CHAPTER 13

Why Words Can Hurt Us
Social Relationships, Stress, and Health

Mark V. Flinn

Many students and other readers of this volume are familiar with coming down with a nasty cold or some other flu-like virus or bacterial infection around the time of final exams and having to spend a good portion of their holidays in bed recovering. The mechanisms by which increased suscepti- bility to pathogens and illness follow particularly stressful social periods, activities, and disappointments are precisely what Flinn explores in his long- running research among children in a rural community on the island nation of Dominica. He emphasizes that not only can sticks and stones "break *(our)* bones," as in the famous folk saying, but additionally, the unkind words that act as substitutes for sticks and stones can still make children sick. Flinn explores the underlying physiological changes that are associated with social processes and interactions and how they affect or are affected by the human immune system. For example, children he studied in Dominica are more than twice as likely to become ill during the week following a stressful event than children who have not recently experienced any significant stressors. In gen- eral, he found that elevated levels of cortisol in response to stress seem to be part of a generalized resistance-lowering response. He broadens his research questions to discuss how and why, from an evolutionary perspective, subjec- tive feelings are often necessary and used to negotiate, sustain, appease, and integrate ourselves into our respective groups and subgroups. Flinn shows here why the long period of childhood (and vulnerability to stress) serves a purpose, along with family systems, to mediate a child's responses to stress, illustrating why understanding cortisol production alone is an insufficient measure by itself to provide a true picture of the relationship of stress and illness. Accordingly, stress related to social situations is but one part of a much larger human adaptive system necessary for acquiring survival-related information and for gaining practice in building and refining the "mental algorithms critical for negotiating social coalitions"—abilities key to the success of our species.

> Sticks and stones will break my bones, but words will never hurt me.
>   English proverb

We humans are highly sensitive to our social environments. Our brains have special abilities such as empathy and social foresight, which allow us to understand each others' feelings and communicate in ways that are unique among all living organisms. Our extraordinary social brains, however, come with some significant strings attached. Our emotional states can be strongly influenced by what others say and do. Our hearts can soar, but they also can be broken. Our bodies use internal chemical messengers—hormones and neurotransmitters—to help guide responses to our social worlds. From romantic daydreams to jealous rage, from orgasm to lactation and parent–child bonding, the powerful molecules produced and released by tiny and otherwise seemingly insignificant cells and glands help orchestrate our thoughts and actions. Understanding this chemical language is important for many research questions in evolutionary medicine. Here I focus on the question of why social relationships can affect health—why it is that words *can* hurt children, despite the attempts by parents to protect them with rhymes. Stress hormones appear to play important roles in this puzzle.

Human stress hormone systems are highly sensitive to social challenges. For example, levels of the glucocorticoid stress hormone cortisol increase acutely in response to events such as public speaking (Kirschbaum & Hellhammer, 1994), school exams (Lindahl, Theorell, & Lindblad, 2005), domino matches (Wagner, Flinn, & England, 2002), and a wide variety of other social–cognitive demands (Dickerson & Kemeny, 2004). Elevation of stress hormones can have short- and long-term health costs (Ader, 2006; McEwen, 1998b; Sapolsky, 2005), presenting an evolutionary paradox. We do not have good explanations for why there are links between the parts of the brain that assess the social environment and the hormonal systems that control stress hormones such as cortisol and epinephrine (adrenaline). Furthermore, we do not understand why these links are modifiable during child development, such that early experiences may permanently alter hormonal response to social threats.

Evolutionary medicine is based upon the integrative evolutionary paradigm of Nobel laureate Niko Tinbergen (1963), who emphasized the importance of linking proximate physiological explanations (mechanisms; the nuts and bolts of how our bodies work) with ontogeny (development), phylogeny (ancestry), and adaptive function (how it was favored by natural selection). Using this approach to try and understand the paradox of stress response to social threat involves several steps. First, I briefly discuss why humans evolved what appears to be an unusual sensitivity to social and cultural environments. I then explore relations between physiological stress response and the development of social skills.

Hypotheses are evaluated with a review of an 18-year study of child stress in a rural community on the island of Dominica. My limited objective here is to provide a plausible model and some new pieces of the puzzle linking stress response and health outcomes to the neural plasticity that helps us respond to the dynamic human social environment. Resolution of the paradox of why humans evolved psychological and hormonal systems that can result in "words making us sick" may have significant consequences for public health because it could provide new insights into associations

among stress response, social disparities, psychopathologies such as autism, and peri-natal programming.

HORMONAL STRESS RESPONSE TO SOCIAL EVENTS:
A BRIEF LOOK AT STRESS IN A CHILD'S WORLD

> Danny was roaming the Fond Vert area of the village with two of his closest friends on a rainy Saturday morning. They had eaten their fill of mangoes, after pelting a heavily laden tree with stones for nearly an hour, taking turns testing their skill at knocking down breakfast. Now Danny was up the cashew tree in Mr. Pascal's yard, tossing the yellow and red fruits to the smaller children below who had gathered to benefit from this kindness. Suddenly the sharp voice of his stepfather rang out from the nearby footpath. The bird-like chatter and laughter of the children immediately stopped. Danny's hand froze mid-way to its next prize, and his head turned to face the direction of the yell with a mixed expression of surprise and fright. Ordered down from the tree, Danny headed quickly home, head bowed in apparent numb submission (from MVF field notes, July 14, 1994).

During the event described above, Danny's salivary cortisol level rose from 2.2 to 3.8 µg/dl in little more than an hour. That afternoon, his secretory immunoglobulin A levels dropped from 5.70 to 3.83 mg/dl. Three days later he had common cold symptoms: runny nose, headache, and fever (Figure 13-1). His two companions resumed their morning play, exhibiting a normal circadian decline in cortisol, and remained healthy over the next two weeks.
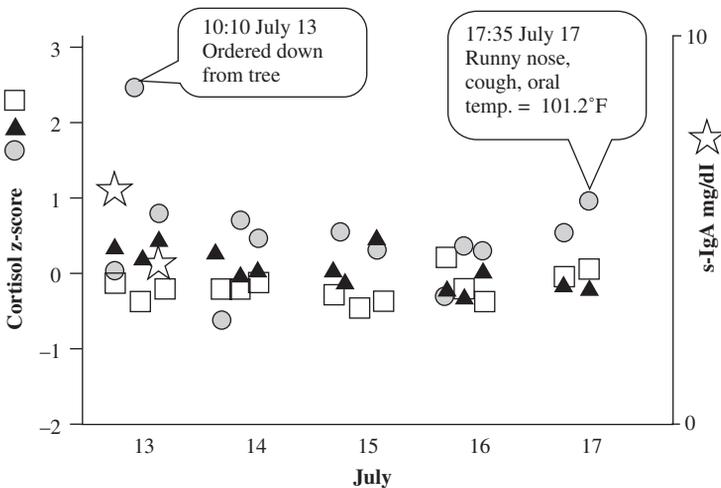

FIGURE 13-1 Morning, mid-morning, and afternoon cortisol levels of Danny and his two friends during summer 1994. Danny's cortisol levels were elevated and his s-IgA levels diminished after being reprimanded by his stepfather on the morning of July 13. Danny exhibits symptoms of an upper respiratory infection with slight fever on the afternoon of July 20. (Adapted from Flinn & England, 1997.)

This anecdotal case example contributes to a common pattern: children in this rural Dominican community are more than twice as likely to become ill during the week following a stressful event than children who have not recently experienced any significant stressors (Flinn & England, 2003). Humans respond to challenges in their social environments by elevating cortisol levels (Dickerson, Gruenewald, & Kemeny, 2004), often with negative consequences for their health (Marmot, 2004). This may be one reason why college students have higher rates of illness associated with final exams. Children lacking social support, including parental warmth and other factors that influence emotional states, seem to be at risk (Belsky, 1997; Davidson, Jackson, & Kalin, 2001; Field, Diego, Hernandez-Reif, Schanberg, & Kuhn, 2003). Why do social interactions, and a child's perceptions of them, affect stress physiology and morbidity? And, more generally, why is the social environment of such paramount importance in a child's world? From the perspective of evolutionary medicine, these "why?" questions ultimately involve understanding the evolutionary design of the psychological development of the human child (e.g., Bjorklund & Bering, 2003).

In Danny's village, located on the east coast of the island of Dominica, where I have lived and studied part-time over the past 18 years, most of a child's mental efforts seem focused on negotiating social relationships with parents, siblings, grandparents, cousins and other kin, friends, teachers, bus drivers, neighbors, shop owners, and so forth. Foraging for mangos and guavas, hunting birds, or even fishing in the sea from rock cliffs are relatively simple mental tasks, complicated by conflicts with property owners and decisions about which companions to forage and share calories with. In this village, children seem more concerned with solving social puzzles than with utilitarian concerns of collecting food. Other populations may have more difficult subsistence practices that require more extensive learning (e.g., Bock, 2005), but negotiating social relationships nonetheless appears universal and cognitively demanding for children in all cultures (Blurton-Jones & Marlowe, 2002; Hewlett & Lamb, 2002, 2005), as it likely was during human evolutionary history (Alexander, 1979; Bowlby, 1969, 1973; Hinde, 1974).

In the following section I review current theories of human life history and the family. I suggest that conspecific social competition was the primary selective pressure shaping the uniquely human combination of physically altricial (helpless) but mentally and linguistically precocial (quick to develop) infancy, extended childhood, and extended adolescence, enabled by extensive bi-parental and kin care. I then turn to the role that the links between psychosocial stimuli and physiological stress response may play in guiding both the acute and long-term neurological plasticity necessary for adapting to the dynamic aspects of human sociality.

EVOLUTION OF THE SOCIAL CHILD

The human child is a most extraordinary organism, possessed of a fantastic mind and yet innocent and helpless—in effect, a larva equipped with an enormous brain. Even relative to other primates, the human infant is unusually altricial and highly dependent upon parents and other relatives for protection, transport, resources (e.g., food), and information (Lamb, Bornstein, & Teti, 2002). The human child has evolved to rely upon extensive investment over a long period of time, often involving multiple care providers in embedded

kin networks (Belsky, 2005; Flinn & Leone, 2006; Lamb, 2005; Quinlan & Flinn, 2005). Humans stand out as "the species that takes care of children" (Konner, 1991, p. 427).

The selective pressures responsible for this unique suite of life history characteristics appear central to understanding human evolution (Alexander, 1987, 2005; Bjorklund & Pellegrini, 2002; Flinn & Ward, 2005; Geary, 2005; Kaplan, Hill, Lancaster, & Hurtado, 2000). The delay of reproduction until almost 20 years of age, much longer than that of our closest relatives the chimpanzees and gorillas, prolongs exposure to extrinsic causes of mortality and lengthens generation intervals. What advantages of an extended childhood could have outweighed the heavy costs of reduced fecundity and late reproduction (Stearns, 1992) for our hominin ancestors?

The physical growth of the child, although a little unusual in its timing (Bogin, 1999; Leigh, 2001), does not appear to be especially difficult. The relatively slow rate of overall body growth during childhood, followed by a rapid growth spurt during puberty, may economize parental resources. A small child requires fewer resources than a large one. Hence, delayed physical growth during childhood may have facilitated shortened birth intervals for parents of such children, providing a demographic advantage (Bogin & Marela-Silva, 2003).

Brain growth, however, has a different trend from overall body growth. The baby human has a large brain with high energetic and developmental costs that consume more than half (!) of its total metabolism to build and maintain (Armstrong, 1990; Holliday, 1986; Leonard & Robertson, 1994). Although neurogenesis (nerve cell production) is mostly completed by the third trimester and synaptogenesis (development of connections among the nerve cells) by the third year of life (at a rate of 1.8 million synapses per second!), reproduction is postponed for another 15 years or more. What requires so much additional time to develop? And why burden the growing child, and its caregivers, with such a large brain that requires so much energy for so long? An evolutionary medicine perspective suggests that for natural selection to have favored this unusual life history schedule, there are likely to be some compensatory benefits.

One possibility is that a lengthy childhood is useful for acquiring complex skills: "immatures are enabled to live a protected existence whilst they learn skills necessary for adult life" (Bowlby, 1969, p. 63). But what information is so important and difficult to acquire that many years are needed for its mastery? Most juvenile primates spend considerable effort playing and practicing with their physical environment and developing fighting skills (e.g., Pellegrini & Archer, 2005; Symons, 1978). Compared with other primates, our basic motor skills do not appear significantly more challenging. Children may need time to acquire knowledge for tool use and complex foraging including hunting (Darwin, 1871; Hill & Kaplan, 1999; see also Byrne, 2002a, b). An extraordinarily long developmental apprenticeship is seen as useful for acquiring learned solutions to ecological problems unique to our niche (Bock, 2005; see also Blurton Jones & Marlowe, 2002). Investment in acquiring skills and knowledge via an extended childhood has been suggested to have a fitness payoff from increased adult foraging ability (Kaplan et al., 2000).

An alternative hypothesis for human childhood involves consideration of the brain as a "social tool" (Alexander, 1989; Bjorklund & Rosenberg, 2005; Brothers, 1990; Byrne & Whiten, 1988; Dunbar, 1998; Humphrey, 1976, 1983). This hypothesis suggests that many human cognitive and psychological adaptations function primarily to contend with

social relationships, in addition to those necessary for physical ecological demands (e.g., hunting or extractive foraging). It appears that some human cognitive competencies, such as theory of mind, or ToM (this involves abilities such as empathy that help us understand what other people are feeling or thinking about), and language, evolved because of social selection pressures, (Adolphs, 2003; Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001). Our particularly well-developed mental abilities of general intelligence and executive functions (e.g., Chiappe & MacDonald, 2005; Geary, 2005; Quartz & Sejnowski, 1999) allow us to use mental simulations, "social scenario-building" (Alexander, 1989), and "mental time-travel" (Suddendorf & Corballis, 1997) to construct and rehearse potential responses to changing social conditions. These complex cognitive processes would be more capable of contending with, and producing, novelties of cultural change and individual-specific differences (Bjorklund & Rosenberg, 2005; Tomasello, 1999).

The informational arms race that characterizes human social competition involves substantial novelty (Flinn, 2006b, Flinn & Alexander, 2007) and hence requires unusual phenotypic plasticity. Although knowledge of the basic neuroanatomical structures involved with human social aptitudes has increased dramatically (e.g., Allman, 1999; Damasio, 2003; Gallese, 2005; Moll et al., 2005), the mechanisms that guide their development remain uncertain. Neuroendocrine stress response to stimuli in the social environment may provide important clues.

STRESS RESPONSE MECHANISMS

Physiological responses to environmental stimuli that are cognitively perceived as "stressful" are modulated by a part of the brain termed the limbic system (amygdala and hippocampus). Here we are primarily concerned with what has traditionally been termed the limbic hypothalamic–anterior pituitary–adrenal cortex (HPA) system. The HPA system affects a wide range of physiological functions in concert with other neuroendocrine mechanisms and involves complex feedback regulation. The HPA system regulates a class of hormones that are called glucocorticoids, primarily cortisol, which is normally released from the adrenal glands into the blood stream in seven to fifteen pulses during a 24-hour period (for reviews, see de Kloet, Sibug, Helmerhorst, & Schmidt, 2005; Ellis, Essex, & Boyce, 2005; Weiner, 1992).

Cortisol is a key hormone produced in response to physical and psychosocial stressors. Cortisol modulates a wide range of bodily functions, including (1) energy release, (2) immune activity, (3) mental activity (e.g., alertness, memory, and learning), (4) neural modification, (5) growth, and (6) reproductive function (e.g., inhibition of gonadal steroids, including testosterone). These complex multiple effects of cortisol make it difficult to sort out its adaptive functions. The demands of energy regulation must orchestrate with those of immune function, and so forth. Cortisol regulation allows the body to respond to changing environmental conditions by preparing for, and recovering from, *specific* short-term demands (Mason, 1971; Munck, Guyre, & Holbrook, 1984).

These temporary beneficial effects of glucocorticoid stress response, however, are not without costs. Persistent activation of the HPA system is associated with immune deficiency, cognitive impairment, inhibited growth, delayed sexual maturity, damage to the hippocampus, enhanced sensitivity of amygdala fear circuits, and psychological

maladjustment. Stressful life events—such as divorce, death of a family member, change of residence, or loss of a job—are associated with infectious disease and other health problems during adulthood (Cohen, Doyle, Turner, Alper, & Skoner, 2003; Maier, Watkins, & Fleschner, 1994; Marmot & Wilkinson, 1999).

Current psychosocial stress research suggests that cortisol response is stimulated by significant perceived uncertainty (Dickerson & Kemeny, 2004; Kirschbaum & Hellhammer, 1994). From a child's view, important events are going to happen, but she is uncertain how best to respond. Cortisol release is associated with unpredictable, uncontrollable events that require full alert readiness and mental anticipation. Temporary moderate increases in stress hormones (and associated neurotransmitters such as dopamine) may enhance mental activity for short periods in localized areas of the brain and prime memory storage, hence improving cognitive processes for responding to social challenges (Beylin & Shors, 2003; LeDoux, 2000). Mental processes unnecessary for appropriate response may be inhibited, perhaps to reduce external and internal "noise" (Servan-Schreiber et al., 1990).

Chronically stressed children may develop abnormal cortisol response, possibly via changes in binding globulin levels and/or reduced affinity or density of glucocorticoid, corticotropin-releasing hormone (CRH), oxytocin, and vasopressin receptors in the brain (De Kloet, 1991; Fuchs & Flugge, 1995). Early experience—such as maternal licking of rat pups (Meaney et al., 1991; Takahashi, 1992; Weaver et al., 2004), some types of prenatal stress of rhesus macaques (Clarke 1993), insecure maternal–infant attachment among humans (Spangler & Grossmann, 1993), and sexual abuse among humans (De Bellis et al., 1994; Heim et al., 2002)—can permanently alter HPA response.

Early theoretical models of stress response did not attempt to directly explain the apparent evolutionary paradox of sensitivity to the social environment. Current perspectives view stress response as an optimal resource allocation problem (Korte, Koolhaas, Wingfield, & McEwen, 2005). Energy resources are diverted to muscular and immediate immune functions and other short-term (stress emergency) functions at cost to long-term functions of growth, development, and building immunity. Under normal conditions of temporary stress, there would be little effect on health. Indeed, there may be brief enhancement of immune (Dhabbar & McEwen, 2001) and cognitive function. Persistent stress and associated hyper- or hypocortisolemia (unusually high or low cortisol levels), however, is posited to result in pathological immunosuppression, depletion of energy reserves, and damage to parts of the brain (e.g., Santarelli et al., 2003; Sheline, Gado, & Kraemer, 2003). This highlights the problems with a stress response system that evolved to cope with short-term emergencies. The chronic stress produced by modern human social environments may present novel challenges that the system is not designed to handle, potentially resulting in maladaptive pathology (Sapolsky, 1994).

The chronic social stress hypothesis, however, is difficult to reconcile with the long evolutionary histories of complex sociality in primates, perhaps especially in our human ancestors. Why, given all the extensive evolutionary changes in the human brain, would selection not have weeded out this apparent big mistake of linking stress response with social stimuli? Modern human environments have many novelties that can elicit stress response (for example, roller coasters, final exams, and traffic jams), but social challenges in general seem to have a much more ancient evolutionary depth and, as suggested in

previous sections, may be a key selective pressure for the large human brain. One possibility is that the energetic, immunological, and mental preparations for potential dangers is an unavoidable costly insurance, akin to expensive febrile (fever) response to pathogens such as the common cold viruses, that are usually benign—the "smoke-detector" principle (Nesse & Young, 2000). The idea is that although physiological stress response to social challenges is costly, and most often wasteful, it may have helped our ancestors cope with rare and unpredictable serious conflicts often enough to be maintained by selection. The benefit/cost ratio could be improved by fine-tuning stress mechanisms in response to environmental conditions during development.

A complementary approach to the mismatch hypotheses suggests that neuroendocrine stress response may guide adaptive neural reorganization, such as enhancing predator detection and avoidance mechanisms (Buwalda, Kole, Veenema, Huininga, De Boer, Korte, & Koolhas, 2005; Dal Zatto, Marti, & Armario, 2003; Le Doux, 2000; Meaney, 2001; Wiedenmayer, 2004). For example, in mice stress response from exposure to cats can have long-term effects on the central amygdala (right side), resulting in increased fear sensitization (Ademec, Blundell, & Burton, 2005; see also Knight, Nguyen, & Bandettini, 2005). The potential evolutionary advantages of this neural phenotypic plasticity are apparent (Rodriguez Manzanares, Isoari, Carrer, & Molina, 2005). Prey benefit from adjusting alertness to match the level of risk from predators in their environments. Social defeat also affects the amygdala and hippocampus, but in different locations than does predator exposure (Bartolomucci et al., 2005), suggesting that stress response helps direct changes in the brain to the appropriate places.

Glucocorticoids, perhaps in combination with other hormones and neurotransmitters, appear to facilitate the neurological processes that underlie some types of learning. The potentiating effects of cortisol on emotional memories and other socially salient information may be of special significance in humans (Fenker, Schott, Richardson-Klavehn, Heinze, & Düzel, 2005; Jackson, Payne, Nadel, & Jacobs, 2006; Lupien et al., 2005; Pitman, 1989).

Adaptive Developmental Changes in Response to Social Environment

Environmental stimuli (in children mainly psychosocial challenges and demands) exert profound effects in neuronal activity through repeated or long-lasting changes in the release of transmitters and hormones which contribute, as trophic, organizing signals, to the stabilization [NE] or destabilization [Cortisol] of neuronal networks in the developing brain . . . destabilization of previously established synaptic connections and neuronal pathways in cortical and limbic structures is a prerequisite for the acquisition of novel patterns of appraisal and coping and for the reorganization of the neuronal connectivity in the developing brain (Huether 1998, p. 297).

If physiological stress response promotes adaptive modification of neural circuits in the limbic and higher associative centers that function to solve psychosocial problems, then the paradox of psychosocial stress would be partly resolved. Temporary elevations of cortisol in response to social challenges could have advantageous developmental

effects useful for coping with the demands of an unpredictable and dynamic social environment. Elevating stress hormones in response to social challenges makes evolutionary sense if it enhances specific acute mental functions and helps guide neural remodeling (e.g., see Bartolomucci, Palanza, Sacerdote, Panerai, Sgoifo, Dantzer, & Parmigiani, 2005; Buwalda, Kole, Veenema, Huininga, De Boer, Korte, & Koolhas, 2005; Francis, Diorio, Plotsky, & Meaney, 2002; Maestripieri, Lindell, Ayala, Gold, & Higley, 2005; Mirescu, Peters, & Gould, 2004; Weaver, Cervoni, Champagne, D'Alessio, Sharma, Seckl, Dymov, Szyf, & Meaney, 2004). In the following sections we will examine the relationships between stress hormone levels, social challenges, and health in the everyday social environments of the children living in Danny's village.

SOCIAL ENVIRONMENT, STRESS RESPONSE, AND HEALTH: THE DOMINICA STUDY

Assessment of relations among psychosocial stressors, hormonal stress response, and health is complex, requiring: (1) longitudinal monitoring of social environment, emotional states, hormone levels, immune measures, and health; (2) control of extraneous effects from physical activity, circadian rhythms, and food consumption; (3) knowledge of individual differences in temperament, experience, and perception; and (4) awareness of specific social and cultural contexts. Multidisciplinary research that integrates human biology, psychology, and ethnography is particularly well suited to these demands. Physiological and medical assessment in concert with ethnography and coresidence with children and their families in anthropological study populations can provide intimate, prospective, longitudinal, naturalistic information that is not feasible to collect in clinical studies. For the past 18 years (1988–present) I have conducted such research with the help of many colleagues and students and the extraordinary cooperation of a wonderful study population.

The Study Village

Bwa Mawego, the village that Danny lives in, is a rural community located on the east coast of Dominica. About 500 residents live in 160 structures/households that are loosely clumped into five "hamlets" or neighborhoods. The population is of mixed African, Carib, and European descent. The community is isolated because it sits at the dead end of a rough road. The community of Bwa Mawego is appropriate for the study of the relationship between a child's social environment and physiological stress response for the following reasons: (1) there is substantial variability among individuals in the factors under study (family environments, social challenges, and stress response), (2) the village and housing are relatively open, hence behavior is easily observable, (3) kin tend to reside locally, (4) the number of economic variables is reduced relative to urban areas, (5) the language and culture are familiar to the investigator, (6) there are useful medical records, and (7) local residents welcome the research and are most helpful. The study involved 282 children and their caregivers residing in 84 households. This is a nearly complete sample (>98%) of all children living in four of the five village hamlets during the period of fieldwork from 1989 until 2006.

Methods and Field Techniques

Our initial objective in 1989 was to assess each child's general stress level as determined by the level of cortisol in their saliva. The idea was to see how this hormone was associated with a child's family environment. We also were fortunate to have saliva samples from different times of day in this initial collection and quickly recognized that very precise control of circadian patterns—in particular sleep schedules and wake-up times—was critical to accurate assessment of HPA stress response (Flinn & England, 1992). More than 30,000 saliva samples later, it seems we have more questions than answers.

In this study, monitoring cortisol levels over long periods of time is used to assess physiological stress response to everyday events, including social challenges. Saliva is collected from children by members of the research team at least twice a day, wherever the children happen to be (usually at their household). The large sample size of cortisol measures for each child (more than 100 samples for most children) in a variety of naturalistic contexts provides a much more extensive and reliable picture of HPA stress response than small sample designs. In the next section I briefly review some of the results from this study that may provide useful insights into relations between health and stress response to psychosocial threats.

Cortisol Response to Naturally Occurring Social Threats

Our analyses of naturally occurring stressors in children's lives in Bwa Mawego indicate that social threats are important stressors, with the emphasis upon the family environment as both a primary source and mediator of stressful stimuli (Flinn & England, 1995, 2003). Temporary, moderate increases in cortisol are associated with common activities such as eating meals, active play (e.g., cricket), and hard work (e.g., carrying loads of wood to bay oil stills) among healthy children. These moderate stressors—"arousers" might be a more appropriate term—usually have rapid attenuation, with cortisol levels diminished to normal within an hour or two (some stressors have characteristic temporal "signatures" of cortisol level and duration).

High-stress events (cortisol increases from 100 to 2000%), however, most commonly involved trauma from family conflict or change (Flinn & England, 2003). Punishment, quarreling, and residence change substantially increased cortisol levels, whereas calm, affectionate contact was associated with diminished (-10 to -50%) cortisol levels. Of all cortisol values that were more than two standard deviations above mean levels (i.e., indicative of substantial stress), 19.2% were temporally associated with traumatic family events (residence change of child or parent/caretaker, punishment, "shame," serious quarreling, and/or fighting) within a 24-hour period. In other words, family problems that we were aware of accounted for about a fifth of all the high cortisol levels, more than any other factor that we examined. In addition, 42.1% of traumatic family events were temporally associated with substantially elevated cortisol (i.e., at least one of the saliva samples collected within 24 hours was >2 SD above mean levels). Hence, family problems appear to reliably elevate cortisol levels.

There was considerable variability among children in cortisol response to family disturbances. Not all individuals had detectable changes in cortisol levels associated with family trauma. Some children had significantly elevated cortisol levels during some

episodes of family trauma but not during others. Cortisol response is not a simple or uniform phenomenon. Numerous factors, including preceding events, habituation, specific individual histories, context, and temperament, appear to affect how children respond to particular situations.

Nonetheless, traumatic family events and social emotions such as guilt and shame (Flinn, in press a) were associated with elevated cortisol levels for all ages of children more than any other factor that we examined. These results suggest that family interactions were a critical psychosocial stressor in most children's lives, although the sample collection during periods of relatively intense family interaction (early morning and late afternoon) may have exaggerated this association.

Children residing in households with a stepparent have high cumulative mean cortisol levels relative to their half-siblings in the same household (Flinn, 1999; Flinn & Leone, in press). Children in bi-parental households have moderate cortisol levels (Flinn & England, 1995), with a higher proportion of elevations occurring in the context of positive affect situations such as competitive play, physical work, and excitement regarding novel situations.

Although elevated cortisol levels are associated with traumatic events such as family conflict, long-term stress may result in diminished cortisol response. In some cases, chronically stressed children had blunted response to physical activities that normally evoked cortisol elevation. Comparison of cortisol levels during "nonstressful" periods (no reported or observed crying, punishment, anxiety, residence change, family conflict, or health problem during the 24-hour period before saliva collection) indicates a striking reduction and, in many cases, reversal of the family environment–stress association (Flinn & England, 2003). Chronically stressed children (those in households with high—top quartile—rates of observed and reported stressful events) sometimes had subnormal cortisol levels when they were not in stressful situations. For example, cortisol levels immediately after school (walking home from school) and during noncompetitive play were lower among some chronically stressed children than their peers (see Long, Ungpakorn, & Harrison, 1993). Some chronically stressed children appeared socially "tough" or withdrawn and exhibited little or no arousal to the novelty of the first few days of the saliva-collection procedure. These subnormal profiles may be similar in some respects to those of individuals with posttraumatic stress disorder (e.g., Yehuda, Engel, Brand, Seckl, Marcus, & Berkowitz, 2005).

Although elevated cortisol levels in children are usually associated with negative affect, events that involve excitement and positive affect also stimulate stress response. For example, cortisol levels on the day before Christmas were more than one standard deviation above normal, with some of the children from two-parent households and those having the most positive expectations exhibiting the highest cortisol (Flinn, in press b). Cortisol response appears sensitive to social challenges with different affective states. Other studies further suggest that the cognitive effects of cortisol may vary with affective states, such as perceived social support (Ahnert, Gunnar, Lamb, & Barthel, 2004; Quas, Bauer, & Boyce, 2004).

There are some age and sex differences in cortisol profiles, but it is difficult to assess the extent to which this is a consequence of neurological differences (e.g., Butler, Pan, Epstein, Protopopescu, Tuescher, Goldstein, Cloitre, Yang, Phelps, Gorman, Ledoux, Stern, & Silbersweig, 2005), physical maturation processes, or the different social

environments experienced, for example, during adolescence as compared with early childhood (Flinn et al., 1996). For instance, young adult women have a higher incidence of depression and associated abnormal cortisol profiles than children or young men in this community.

The emerging picture of HPA stress response in the naturalistic context from the Dominica study is one of sensitivity to social threats, a finding consistent with clinical and experimental studies. The results further suggest that family environments are an especially important source and mediator of stressful social challenges for children. In the next section data on the longitudinal effects of early traumatic experiences are examined to assess the domain specificity of changes in stress response; that is, does exposure to early trauma result in sensitivity to some types of stressors but not to others?

Ontogeny: The Early Trauma Leads to HPA Dysfunction Hypothesis

Early experiences can have profound and permanent effects on stress response. Exposure to prenatal maternal stress or prolonged separation from mother in rodents and nonhuman primates can result in life-long changes in HPA stress response (Meaney 2001; Suomi, 1997; see also Levine, 2005). Research on the developmental pathways has targeted the homeostatic mechanisms of the HPA system, which appear sensitive to exposure to high levels of glucocorticoids during ontogeny. Glucocorticoid receptors (GRs) in the hippocampus that are part of the negative feedback loop regulating release of CRH and adrenocorticotropic hormone can be damaged by the neurotoxic levels of cortisol associated with traumatic events (Sapolsky, 2005). Very high levels of cortisol can actually kill off the nerve cells that are responsible for turning off further cortisol release. Hence, early trauma is posited to result in permanent HPA dysregulation and hypercortisolemia (abnormally high levels of cortisol), with consequent deleterious effects on the hippocampus, thymus, and other key neural, metabolic, and immune system components (Mirescu, Peters, & Gould, 2004). These damaging effects may have additional consequences resulting from the high density of GRs in the prefrontal cortex in primates (de Kloet, Oitzl, & Joels, 1999; Patel, Lopez, Lyons, Burke, Wallace, & Schatzberg, 2000; Sanchez, Young, Plotsky, & Insel, 2000), where much of the executive function or higher learning processes occur.

The specific mechanisms affecting relations between exposure to trauma early in development and subsequent HPA system function in humans are not as well documented as in animal studies. Nonetheless, a similar causal linkage appears plausible (e.g., Essex et al., 2002; Heim et al., 2000; Lupien et al., 2005; O'Conner, Heron, Golding, Glover, & ALSPAC study team, 2003; Teicher, Andersen, Polcari, Anderson, Navalta, & Kim, 2003).

Children in the Bwa Mawego study who were exposed to the stress of hurricanes and political upheavals during infancy or in utero do not have any apparent differences in cortisol profiles when compared to children who were not exposed to such stressors. Children exposed to the stress of parental divorce, death, or abuse (hereafter "early family trauma" or EFT), however, have higher cortisol and morbidity (Figure 13-2) levels at age 10 than other children. Based on analogy with the nonhuman research discussed previously, two key factors could be involved with these results for EFT children: (1) diminished hippocampal GR receptor functioning, resulting in less effective negative feedback regulation of cortisol levels, and (2) enhanced sensitivity to perceived
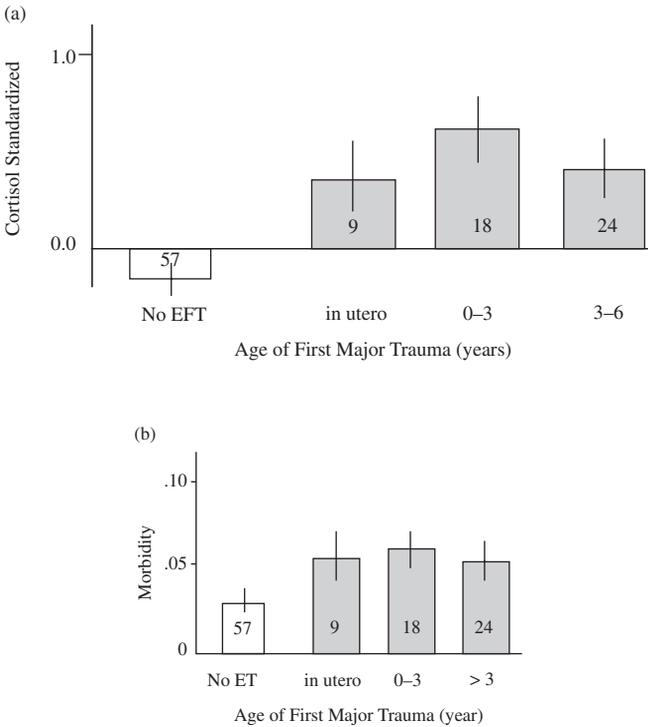
FIGURE 13-2 Children exposed to early family trauma (EFT) in utero or postnatal have higher average cortisol levels at age 10 (a) and higher morbidity (b) than children who were not exposed to early trauma (no EFT). Sample sizes (number of children) are in bars. Vertical lines represent 95% confidence intervals. (Adapted from Flinn, 2006a.)

social threats. Children usually elevate cortisol in response to strenuous physical activity, but rapidly return to normal levels. If EFT has affected the negative feedback loop, then recovery to normal cortisol levels would be slower. Resumption of normal cortisol levels after physical stressors, however, is similar regardless of early experience of family trauma (Figure 13-3). Cortisol profiles following social stressors, however, indicate that EFT children sustain elevated cortisol levels longer than non-EFT children (Figure 13-4).

The enhanced HPA stress response of children in this community that were exposed to EFT appears primarily focused on social challenges, suggesting that the developmental effects of early trauma on stress response may be domain-specific and even context-specific. These results are consistent with studies of the effects of social defeat in rodents and nonhuman primates (e.g., Kaiser & Sachser, 2005; Wiedenmayer, 2004).

Stress and Health Outcomes

A large and convincing research literature confirms commonsense intuition that psychosocial stress affects health (Ader et al., 2006). Retrospective studies indicate that
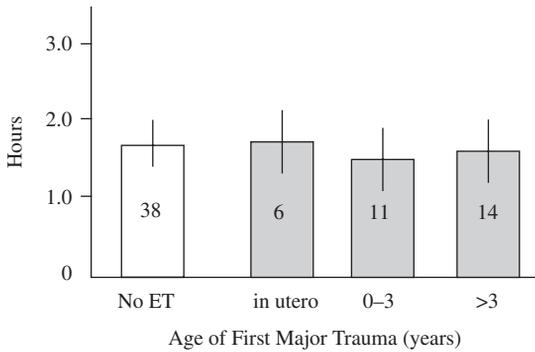
FIGURE 13-3 Children exposed to early family trauma (ET) do not have slower recovery to normal cortisol levels after physical stressors than no-ET children do. Sample sizes (number of children) are in bars. Vertical lines represent 95% confidence intervals. (Adapted from Flinn, 2006a.)
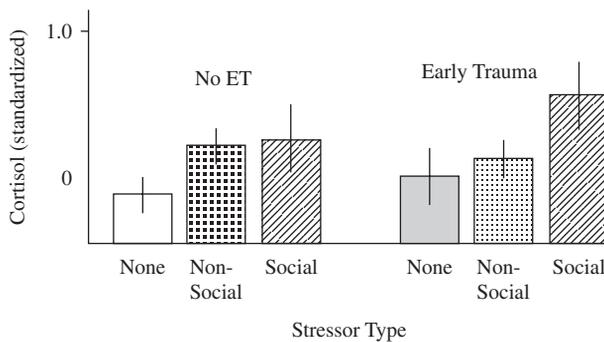

FIGURE 13-4 Children exposed to early family trauma (ET) have higher cortisol levels in response to social stressors, but not nonsocial stressors, than no-ET children. Vertical lines represent 95% confidence intervals. (Adapted from Flinn, 2006a.)

traumatic life events, such as divorce or death of a close relative, are associated with subsequent health problems, such as cancer or cardiovascular disease. Clinical studies indicate that individuals with stressful lives are more susceptible to the common cold (Mason et al., 1979).

Stress response may deplete cellular energy and immune reserves. Although cortisol may provide short-term benefits, the body needs to replenish energy reserves to provide for immunity, growth, and other functions. Hence chronic stress and high average cortisol levels are predicted to be associated with frequency of illness. Chronically stressed children with high cortisol levels tend to be ill more frequently than children in normal stress environments (Flinn & England, 2003). Short-term temporal patterns of cortisol and observed stressful events also are associated with increased risk of illness, as anecdotally illustrated in the previous example of Danny (Figure 13-1), in which illness follows a high stress event. Children in Bwa Mawego have a nearly twofold increased

risk of illness for several days following naturally occurring high-stress events such as a family crisis (Figure 13-5).

These prospective data suggest that stress increases vulnerability to infectious disease; however, they do not demonstrate a direct effect of cortisol. Sleep disruption and poor nutrition often accompany social trauma. Stressful events may be associated with increased exposure to pathogens, resulting, for example, from trips to town by family members or residence changes. Stressful events may be more likely when family members are ill. Common infectious diseases are more prevalent during stressful seasonal periods such as Christmas, start of school, and carnival. A more direct causality would be indicated by immunosuppressive effects of stress.

Numerous (hundreds) of specific interactions between stress endocrinology and immune function have been identified (Ader et al., 2006). Indeed, so many different and complex mechanisms appear to be involved in psychoneuroimmunological (PNI) interactions that a general explanation remains elusive. It seems paradoxical that an organism would suppress immune response during periods of stress when exposure and vulnerability to pathogens may be high.

Several nonexclusive, complementary hypotheses appear feasible:

1. Allocation of energy to "emergency" demands may favor diversion from immunity (Sapolsky, 1994).

2. Overactive defensive responses to stress can result in autoimmunity; anti-inflammatory effects of glucocorticoid stress hormones may be protective of some types of tissues (Munck, Guyre, & Holbrook, 1984).

3. The possibility of damage to peripheral tissues generating novel antigens (e.g., collagen in joints) during exposure to stressors, such as disease and strenuous physical or mental activity, may require particular suppression of immune function.
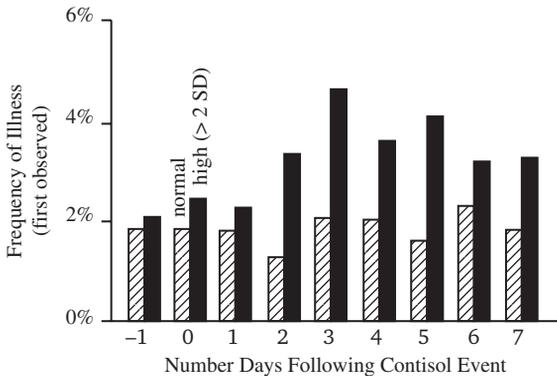

FIGURE 13-5 Temporal association between naturally occurring stress events and frequency of illness. Children had higher frequencies of illness for 3–5 days following a stress event (observed or reported stressor that was accompanied within an 8-hour period by an elevated cortisol level of more than two standard deviations above mean levels, illustrated by solid black bars), than when no stress event had occurred (diagonally striped bars). (Adapted from Flinn, 1999.)

4. The movements of immune cells may be enhanced or focused by localized overrides of the general immuno-suppressive effects of cortisol.

The complexity and dynamics of the immune system make assessment of immune function difficult. We have conducted an exploratory investigation of several components of immune function among children in Bwa Mawego using saliva samples. Preliminary analyses of these data suggest that psychosocial stress may have different effects on the different components of immune function. Apparent differences between immune functioning of chronically stressed and normal children include lower levels of s-IgA and neopterin (Flinn & England, 2003). These measures change in response to stress events and illness. Temporal patterns of immune function appear to differ slightly between normal and chronically stressed children. We do not know if these differences affect morbidity for any specific pathogen, but they are suggestive of possible links among psychosocial stress, immune function, and illness.

SUMMARY AND CONCLUDING REMARKS

Hormonal stress response may be viewed as an adaptive mechanism that allocates energy resources to different bodily functions, including immunity, growth, muscle action, and cognition (McEwen, 1995; Sapolsky, 2005). Understanding stress response is important because of consequences for health and psychological development. The perspective of evolutionary medicine provides new ways of looking at this important problem.

The objective of the long-term bio-cultural study in Bwa Mawego is to monitor children's social and physical environment, behavioral activities, health, and physiological states in a naturalistic setting so as to better understand relationships among family environment, stress responses, and health. Analyses of data indicate that children living in households with intensive, stable caretaking usually had moderate cortisol levels and low frequency of illness. Children living in households with nonintensive, unstable caretaking were more likely to have abnormal (usually high and variable, but sometimes low) cortisol levels. Traumatic family events were associated temporally with elevated cortisol levels. Some children with caretaking and growth problems during infancy had unusual cortisol profiles. These associations indicate that family environment was a significant source of stress and illness risk for children living in Bwa Mawego. The variability of stress response, however, suggests a complex mix of each child's perceptions, neuroendocrinology, temperament, and specific context.

Relationships between family environment and cortisol stress response appear to result from a combination of factors. These include frequency of traumatic events, frequency of positive affectionate interactions, frequency of negative interactions such as irrational punishment, frequency of residence change, security of attachment, development of coping abilities, and availability or intensity of caretaking attention. Probably the most important correlate of household composition that affects childhood stress is maternal care. Mothers in socially secure households (i.e., permanent amiable co-residence with mate and/or other kin) appeared more able and more motivated to provide physical, social, and psychological care for their children. Mothers without mate or kin support were likely to exert effort attracting potential mates and may have viewed dependent

children as impediments to this. Hence, co-residence of father may provide not only direct benefits from paternal care, but may also affect maternal care (Belsky et al., 2005). Young mothers without mate support usually relied extensively upon their parents or other kin for help with childcare (Flinn & Leone, in press).

Children born and raised in household environments in which mothers have little or no mate or kin support were at greatest risk for abnormal cortisol profiles and associated health problems. Because socioeconomic conditions influence family environment, they have consequences for child health that extend beyond direct material effects.

Returning to the paradox of why natural selection favored sensitivity of stress response to social stimuli in the human child, several points emerge. Childhood is necessary and useful for acquiring the information and practice to build and refine the mental algorithms critical for negotiating the social coalitions that are key to success in our species. Mastering the social environment presents special challenges for the human child (e.g., Lamb, 2005). Social competence is difficult because the competition—one's peers—is constantly changing and similarly equipped with theory of mind and other cognitive abilities. Results from the Dominica study indicate that family environment is a primary source and mediator of stressful events in a child's world. The sensitivity of stress physiology to the social environment may facilitate adaptive mental responses to this challenging aspect of a child's world.

Coping with social problems, however, can have significant health consequences, ranging from dysregulation of emotional control and increased risk of psychopathology (Gilbert, 2001; Nesse, 1999) to broader health issues associated with social and economic disparities (Marmot & Wilkerson, 1999). The potential for intergenerational cycles that perpetuate social relationships that affect stress (Belsky, 2005; Belsky, Jaffee, Sligo, Woodward, & Silva, 2005; Maestripieri, Lindell, Ayala, Gold, & Higley, 2005) and poor health are especially concerning.

We are still far from identifying the specific mechanisms linking stress response to psychological development and health outcomes. An evolutionary medicine perspective can be useful in these efforts to understand this critical aspect of a child's world by integrating knowledge of physiological causes with the logic of adaptive design by natural selection. It reminds us that medical practice and public health can benefit from consideration of our evolutionary history as extraordinarily social creatures. We evolved to have feelings and thoughts focused on social relationships. Our thoughts and feelings, however, are not without costs; they can affect our health, sometimes in very important and significant ways. Cancer, atherosclerosis, infectious disease, and many other health problems are linked to our social and emotional well-being (Ader et al., 2006). Our stress response systems appear to have an important evolved role in this connection.