Toward a new biology of social adversity

W. Thomas Boyce[a,b,1], Marla B. Sokolowski[b,c], and Gene E. Robinson[d]

[a]*School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, BC V6T 1Z3, Canada;* [b]*Experience-Based Brain and Biological Development Program, Canadian Institute for Advanced Research, Toronto, Canada M5G 1Z8;* [c]*Department of Ecology and Evolutionary Biology and Fraser Mustard Institute for Human Development, University of Toronto, Toronto, ON, Canada; and* [d]*Institute for Genomic Biology, Department of Entomology, Neuroscience Program, University of Illinois at Urbana–Champaign, Urbana, IL 61801*

Ernest Hemingway wrote in *A Farewell to Arms* that "The world breaks everyone and afterward many are strong in the broken places" (1). With the advent of industrialization, the forcible employment of children, and the 19th century child labor laws that followed, a broad recognition emerged that even childhood (or perhaps especially childhood) can be "broken" by the adversities of life in a harshly exploitative society (2). The early 20th century ethnographic work of James Agee and Walker Evans (3) depicted the privations and afflictions of poor children reared in impoverished settings, and the psychiatrist Robert Coles (4) documented the extraordinary hardships faced by young, black children during the Civil Rights Movement in the American South. The work of Yehuda et al. (5) and others (6, 7) illuminated the systematic vulnerabilities sustained by children of the Holocaust and famine survivors, and research by Evans and Schamberg (8), Shonkoff and Phillips (9), Hackman and Farah (10), Neville and colleagues (11), Lupien et al. (12), and Felitti et al. (13) has systematically documented the neurodevelopmental and health consequences of rearing in conditions of poverty and adversity. Most recently, studies by Rutter (14), Gunnar and colleagues (15), Smyke et al. (16) and Nelson et al. (17) have described the socioemotional and cognitive deficits sustained by children growing up in orphanages and other institutional settings with nonparental care. Hertzman and Boyce (18) and Hertzman and coworkers (19) have geographically mapped such deficits, linking developmental vulnerabilities at primary school entry to the unique geosocietal circumstances of individual communities. These observations, spanning a century and a half of historical time, have convincingly depicted the disordered development and fragile health incurred by children with exposures to deprivation, distress, and early life difficulties. Nonetheless, and against the odds, not all children are adversely affected by such struggles and misfortunes, and in virtually every population examined, stories emerge of resilient children who prosper and thrive, despite the harsh and often damaging realities of their young, troubled lives (20–22).

What then are the developmental and biological consequences of early exposures to penury, strife, and hardship? How do experiences of childhood adversity get "under the skin" and affect physiological and cellular pathways leading to disease susceptibility? How are the adverse circumstances of children "biologically embedded" into the molecular, genomic systems that determine expressions of vulnerability and resilience? Why do some children flourish, whereas most others founder in the face of severe childhood conditions? These (and others) are the questions addressed—head-on, at multiple analytic levels, and from a variety of disciplinary perspectives—in the collection of papers contained in this special issue of PNAS: papers that have formed the collective product of an Arthur M. Sackler Colloquium in December 2011, cosponsored by the NAS and the Canadian Institute for Advanced Research (CIFAR). Most papers presented at the colloquium and collected in this special issue of PNAS were authored by members of CIFAR's Experience-Based Brain and Biological Development Program. Launched in 2003, this unique international collaboration inspires original, multidisciplinary understandings of how social experiences affect early development. We believe that the assembled work not only traces the present, defining circumference of a unique "biology of social adversity," but presages, as well, the shape and direction of research yet to come, that is, the "growing edges" of a developmental neuroscience of early stress and disadvantage.

The present harvest of findings, gathered together for this PNAS issue, reflect a maturing and productive field, well-populated with promising discovery and unique insight. Following an overview of the field and its challenges by one of its leading progenitors, child psychiatrist Sir Michael Rutter (23), a set of papers on the origins and consequences of early social adversity addresses a broad range of social contextual stressors, ranging from poverty and deprivation to acute and chronic life stress, to the experiences of societal stratification, subordination, and social network affiliation. The paper by Adler et al. (24) surveys and critiques the now broad literature linking socioeconomic status and health, and Hertzman (25) offers an historical perspective on how early, socioeconomically graded adversities become biologically embedded. Boyce et al. (26) report the same partitioning of disordered behavior by social position within networks of 5-y-old kindergarten children, suggesting that a conserved propensity toward hierarchical organization effects a gradient in health, even within the "microsocieties" of primary school classrooms. The study by Schneider et al. (27) uses fruit flies to report on how nonrandom social networks arise through chemosensory cues and how different strains of flies form networks with quantitatively distinctive properties. An important observation emanating from these broadly differing representations of social conditions and structures is that understanding any one of them demands comparisons across different types. With their assertion of the import of this comparative approach, the papers also collectively reveal the utility of an evolutionary, cross-species consideration of graded social environments.

A second group of papers, on the neuroscience of social signaling and stress, brings into focus neurobiological advances in understanding central and peripheral neural responses to psychosocial stressors. Neurobiologist Bruce McEwen (28) summarizes and broadly reviews current studies of allostatic load, the cumulative, physiological "wear and tear" that attends exposures to chronic, recurrent stressful events. The paper by Kolb et al. (29) examines current knowledge of experiential effects on the development and function of the prefrontal cortex in rats. Fernald and Maruska (30) ask the question "How does social information change the brain?" and review evidence for social status effects on physiological, cellular, and molecular processes in an African cichlid fish species. From the Meaney laboratory,

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[1]To whom correspondence should be addressed. E-mail: tom.boyce@ubc.ca.

the paper by Bagot et al. (31) shows how maternal behavior induces epigenetic modifications of a glutamate receptor gene that affect synaptic plasticity in the hippocampus of the rat pup. Finally, the article by Hostinar et al. (32) reports on prefrontally mediated impairments in executive functioning among children partially reared in early life institutional settings. Collectively, these papers document the increasingly articulated neuroscience of stress and adversity as well as the effects of development on socially generated perturbations in neural processes. Importantly, the papers also demonstrate how such perturbations in social signaling can be evoked and studied at multiple levels of analytical complexity.

The impact of early experience on social, perceptual, and cognitive systems is considered in the third group of reports, using both rodent and human models of development. The paper by Yang et al. (33) uses a mouse experimental model to study how the timing of early critical periods for the acquisition of anxiety symptoms can be manipulated by pharmacological and perceptual (e.g., music exposure) means. In a parallel human experiment, Weikum et al. (34) describe how a serotonin reuptake inhibitor antidepressant and prenatal maternal mood co-operate to shift developmental milestones related to language acquisition. Finally, Almas et al. (35), in data from their ongoing, random assignment experiment among previously institutionalized Romanian children, report statistical interaction effects of attachment security and EEG activity on the acquisition of social skills. These papers provide substantive and unique insights into how the acquisition of skills and capacities, within specific developmental domains and during critical periods of heightened environmental sensitivity, can be altered by perceptual, pharmacological, and social signaling. The developmental plasticity collectively displayed will be important for the conceptualization of a new generation of early interventions among children at risk.

Fourth, a group of papers on gene–environment interplay in development and behavior reflects the compelling and now flourishing enterprise of studying how inherited and environmental factors work together to shape both adaptive and maladaptive developmental and behavioral outcomes. Such observations lie at the heart of current efforts to describe and understand the genesis of deviations from normative development and alterations in physical and mental health. Mashoodh et al. (36) report an evolutionarily important finding that prior paternal experience in the rat can influence offspring development, even in the absence of paternal care or presence, by affecting mothers' postpartum care of their young. Burns et al. (37) provide a strong example of gene-by-environment (GxE) interaction in the fly that is explicated to the level of a specific gene, acting within a specific brain region. The paper by Drnevich et al. (38), from the Clayton laboratory, presents evidence that although many brain regions show large transcriptomic responses to social experience in songbirds, the responses vary tremendously from region to region. Lam et al. (39) show that peripheral blood cells can be used to identify biological, demographic, and psychosocial factors that shape the epigenome and to determine the functional relationship between DNA methylation and gene expression. Karmiloff-Smith et al. (40) present an insightful discussion of how to investigate genetic and environmental vulnerabilities that dynamically change over developmental time. Finally, the article by Suderman et al. (41) compares broad patterns of hippocampal DNA methylation among rats exposed to low vs. high maternal care and human suicide victims with and without experiences of early maltreatment, focusing, in both cases, on a genomic region centered on the glucocorticoid receptor gene. Such observations provide strong, previously undescribed evidence for how organismic, constitutional susceptibilities operate in conjunction with specific dimensions of social environmental influence to codetermine developmental and health outcomes. They also reveal how such gene–environment interplay can involve differences in environmental influence by allelic variation and also by epigenetic modifications in which chromatin structure is altered without changing DNA sequence.

Fifth, a group of papers on the health consequences of social position and relationships closes the special issue with a series of international observations and commentaries tying the character of early social relationships to health outcomes and arguing that the maldistribution of morbidity in human populations is attributable, in part, to the adversities derived from troubled or suboptimal social connections. Fernald et al. (42) report, using population-based data from four areas of the majority world, that even within contexts of poverty, graded associations exist between measures of social status and child development. McDade (43) reviews recent evidence linking nutritional and microbial exposures in childhood to the regulation of immune competence and inflammation in adult life. In an analysis of data from the US Panel Study of Income Dynamics, Ziol-Guest et al. (44) report that exposures to poverty very early in life (between the prenatal period and the second postnatal year) are associated with adult hypertension, arthritis, and activity limitations, suggesting a possible, specific link with immune-mediated forms of morbidity. Barr's essay (45) on abusive head trauma in human infants reveals how catastrophic failure within a common, iterative parent–infant interaction can lead to the shaken baby syndrome, a destructive and often fatal form of "biological embedding" of early adversity. Finally, Shonkoff (46) thoughtfully reflects on how a more elaborated biology of social adversity may hasten the advent of new, more effective interventions to lessen social disparities in health. The conjunction of these observations and commentaries brings greater clarity to the ubiquity of social environmental influences on early health and development, and renders efforts to understand, address, and diminish socioeconomic disparities even more compelling.

Taken together, these broad, diverse contributions to this special issue tell an emerging story of singular importance to those concerned with the physical embodiment and health consequences of early social conditions: from molecular geneticists, evolutionary biologists, and neuroscientists to social and behavioral scientists, epidemiologists, and those involved in the formulation of national health policy. The nascent but now substantial and increasingly coherent story traces many of the chronic morbidities, behavioral proclivities, and lasting afflictions of adulthood to experiences of adversity, maltreatment, and subordination sustained over the early years of life. Such a view of the origins of chronic disease and maladaptive behavior suggests that many should be reconceptualized as "developmental disorders," rooted as they are within the sometimes troubled social contexts of childhood (47, 48). Beyond this core collective message, some of the growing edges of this new developmental science can also be discerned in the challenging and convergent themes that wind through the research reports, essays, and reviews that follow. Among such themes are the following:

i) Studies examining the developmental biology of adversity show that we are on the cusp of providing deep mechanistic explications of the important, earlier insights of Waddington (49, 50), Gottlieb (51), and others (52–54) that organismic development is guided by the combined, interactive influences of genes and experiences. We now know that development includes not only gene expression regulation through experiential modification of chromatin structure but by real GxE interactions and the joint, interactive effects of allelic variation and chromatin modification [e.g.,

the papers by Lam et al. (39) and Rutter (23) in this and other publications (55)]. As asserted here and elsewhere, the simple partitioning of developmental variance into genetic and environmentally determined components now falls far short of a truly interactive view of the operation of nature and nurture (54). As the fields reporting various forms of interactions between genes and environments exponentially grow, what is now critically needed are programs of research examining the questions of how and by what mechanisms genes and early social contexts codetermine trajectories of behavioral and biological development. With respect to differences in complex behavior and its disorders, a focus on proximal, neurobiological processes must come strongly to the fore, as illustrated by recent work in an emerging "imaging genomics" (e.g., 56, 57).

ii) The origins, dimensions, and consequences of individual differences in phenotype are emerging as essential components in a full understanding of the biology of social adversity. Biology is teeming, of course, with both between- and within-species variation that bears convincing witness to the evolutionary uses of diversity, and elegant ethological and epigenetic work, such as that by Meaney (54), McGowan and Szyf (58), and Suomi (59), reveals the adaptive benefits of phenotypic diversification. For example, the maternally and epigenetically regulated differentiation of rat pups' adrenocortical responsivity produces a range of low- to high-reactivity phenotypes, each of which may maximize survival and fitness within particular early life and later life environments (60). Similarly, neither the aggressively uninhibited nor the shy, neophobic phenotypes of young rhesus macaques can be warranted as "normal" or optimal; rather, each has adaptive value within specific social and physical contexts (61, 62). What is salient and important about phenotypic variants is their capacity for enhancing fitness within the diversity of species-typical environments encountered.

An illustrative case of taking into account individual variation in humans is children's variation in susceptibility to social environmental influence. There is growing evidence for a generalized sensitivity to social contexts within a subset of human populations [i.e., highly sensitive or environmentally "permeable" individuals showing maladaptive outcomes in conditions of adversity but relatively more positive outcomes in settings characterized by support, predictability, and protection (e.g., 63–66)]. Such individuals thus show either the least or most adaptive outcomes within the population, depending on the character of the proximal social contexts in which they are reared. Studies demonstrating this greater susceptibility of neurobiologically responsive children to both positive and negative aspects of their environments have implicated a wide variety of stressors and adversities, including paternal depression (67), marital conflict (68, 69), parental psychopathology (70), and overall family distress (71); of positive environmental features, including parental warmth (72) and supportive interventions (73); and of defining biological parameters, including physiological reactivity (e.g., 74, 75), differences in brain circuitry (76), and gene polymorphisms (77, 78). Most importantly, highly susceptible children show bidirectional effects on outcomes in contrasting low- and high-stress settings, not simply an attenuation of negative effects in low-stress circumstances. Such differences in neurobiological sensitivity, likely based, in part, on genetic and epigenetic variation, are figuring prominently in the field's exploration of the biological embedding of early stress. Understanding phenotypic variation will also likely play a key role in the development of newly individualized approaches to "precision medicine" (79).

iii) Already coming into view through the present and other (80–86) collections of papers is a new corpus of research examining the social brain. Such work has begun to address a neurogenomic basis for complex social cognitions, including the capacities for inferences about others' thoughts and emotions (a cognitive ability referred to in the child development literature as "theory of mind"), recognition of self, processing of facial information, differentiation of social opportunities and challenges, and control of socially evoked emotion. The substrates for these capacities are already known to lie, at the neural circuit level, in functional connectivity between limbic structures, such as the amygdala, hippocampus, and basal ganglia, and prefrontal cortical regions, including the dorsolateral, orbitofrontal, and anterior cingulate, as well as the posterior superior temporal sulcus at the temporoparietal junction. At the molecular level, there is evidence for perturbations in the functionality of such circuits related to allelic and epigenetic variation in genes, such as those coding for the serotonin transporter (83), oxytocin (82), and endorphins (87). To date, there is no single definition of the social brain, but a consensus appears to be forming that a subset of autonomic, neuroendocrine, neural, and genomic processes influences and is influenced by aspects of social cognition and behavior (85, 86). Although it will be important to avoid a simplistic attribution of complex cognitive and perceptual events to discrete neural, endocrine, or cellular structures (82), there is clearly much to be learned about the nature of sociality, the mechanisms that underpin it, and the degree to which these mechanisms are conserved in animal phylogeny.

iv) As also reported in the set of papers collected here, a remarkable diversity of early, social environmental dimensions has been linked to important differences in mental and physical health, trajectories of development, and individual differences in behavior. Such dimensions include but are not limited to: social stratification and subordination; acute and chronic stressors; poverty and subjective social marginalization; and the absence of positive contextual factors, such as good parenting or a child-supportive community. As attention to epigenetic development grows, the capacity to place a finer, more exacting point on the specific kinds of environments that interact with particular allelic and epigenetic variants will be important and likely illuminating. Evolutionary perspectives on social adversity will also be essential to understand how difficult "environments of evolutionary adaptedness" shaped human and infrahuman biology (e.g., 64, 88), how contextual stressors might have generated species diversity (89), and how adversity may have contributed to the emergence of social cooperation (90). We need far finer and more precise renditions of the social environmental dimensions that interact with genes and produce negative and positive outcomes salient to population and public health.

v) Our collection of papers attests to the cross-species, evolutionary conservation of social structural organization, for both good and bad, and to the benefits of empathy, altruism, and sociality. The hierarchical and networked social structures found across phylogeny, literally from fruit flies (fish and primates) to human kindergartners [papers by Schneider et al. (27), Fernald and Maruska (30), and Boyce et al. (26) in this issue], suggest an evolved predisposition with implications for survival, reproduction, and safety. The papers

also raise important questions about how regulatory gene sequences influence the development of neural circuits supporting social behavior and higher order social structures (85). Thus, an important subtext running through this issue is the extraordinary value of cross-species, animal–human, comparative studies, which, together, not only inform the evolutionary biology of social organization and its consequences but enable experimental studies capable of bolstering the causal inferences disallowed by human research.

vi) The central role of time—evolutionary, historical, developmental, neurogenomic, and neurophysiological—in determining phenotypic variation is another recurrent if often implicit theme in the papers collected here. Much of the biological embedding of current social contexts reflects response predispositions established, selectively and epigenetically, through adaptations to the temporally distant environments of early hominids (91, 92). Social disparities in health—products, in part, of the social, economic, and health policies of contemporary societies—wax and wane within historical time according to the era's dominant sociopolitical philosophies (93, 94). As noted by several of the current authors, developmental time is uneven in its potency, intensity of change, and accessibility to environmental influence. Thus, for example, critical or sensitive periods exist for the acquisition of language and the discrimination of speech sounds in human infants [Weikum et al. (34)], and exposure to music can change auditory preferences in young mice through changes in prelimbic and infralimbic medial prefrontal cortex during an early critical period [Yang et al. (33)]. At the level of neurogenomic time, honey bees encode spatiotemporal mappings of foraging sites through differential gene expression signatures, allowing bees to remember not only geographic locations of food but the circadian patterning of food availability (95). Finally, at the level of neurophysiological time, even fleeting social interactions can trigger changes in neural firing and secretory action, as demonstrated elegantly in cichlid fish (85). Thus, at strikingly different levels of temporal resolution, time and timing appear to play crucial but not yet fully explored roles in guiding societal, organismic, and neurobiological responses to the conditions of early life.

vii) A systematic and useful biology of social adversity will necessarily involve not only a search for the mechanisms (i.e., mediators) underpinning associations across stress, development, and morbidity but the effects of modifiers (i.e., moderators) that reveal when, at what ages, or in what subgroups such associations hold (96–98). Understanding the mechanistic processes by which an environmental exposure is linked to disordered development can be a powerful aid to elucidating pathogenesis [e.g., the role of HDL transport of cholesterol as a mediator of the association between dietary fat and coronary heart disease (99)] and imagining novel interventions [e.g., changing mother–infant relationships as a means of altering the association between poverty and child development (100)]. On the other hand, grasping mediational linkages may be a necessary but insufficient condition for understanding causation, and the parsing of populations into subgroups of varying exposure susceptibility, through the discovery of moderator variables, can also advance comprehension and the tractability of a given association [e.g., changes in the potency of stress–illness associations by differences in individual sensitivity to social contextual effects (63, 64, 101)].

viii) Successfully pursuing a new developmental science of childhood adversity will surely also involve the perspective of complex adaptive systems. Traditional epidemiological strategies for understanding the health effects of social environmental factors involve the ascertainment of such factors' "independent" influences on a health end point through the use of multiple hierarchical regression models (102). Although such an approach allows estimation of the isolated effects of single independent variables, it belies the reality that most human disorders are etiologically complex, with multiple interacting "causes." Even detecting GxE interactions likely underserves the true complexity of pathogenic processes, because allelic variation in a single gene likely interacts with polymorphisms in several other genes and multiple dimensions of the environment may also interactively influence outcomes. In such circumstances—circumstances that may eventually prove to predominate in disease causation—the use of more sophisticated models and analytical tools may be required to understand the multiply interactive networks of risk factors involved in the ontogeny of disordered development and health (103, 104). If so, one such approach with increasingly demonstrable efficacy is the use of complex systems analysis, involving descriptive inventories of system components, nonlinear mathematical modeling, and the construction of agent-based models of causal networks (102, 105).

These broadening areas of scientific advancement, along with the collection of papers assembled for this PNAS issue, trace the perimeter of an emergent field. But we would be remiss if we did not mention the roots of this emergent field. That such a field of study has arisen and flourished is partly attributable to the late Dr. Fraser Mustard—celebrated Canadian health scientist, founding president of CIFAR, preeminent advocate for the abatement of health disparities around the globe, and one whose convictions about the centrality of childhood to the health of nations was profoundly and enduringly persuasive. Fraser pointed out the central importance of childhood adversities to the maldistribution of disease within human populations (106). He sought and procured the attention of policymakers, research administrators, politicians, and scientific leaders around the world and was eminently responsible for the establishment of the *developmental biology of social adversity* as a recognized and advancing field of study. It is thus to a remembrance of Fraser Mustard—mentor, role model, provocateur, and friend—that this special issue of PNAS is warmly and rightfully dedicated.

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