relationships. Early stress also leads people to develop poor self-regulation skills, wherein the future is highly discounted in favor of immediate gratification, and there is a resulting propensity to engage in unhealthy behaviors. Together, these social difficulties and unhealthy lifestyle serve to amplify the chronic inflammatory state. Also contributing to this process are dysregulated patterns of endocrine and autonomic discharge, which consign monocytes/macrophages to operate in a milieu that accentuates their pro-inflammatory tendencies. The ensuing chronic inflammation is thought

to drive forward various mechanisms of pathogenesis, including high blood pressure, insulin resistance, plaque growth, tissue destruction, and tumor progression.

As readers will notice the ideas in this model aren't novel. We've simply argued for a hybrid approach that joins notions from the other viewpoints, and fuses them with some hypotheses about the role that inflammatory biology plays in disease pathogenesis. The same approach could be taken as we formulate a model about victimization. That said, it's worth keeping in mind that conceptual integrations like these have their own set of problems. Like this one, they're often too ponderous and lumbering to be tested in a definitive manner, at least a coherent whole. Bits and pieces can be falsified, but that's often about it. These problems get even more difficult to address when critics - in a totally reasonable argument – highlight the many other puzzle pieces that a supposedly integrative model ignores. What about genetic liabilities? Pollutants, toxicants, carcinogens? And the list goes on. The point here is that there's an inherent tension in model building that pits being thorough versus being falsifiable.

What Are The Translational Implications?

What does all this mean for improving the lives of victimized children? We're still a long ways off from knowing exactly how to do that. However, the process of creating, testing, and refining models will provide insights that, if taken seriously, should maximize the chances that we'll ultimately develop interventions that succeed. From the theory-building process we'll be in a better position to accurately stratify risk and thus identify persons who'll benefit from intervention. We'll also gain insights about what processes to target, at what points in the lifecourse, and what the downstream effects of an intervention might be. For example, if the lifecourse notions about chaining turn out to be accurate, we'd expect an childhood intervention directed at enhancing self-regulation to have later consequences for health-relevant behaviors, etc. And if the programming models are right about early stress getting embedded in certain tissues more or less permanently, we'd probably want to direct our treatment resources towards changing behaviors that compound the problem rather than changing the systems themselves through pharmacology (e.g., targeting smoking and exercise across the lifecourse to prevent further inflammation, rather than trying to modify the manner in which cells respond to stimuli.) At the most basic level, a theory will help us generate some educated guesses about what kinds of interventions might help victimized individuals, how those treatments might operate mechanistically, and what kinds of things we might do to optimize their impact.

References

1. Slavich GM, O'Donovan A, Epel ES, Kemeny ME (2010): Black sheep get the blues: a psychobiological model of social rejection and depression. *Neurosci Biobehav Rev* 35:39-45.
2. Gruenewald TL, Kemeny ME, Aziz N, Fahey JL (2004): Acute threat to the social self: shame, social self-esteem, and cortisol activity. *Psychosom Med* 66:915-924.
3. Chen E, Langer DA, Raphaelson YE, Matthews KA (2004): Socioeconomic status and health in adolescents: the role of stress interpretations. *Child Dev* 75:1039-1052.
4. Tomaka J, Blascovich J, Kelsey RM, Leitten CL (1993): Subjective, physiological, and behavioral effects of threat and challenge appraisal. *J Pers Soc Psychol* 65:248-260.
5. Miller GE, Chen E, Cole SW (2009): Health psychology: developing biologically plausible models linking the social world and physical health. *Annu Rev Psychol* 60:501-524.
6. Barker DJ (1992): *Fetal and Infant Origins of Adult Disease*. London: British Medical Journal.
7. Godfrey K (2006): The 'developmental origins' hypothesis: Epidemiology. In: Gluckman P, Hanson M, eds. *Developmental Origins of Health and Disease*. New York, NY: Cambridge University Press, 6-32.

8. Gluckman PD, Hanson MA, Cooper C, Thornburg KL (2008): Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 359:61-73.
9. Gluckman P, Hanson M (2006): The conceptual basis for developmental origins of health and disease. In: Gluckman P, Hanson M, eds. *Developmental Origins of Health and Disease*. New York, NY: Cambridge University Press, 33-50.
10. Robison AJ, Nestler EJ (2011): Transcriptional and epigenetic mechanisms of addiction. *Nat Rev Neurosci* 12:623-637.
11. C.W. K, Thayer ZM (2011): Timescales of human adaptation: the role of epigenetic processes. *Epigenomics* 3:221-234.
12. Pollak SD (2005): Early adversity and mechanisms of plasticity: integrating affective neuroscience with developmental approaches to psychopathology. *Dev Psychopathol* 17:735-752.
13. Crick NC, Dodge KA (1994): A review and reformulation of social information processing mechanisms in children's social adjustment. *Psychol Bull* 115:74-101.
14. Caspi A, Bem DJ, Elder GH (1989): Continuities and consequences of interactional styles across the life course. *Journal of Personality* 57:375-406.
15. Lynch J, Smith GD (2005): A life course approach to chronic disease epidemiology. *Annu Rev Public Health* 26:1-35.
16. Pollitt RA, Rose KM, Kaufman JS (2005): Evaluating the evidence for models of life course socioeconomic factors and cardiovascular outcomes: a systematic review. *BMC Public Health* 5:7.
17. Kuh D, Ben-Shlomo Y (2004): *A life-course approach to chronic disease epidemiology*. Oxford: Oxford University Press.
18. Repetti RL, Taylor SE, Seeman TE (2002): Risky families: Family social environments and the mental and physical health of offspring. *Psychol Bull* 128:330-366.
19. Taylor SE, Lehman BJ, Kiefe CI, Seeman TE (2006): Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. *Biol Psychiatry* 60:819-824.
20. Lehman BJ, Taylor SE, Kiefe CI, Seeman TE (2005): Relation of childhood socioeconomic status and family environment to adult metabolic functioning in the CARDIA study. *Psychosom Med* 67:846-854.
21. Meaney MJ (2001): Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu Rev Neurosci* 24:1161-1192.
22. Miller GE, Chen E, Parker KJ (2011): Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychol Bull* 137:959-997.
23. Repetti RL, Robles TF, Reynolds B (2011): Allostatic processes in the family. *Dev Psychopathol* 23:921-938.