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Chapter 1

TIMING, BONDING, AND TRAUMA: APPLICATIONS FROM EXPERIENCE-DEPENDENT MATURATION AND TRAUMATIC STRESS PROVIDE INSIGHTS FOR UNDERSTANDING ENVIRONMENTAL ORIGINS OF DISEASE

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ABSTRACT

Parent-child relationships play a crucial role in shaping our developing nervous systems, exerting a particularly strong influence in early life during pregnancy, labor, and delivery. Their vital role continues through infancy, into adolescence and beyond. Indeed, these relationships affect us across multiple generations, influencing not only our genes and behaviors, but impacting our nervous systems and physiologies as well. Because the nervous system regulates and interacts with all other organ systems, factors that influence its regulatory relationships and patterns may also have an impact on health and risk for disease.

Early relationships and traumatic life events represent environmental factors that interact with genes to shape our capacities for self-regulation. These factors also influence how we respond to life in general, and to stress in particular. A model for understanding the role of environmental factors in the origins of chronic illness is proposed, applying growing scientific research from the psychophysiology, neurology, and biology of bonding and traumatic stress as a means for elucidating findings from clinical, pathophysiological, and epidemiological studies of chronic illness. The integration of this multidisciplinary information suggests a link between early life events and relationships, long-term health, and risk for disease. These perspectives also have meaningful implications for individual, societal, and global health, and offer insights regarding the development of effective strategies for prevention and treatment.

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INTRODUCTION

Environmental factors play a significant role in the origins of many chronic diseases, yet the nature of these contributions remains difficult to elucidate. Conflicting findings are common among studies seeking to identify and explain the manner in which non-genetic factors affect risk for specific diseases such as type 1 diabetes, asthma, and inflammatory bowel disease, among others. While factors such as obstetrical complications, duration of breastfeeding, and exposure to stressful life events are increasingly identified in association with risk for disease, there is a need for an organizing perspective from which to understand the role of such events in pathogenesis. This chapter proposes such a model by integrating data from our increasing understanding of how environmental factors affect the maturation and development of regulatory patterns in the nervous, immune and other organ systems with findings from epidemiological, physiological, and clinical data for disease.

The first section of this chapter summarizes knowledge gained from the fields of experience-dependent maturation and traumatic stress. These data demonstrate how events in early life, which involve the highly underestimated role of parent-child relationships, are genetically designed to influence organ system development during critical periods of maturation. In optimal situations, strong parent-child attachment bonds and familial support systems work synergistically to facilitate resiliency and flexibility in patterns of physiologic, emotional, cognitive, and behavioral self-regulation in the child, whether the primary adult caregiver is the biological or adoptive parent, or someone else. When components of this system are taxed, however, the growing infant is at risk of developing altered patterns of regulation. Findings from the field of critical period programming suggest that the timing of exposure to environmental factors affects organ systems undergoing rapid development and influences future patterns of structural or functional development in these organ systems.

The extensive literature in traumatic stress and posttraumatic stress disorder (PTSD) provides insights for explaining contributions of perception and stressful life events in the initiation, perpetuation, and precipitation of risk for disease, as well as variability in age of onset. Findings further suggest that experiences of stress are idiosyncratic and are related to an individual's unique history. This provides a useful lens for explaining and predicting contradictory findings regarding the long-term effects of stress in the variability of symptom exacerbations following onset of disease.

In the second section of the chapter, environmental contributors to three diseases are evaluated in light of perspectives gained from our understanding of experience-dependent maturation and traumatic stress. Type 1 diabetes, asthma, and inflammatory bowel disease are all associated with clear pathophysiological processes that can be assessed through objective tests. Type 1 diabetes and asthma are also two of the most common diseases in childhood, although onset can also occur in adults. The age of onset of inflammatory bowel disease has been decreasing, and can begin in childhood as well as in early or late adulthood. Environmental factors appear to play an important role in the origins of these diseases, although the mechanisms for these effects have been unclear and findings often contradictory or paradoxical. The application of knowledge from multiple disciplines supports over 70 years of research in the study of stress (for a review, see Rabkin [1]) and suggests that similar patterns occur in the evolution of these, and other diseases.

The pattern consists of 1) initiation and predisposition to risk following exposure to traumatic events in early life, 2) determination of disease specificity according to timing of exposure during critical periods of development, 3) promotion of states of altered regulation through subsequent exposure to relevant stressors of sufficient frequency and intensity, 4) precipitation of clinical symptomatology through unmasking of pre-existing states of dysregulation following exposure to a wide variety of stressors, 5) variability in symptom expression following the onset of disease in association with exposure to idiosyncratic stressors, and 6) variation in frequency, severity, and perception of stress in different racial groups, social classes, and minorities. Furthermore, these studies have also found that individuals who are vulnerable to disease do not necessarily progress to overt expression if they are not exposed to sufficient stressor intensity and frequency [1]. Evidence for environmental contributions in transgenerational transmission is seen in all three diseases, and is also discussed.

I. Findings from Experience-Dependent Maturation and Traumatic Stress

Experience-Dependent Maturation

Gene-Environment Interactions

Experience-dependent maturation refers to the interactions that occur between genes and experience, in which some characteristics of organ development are dependent upon exposure to specific life experiences in order for full functionality and regulatory capacity to emerge (see reviews in Schore [2], National Research Council and Institute of Medicine [3], Siegel [4], and Rice [5]). During experience-dependent maturation, genes determine the *timing* of different aspects of organ system development, such as cellular differentiation, migration, and myelination. The processes of maturation and development are characterized by predictable periods of overabundance of neurons and synaptic connections, followed by equally predictable periods of selective pruning and programmed cell death (apoptosis) [6].

Environmental factors such as cellular and hormonal events, social interactions, physical activity levels, and exposure to substances such as toxins also influence developmental processes. These processes include gene transcription and expression, cellular proliferation and differentiation, as well as strength, number, and density of synaptic connections. Increased activity of particular nerve pathways, such as through reinforcement with use, facilitates greater stabilization and myelination of these pathways, whereas underutilization is associated with pruning and apoptosis [5].

Critical Periods

Peaks in synaptic development occur at times unique to each tissue and organ system. Organ systems are most sensitive to environmental influences, and therefore also most vulnerable, during periods of high growth. These stages of development are therefore referred to as “critical periods”. The impact of events occurring during these periods can be lifelong and can be initiated during prenatal life, throughout childhood, and sometimes in adolescence and beyond [7].

Timing

Exposure to environmental factors such as toxins and stress can have varying levels of impact depending on the timing of exposure. When exposure occurs during structural development, for example, congenital malformations can occur. When events occur later in development, they may affect a multitude of less obvious functional processes such as cellular differentiation, apoptosis, or myelination [8]. Risk for congenital malformations is greater during the initial weeks following conception and is easier to pinpoint in time than periods affecting functionality of physiology and other regulatory processes [9], in large part because patterns of structural development are easier to identify. Defects associated with environmental exposures thus appear to be associated with critical windows of development that affect specific organ systems [9]. Similarly, timing of environmental exposures appears to affect risk for diseases associated with these particular organ systems [8] (see Figure 1).

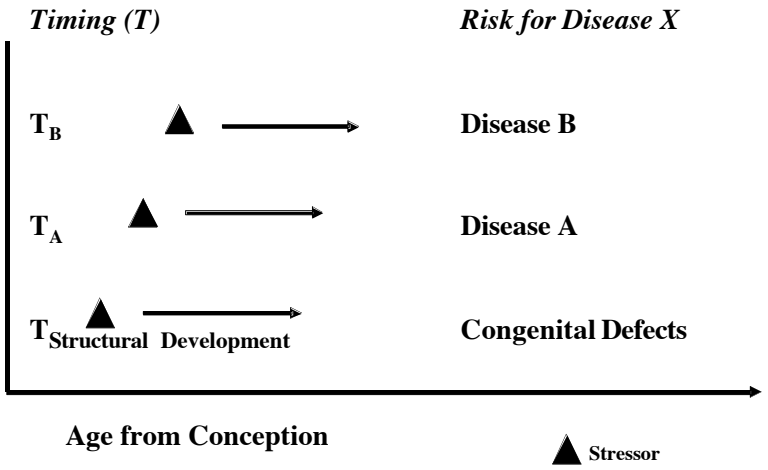

Figure 1. Timing of exposure determines specificity of disease.

> Exposure to environmental events influences structure and function of organ systems undergoing critical periods of development at the time of exposure. Events occurring during structural development affect risk for congenital defects in the related organ system. Likewise, events occurring during development of organ system A (Time $_A$) are hypothesized to predispose individuals to risk for altered patterns of regulation in this organ system and to consequently affect risk for Disease A.

Critical Periods are not Limited to Prenatal Life

Organ systems undergo multiple critical periods during development and most organ systems, including the nervous [2, 10], immune [11], respiratory [12], and endocrine [13] systems, among others, are immature in humans at birth. Critical periods of nervous system development begin at conception and last at least into adolescence, although remodeling in response to genetic and environmental factors continues throughout adulthood [5]. Lung maturity is not reached until adulthood [14] and a large part of lung development, including

approximately 80% of alveolar formation [12], occurs postnatally [15]. The process of myelination, which increases the speed and stability of message transmission through nerves, continues into adolescence [16], and can be delayed by factors such as malnutrition [5] and exposure to glucocorticoids in prenatal life [17, 18]. Prenatal nutritional stress also influences the number and size of pancreatic ß-cells, the amount of insulin produced by these cells, as well as rates of programmed cellular proliferation and apoptosis [19]. Patterns of altered regulation such as glucose intolerance are unmasked with aging in offspring of these prenatally stressed rats and are transmitted to *their* offspring in a process that occurs across multiple generations [19]. Malnutrition during prenatal life also affects the structure and function of the cardiovascular system, kidneys, and fat cells to influence birth weight, risk for elevations in blood pressure and growth rates, as well as obesity later in life. The role of prenatal malnutrition has been studied extensively as part of the adult origins of disease hypothesis (previously referred to as Fetal Programming), and will be discussed later in more detail [19].

Critical Periods and the Immune System

The immune system is involved in a great many diseases, whether in association with increased inflammation in heart disease, rheumatoid arthritis, inflammatory bowel disease, and asthma, or in autoimmune processes, whichdestroy tissues that should be recognized as "self", such as occurs in type 1 diabetes and systemic lupus erythematosus. Critical periods in immune system development therefore appear important in risk for disease.

The number of white blood cells in the immune system is comparable to the cell mass in the brain or liver [20]. White blood cells develop in the primary lymphoid organs such as the thymus, which begins to grow prenatally and continues to develop into adolescence, maintaining functionality into adulthood [21]. White blood cells that survive to maturation migrate to secondary lymphoid organs, which is predominantly where they react with foreign antigens [20]. These secondary organs include the epithelium-based tissues of the skin, lungs, and intestines, as well as the lymph nodes, spleen, and appendix, among others [20]. Removal of these organs has little effect on local immune responses because determination of antigen-specificity reactions occurs in the primary lymphoid organs [20].

Exposure to antigens prior to maturation of white blood cells leads to long-lasting non-responsiveness of the immune system to these particular antigens, and cells that react to "self" are eliminated or inactivated during development in early life [20]. Once a lymphocyte reacts to a particular antigen, it is believed that every clone in that cell line is also predisposed to react to the same antigen, even though it has never itself been exposed [20].

Healthy neonates have low responses to allergens during the prenatal period and the first year of life, and exposure to microbes during this period appears critical to the development of long-term patterns of immune system responses to these stimuli [22]. Exposure to environmental factors such as breast milk [23] and intestinal microflora facilitate the development of a balance between immune responses to antigens that are identified as harmless, and reactivity to antigens that may be pathogenic [22]. Mode of delivery at birth appears to be an important event in this maturational process and the sterile neonatal gut becomes colonized by nonpathogenic microbes upon exposure to maternal fecal and vaginal flora during vaginal delivery [22].

Cascade of Effects

Because the nervous system and other developing organ systems are influenced by environmental factors in a process of experience-dependent maturation, any alteration in early structure or function affects future interactions of a system with its environment [8]. The complex nature of these interactions makes it difficult to distinguish events that initiate a disease from those that represent secondary insults to further increase risk. Ultimately, however, events occurring during critical periods can be additive in affecting risk for disease [8].

Latency Periods

Evidence that injury to structural or functional development has occurred may be delayed until new demands unmask their effects. Normal changes in growth and function [5, 8], for example, require increasing availability of oxygen [12] and glucose [24], thus exerting greater needs on the developing pancreas or lungs during growth in early life. The impact of early developmental insults may therefore not become clinically visible until demands overwhelm a poorly functioning system, or synaptic interconnections are reduced as a consequence of programmed cell death. Apoptosis is a normal aspect of development and also occurs with aging [5] as well as challenging (stressful) environmental events [8]. The process of delays in expression of altered function appears to be one factor contributing to the sometimes lengthy latency periods that exist between initiation and onset of a disease.

Psychobiological Regulation

The presence of the adult caregiver's mature nervous system serves as an external regulator for the neonate, who is unable to regulate states of high arousal and whose immature nervous and other organ systems require external regulatory support. The physical presence and proximity of the parent modulates infant emotional and physiological arousal; autonomic, neurochemical, hormonal, and behavioral states; and biological rhythms such as temperature, heart rate, sleep cycles, and digestion [25-27]. Early parent-infant interactions help shape the baby's developing organ systems and regulatory patterns, including the capacity of the sympathetic and parasympathetic nervous systems to interact with and inhibit one another [2]. This process is referred to as psychobiological regulation [10, 26, 28] and is facilitated by the attachment bond between parent and infant [2].

Bonding and attachment represent genetically programmed behaviors that coincide with the development of specific neural pathways in the infant [2]. These behaviors are facilitated through metabolism and nutrient intake (such as digestion of breast milk), as well as with the sight of the caregiver's face and other sensorimotor cues [25, 29]. Parent-infant interactions that facilitate regulation in the child include such everyday events as gazing, touching, holding, and soothing [2] and shape individual responses to the environment. These idiosyncratic styles of regulation appear to be nature's way of preparing her young for their own unique habitats [30, 31]. When children grow up in optimal environments, they develop self-regulatory capacities for effectively coping with novel stimuli and other forms of stress, as well as for managing and recovering from states of arousal and transitioning into states of alert inactivity, rest, and recovery [2].

One important aspect of an optimal early environment involves a high degree of attunement between parent and infant, which facilitates synchronicity in their interactions. With maturation, these early experiences inform developing patterns of communication, social interaction, and regulation as children internalize their own capacities for independent regulation of homeostasis [2]. Early parent-infant contact, especially during the period immediately following birth, promotes healthy patterns of regulation. Loss of early regulatory support, such as occurs with early separation, on the other hand, can disrupt the parent-infant bond and alter developing states of regulation to ultimately influence risk for health and disease [2, 25, 27]. The following paragraphs describe the impacts of stress and traumatic stress, and then link these two knowledge bases to describe long-term impacts of life events occurring during pregnancy, labor and delivery, and in the period immediately following birth.

Traumatic Stress

Difficulties in understanding the role of stress in the origins of disease and in symptom exacerbations have occurred, at least in part, due to methodological problems [1]. Our increasing understanding of brain plasticity as well as interactions between genes and the environment provide new insights for understanding links between stress and disease. In addition, data from studies in traumatic stress further delineate the role of stressful events and may help to explain the frequently paradoxical findings identified in clinical studies by providing a continuum from which to better define the concept of "stress" (for in-depth reviews, see Scaer [32, 33], van der Kolk et al. [34] and Levine [35]).

In its simplest form, stress refers to experiences of psychological or physical challenge, as well as the metabolic, behavioral, and emotional responses to events that threaten or are perceived to threaten homeostasis [36]. Stress can thus result from simple and non life threatening events such as the intake of food, which requires changes in physiological and metabolic processes associated with digestion and the use of nutrients. An experience of stress can also occur following exposure to novel situations, such as to an unfamiliar environment [37].

Traumatic stress differs from ordinary concepts of stress according to degree, and is associated with an experience that is perceived as life-threatening in the context of helplessness and vulnerability. Experiences associated with high emotional charge, as when survival is threatened, are associated with the inability to modulate arousal and are capable of reprogramming the hypothalamic-pituitary-adrenal (HPA) axis to consequently affect risk for persistent and long-term states of altered autonomic regulation [33, 35] such as seen in PTSD. Factors that affect the manner in which an event is perceived play an important role in determining susceptibility to the long-term effects of traumatic stress. These factors, which are discussed below, include age, life experiences, prior exposure to stress and traumatic stress, ability to successfully cope with a situation, and the presence of available support, among others. Events that may be experienced as traumatic are not limited to physical, emotional, sexual, or verbal abuse but also include neglect, betrayal and abandonment during childhood, experiencing or witnessing violence, catastrophic illness or illness associated with accidental poisoning or high fever, prolonged immobilization such as splinting for scoliosis,

war, natural disasters, car accidents, invasive medical procedures, loss of loved ones, and birth stress [32-35].

Survival Responses and Mobilization

Traumatic responses elicit innate nervous system defense responses such as fight and flight, which represent states of high sympathetic arousal, and the freeze response, which is facilitated by parasympathetic dominance associated with vagal tone. Surges of hormones, neuropeptides, and other chemicals associated with sympathetic arousal facilitate the ability to flee or fight. Mobilization utilizes these substances and communicates successful survival to the nervous system, indicating that arousal levels may be down-regulated [38].

The freeze response is also referred to as an immobility or passive coping response. It is highly appropriate in certain contexts, such as when facing a large angry dog or bear, in which case the event is (correctly) perceived as inescapable, fighting or fleeing are likely to increase the danger, and freezing is the most appropriate response. Freeze responses are generally preceded by states of elevated sympathetic arousal such as fear, and wild animals who freeze later mobilize the energy of sympathetic arousal through spontaneous involuntary movements such as trembling, shaking, and changes in breathing, which occur once the threat is no longer present [32, 33, 35, 39].

An important factor believed to be associated with risk for PTSD and states of altered regulation following exposure to traumatic stress is the failure of mobilization to occur after a freeze/immobility response [33, 35]. Mobilization may be prevented by many factors, such as the presence of new or ongoing threat. This is exemplified by the experience of a child living in a home where the parent is the perpetrator. It may also be thwarted by interruption due to social inhibition, which is common in humans, or by other tasks requiring immediate attention, such as the need to fill out paperwork and speak with law enforcement officials following a car accident. An example of thwarted mobilization is seen in animals subjected to repeated and inescapable shock who become immobilized after further shock and do not flee even when escape routes are provided. Prolonged or repeated activation of freeze states and lack of mobilization are associated with risk for PTSD and are also believed to influence risk for chronic illness [32, 33, 35, 38, 40].

Memory and Idiosyncrasy

Events that are emotionally significant, such as those associated with great excitement or extreme life threat, tend to be associated with high arousal and emotional charge [32, 33, 41]. Stress hormones and other factors associated with arousal facilitate the imprinting of memories for such events. Consequently, experiences of extreme fear, helplessness, and life threat are deeply imprinted in the nervous system. This aspect of memory formation is part of an evolutionary survival strategy designed to facilitate rapid responses upon re-exposure to similar threats in the future. Because of their formation during states of high arousal, memories of life-threatening events are remarkably accurate and stable over time, usually remain outside of conscious awareness, and then to have little or no associated verbal content [33, 41].

As with other memories, the imprinting of events associated with traumatic stress tends to incorporate context [42, 43]. The context for a traumatic event is deeply imprinted as a result of high arousal and often includes very specific fragments of images, smells, sounds, or kinesthetic sensations, as well as emotions. Memories and contextual cues are therefore unique to the individual and to each person's experience of a specific traumatic event.

Intensity

The strength of a traumatic memory, as well as the degree of hormonal output associated with evocation of such a memory, correlates with the perceived intensity of the original experience [41]. Upon future exposure to events or states of arousal similar to the original traumatic stressor [32, 33, 44], these contextual cues and sensations are re-experienced as physiological, emotional and/or behavioral flashbacks that feel as real as if they were occurring in the present moment [41]. With each experience of another traumatic event, stress hormones are released, further strengthening or "kindling" the original memory trace and increasing the facility with which a memory and consequent responses will become reactivated.

Self-Perpetuation

As the process of exposure to subsequent stressors occurs and kindling strengthens the activation of trauma-related memories, cues increasingly unrelated to the original traumatic event also begin to stimulate traumatic responses of arousal. Subtle events that trigger and perpetuate trauma responses are idiosyncratic, and can be internal or external. Internal cues that trigger the response may be ordinary physiologic processes such as increases in heart rate that occur while walking or when feeling excited, and which trigger anxiety and other signs and symptoms of thwarted fight or flight responses. An example of an external cue is the sight of a cloudless sky. Although neutral or even positive for many people, this is a trigger in some individuals exposed to the bombings of the World Trade Centers on September 11th [45], which occurred on a beautiful clear day. Over time, trauma responses and states of altered regulation become activated with increasing ease and frequency when triggers of sufficient intensity and relevance occur, and the effects of traumatic stress are inherently self-perpetuating. This is a cycle that eventually leads to PTSD and then further perpetuates these symptoms once PTSD is established. It is also hypothesized to influence risk for disease (see Figure 2).

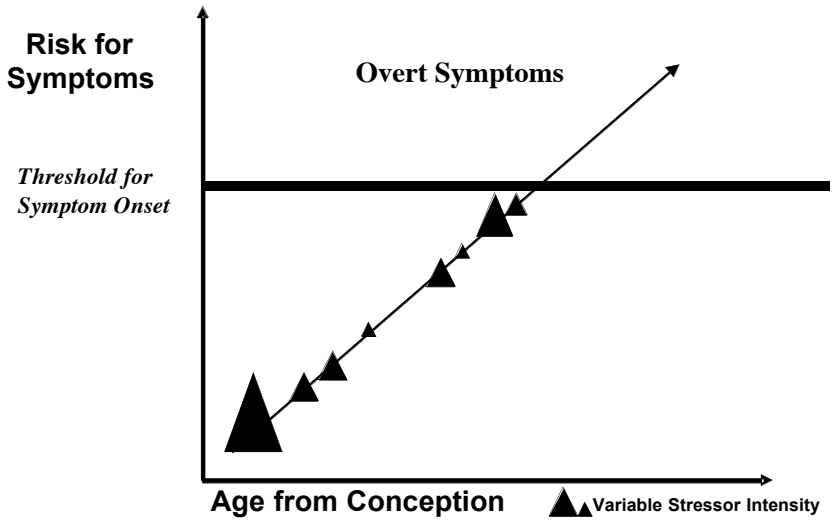

Figure 2. Stressor intensity affects risk.

The severity and frequency of exposure to stressors influences risk for symptoms of PTSD and is hypothesized to influence risk for disease.

Concepts of self-perpetuation in traumatic stress are similar to the description of a cascade of effects in experience-dependent maturation. In each of these processes, the impact of environmental events tends to be additive. The long-term effects are also influenced by the uniqueness of individuals and their environments, and exposure to the same event elicits different responses in each individual (see Figure 3).

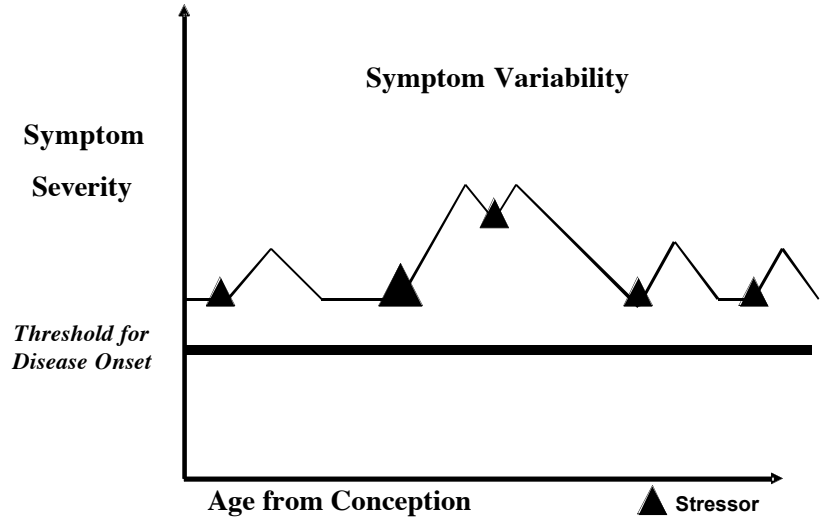

Figure 3. Idiosyncratic stressors affect symptom variability.

Symptom exacerbations vary according to exposure to idiosyncratic stressors. Whether an event is experienced as stressful is influenced by perception and history of life events for each person.

Not everyone involved in a severe car accident develops PTSD, for example, yet some people develop severe symptoms following even mild accidents [46]. Indeed, severity of symptoms following mild stressors suggests prior exposure to traumatic stress [47]. These differences suggest that variability in the expression of a disease, including severity, frequency of exacerbations, and extent of complications may be the result of differences in exposure and response to stressful and triggering life events, rather than to some isolated genetic factor per se. In essence, individual reactions to traumatic stress, as well as symptoms of PTSD, are unique to the individual rather than to the event.

Perception

Although some types of events such as natural disasters, life-threatening illness, or the witnessed murder of a loved one are more likely to be experienced as traumatic, it is the subjective experience and the manner in which an event is perceived that determines whether it is enjoyable, neutral, stressful, or traumatic. Perception develops according to previous experiences of stress and trauma, including prenatal and perinatal events such as bonding disruptions, which will be discussed in detail below. Perception, and consequently, the experience of stress, are also influenced by the presence of social support networks and attachment bonds [32, 33, 35, 43], and such events buffer the impact of stress and other major life events (see Figure 4).

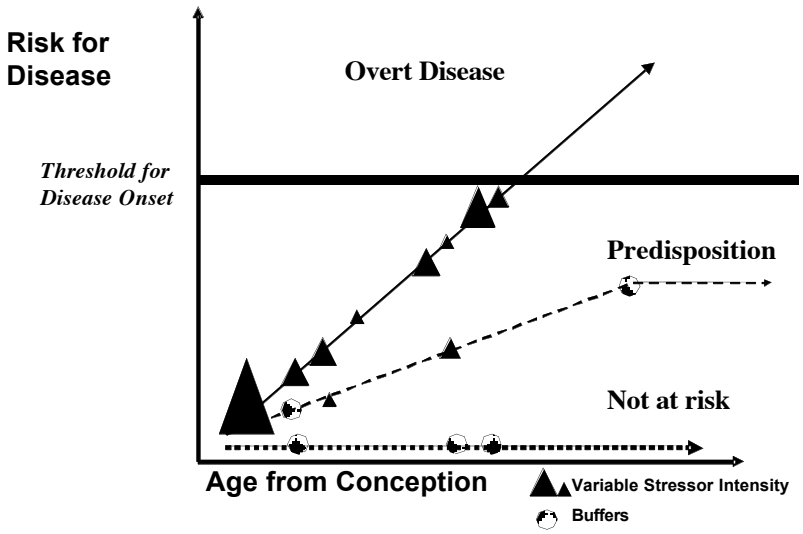

Figure 4. Stressors and buffers affect risk.

Intensity of stressful events, including severity and frequency, influences risk for PTSD and is proposed to similarly affect risk for symptom expression in disease. If buffers are present and exposure to stressors is insufficient or occurs outside of a critical window of time, risk may be non-existent or predisposition and progression to disease may fail to occur.

Children are the Most Vulnerable

Infants are inherently helpless, have immature nervous systems incapable of regulating states of high arousal, and are undergoing significant critical periods of maturational development [2, 48]. As a result, they are at greatest risk of experiencing even apparently mild stressful events as life threatening and traumatic [33, 49]. This is evident in studies of PTSD, which indicate that adults exposed to trauma in childhood show more profound states of physiological dysregulation than people who develop PTSD as adults [50].

Long-term adaptations in children following trauma are different in complexity, severity, and expression from symptoms seen in adults and are affected by the developmental level of the child at the time the trauma occurs [49]. The effect of trauma on children may influence biological, psychological, and emotional maturation and may even arrest development or slow progression to subsequent stages of development [32, 33, 43].

Trauma in the Context of Relationship

Because psychobiological regulation is such an important element in the development of self-regulation, trauma that occurs in the context of a relationship with another human being is one of the most important risk factors for altered regulation such as PTSD. Early separation from parents is an important risk factor for PTSD [51, 52] and secure attachment as well as strong parent-child bonds [52] are factors that buffer children from risk for PTSD [43].

Latency Periods and Rates of Progression

Symptoms of PTSD may develop days, weeks, or even years following the original event [32-34] Onset is facilitated by the initial intensity of perceived life-threat as well as frequency and severity of subsequent exposures to idiosyncratic stressors[52]. If sufficient social support systems and buffers are available following a traumatic event, and/or few additional stressors occur, symptoms may never arise, or may resolve spontaneously within a short period [34](See Figure 5).

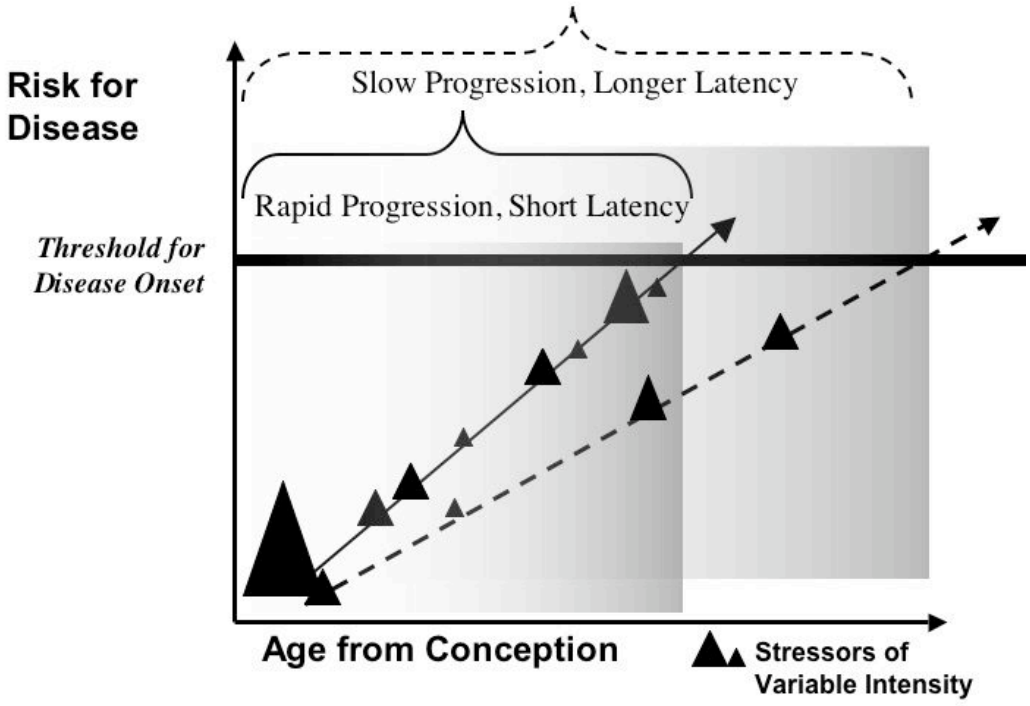

Figure 5. Latency and rates of progression.

Intensity and rate of exposure to stressful events perpetuates risk in individuals predisposed to risk for PTSD. A similar pattern is hypothesized to occur in disease, in which exposure to a larger number or greater intensity of perceived stressors increases rates of progression and decreases age of onset.

The nature and severity of PTSD symptoms is idiosyncratic, and is influenced by an individual's unique life experiences. Although PTSD occurs in relatively few people following exposure to traumatic events, symptoms tend to be remarkably refractory to treatment once they develop [34]

PTSD Follows a Pattern

Events leading to clinically visible symptoms of PTSD follow a pattern [33]. First, a clearly identifiable specific event, such as a car accident, is unconsciously perceived as life-threatening and inescapable and imprints in procedural memory to predispose an individual to risk for PTSD. Next, the memory trace becomes reinforced through repeated exposure to idiosyncratic cues, which may be increasingly unrelated to the original traumatic event. Third, symptoms of PTSD become clinically visible following a variable latency period in which

duration is determined by the intensity and frequency of exposure to triggering events. These triggers involve contextually relevant cues, and may occur hours, days, months or even years following the initiating event [32, 33, 35, 43] (see Figure 6).

A car accident may be the initiating event for PTSD. If it is a mild accident or if the symptoms of PTSD are severe, however, it is more likely to represent a precipitating factor. A car accident may therefore stimulate and unmask pre-existing subclinical patterns of altered regulation initiated decades earlier through exposure to other traumatic experiences, such as prenatal and perinatal stressors, a childhood accident, child abuse or neglect, or the loss of a parent [32, 33, 35, 43] (see Figure 7). This perspective is useful when considering the role of stressful life events in the origins of disease because many diseases occur within a year or two of both significant and seemingly non life threatening events.

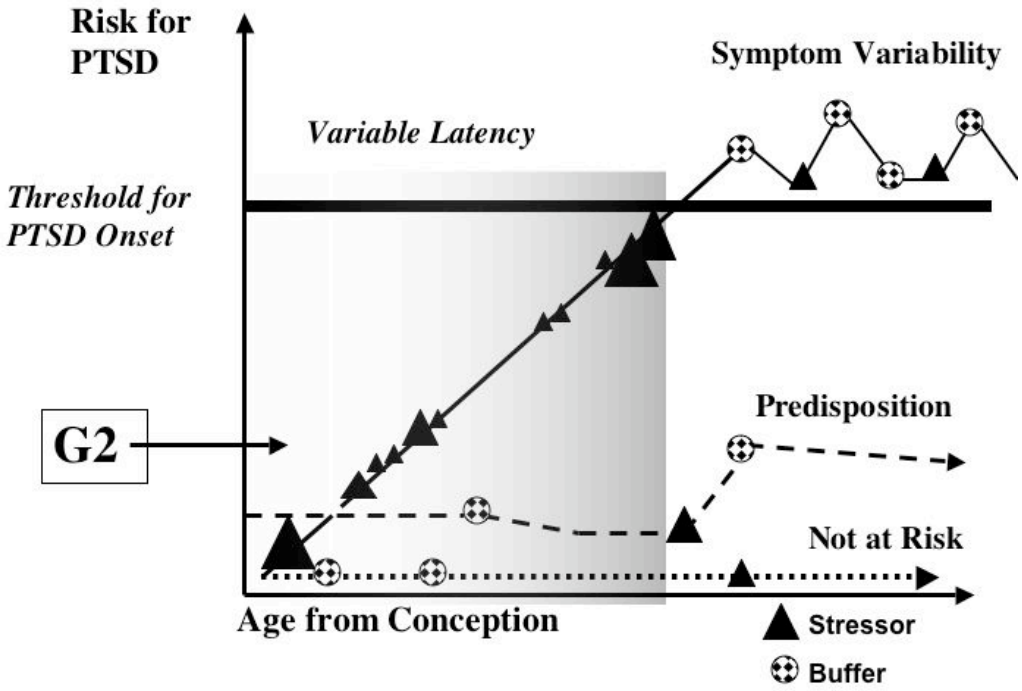

Figure 6. Patterns in the evolution of PTSD.

Events leading to PTSD include initial exposure to perceived life threatening events, including experiences involving primary caregivers (G2 – generation 2), such as the loss of a parent, parental divorce, and parental behaviors such as neglect, abuse, etc., followed by exposure to sufficient frequency and severity of stressors. Symptom exacerbations are influenced by idiosyncratic stressors.

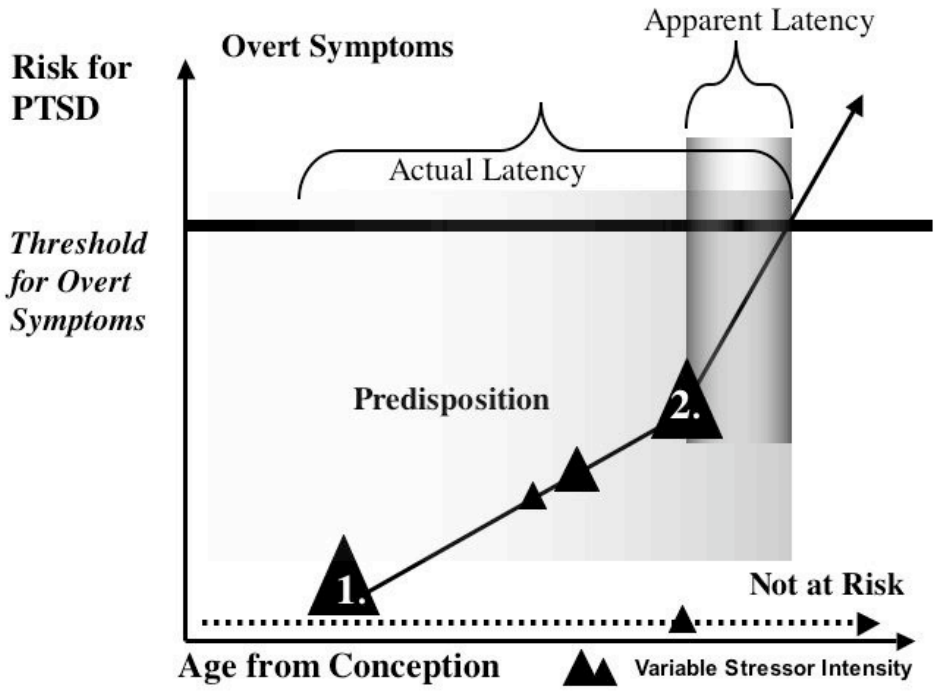

Figure 7. Initiating and perpetuating events in PTSD.

Severity and frequency of exposure to initial stressors (1) influences risk for development of clinically overt symptoms of PTSD and also affects the duration of the latency period. PTSD may occur following a seemingly mild precipitating event (2) although predisposition may have been initiated by exposure to earlier events (1).

Traumatic Stress and Risk for Disease

Symptoms and diseases proposed to be initiated or precipitated by traumatic stress include 1) autoimmune illnesses such as type 1 diabetes, multiple sclerosis, systemic lupus and rheumatoid arthritis, 2) syndromes such as chronic fatigue, fibromyalgia, and multiple chemical sensitivities, and 3) acute or chronic symptoms ranging from chronic pain, interstitial cystitis, irritable bowel syndrome, migraines, and dysautonomia, to sleep disorders such as cataplexy and narcolepsy [32, 33]. Childhood exposure to abuse and household dysfunction (violence against the mother, living with household members who are substance abusers, mentally ill or suicidal, or ever imprisoned) is associated in a graded relationship with increasing risk for ischemic heart disease, cancer, chronic lung diseases, skeletal fractures, liver disease, hepatitis or jaundice and with smoking and other behaviors [53]. Risk for type 1 and type 2 diabetes is also increased, although not in a dose-response relationship

[53]. Exposure to severe, continual family tension, especially marital discord, has also been closely associated with childhood morbidity, including general ill-health, neurological dysfunction, developmental delays and behavioral disturbances [54]. Perceived baseline family stress is predictive of higher social stressors and health-related outcomes, including increased frequency of health-care follow-ups, severity of illness during follow-ups, and frequency of referrals and hospitalizations [55]. Financial stress is also predictive of frequency of referrals and hospitalizations, although perceived family stress is a stronger predictor [55].

Traumatic Stress during Experience-Dependent Maturation

Bonding

The bond between caregiver and child is one of the most important factors affecting attunement and plays a vital and frequently underestimated role in determining the quality of learned self-regulation in the infant. Because of their effects on psychobiological regulation, bonding disruptions increase risk for altered states of regulation in the offspring, and consequently influence risk for disease [2, 26] (for reviews, see Klaus and Kennell [27, 56]).

Mothers are physiologically sensitized to the behavioral cues of their infants in the early perinatal period [27] and a baby's activity triggers parental attachment behaviors [57]. The first hour after birth appears to be a particularly sensitive period for bonding in humans, and babies enter a state of alertness and exploratory behavior during this period that does not occur again to the same extent for several weeks [27].

The nature of the parent-infant bond is influenced by many factors, including a) the mother and infant's experience of pregnancy, as well as whether or not it was planned, b) whether the pregnancy occurs in the context of a supportive relationship, which can buffer the mother's responses to stress, c) the mother's response to awareness of her fetus as a separate individual, which occurs when she begins to feel his or her movements, d) levels of stress during pregnancy, e) the experience of labor and delivery, and f) whether mother and baby are separated at birth, and for how long [27].

A mother's prior life experiences, including the quality of bonding and attachment to her own parents during childhood [27, 58, 59] affect her mothering experience. Personal experiences and life events, including a history of trauma or violence or parental separation during childhood, also affect the potential quality of the parent-child bond.

Breastfeeding

Babies whose mothers received no pain medication during labor and delivery and who are dried and placed on the mother's abdomen after delivery follow a 5-part sequence of recovery during the hour after birth. After resting and occasionally looking at their mothers during the first 20 minutes, the newborn begins to drool and crawl up the mother's abdomen, eventually attaching to her nipple [29, 56]. Onset of breastfeeding, as well as the quality of nutrient sucking by the neonate is facilitated by olfactory cues in rat pups [60] and humans [56] and breastfeeding has multiple effects on developing organ systems.

Breastfeeding provides a genetically programmed means for optimizing proximity and positioning that facilitates attachment interactions [27], reduces maternal perceptions of and

reactivity to stress [61], and facilitates psychological and physical health in the mother including reductions in gastrointestinal and respiratory symptoms in the postpartum period [62, 63]. Even gastric distension associated with feeding, for example, affects regulation in the newborn, and has been found to be an independent factor influencing neonatal regulation of heart rate in rat pups [26].

Breastfeeding is associated with early maternal-infant contact [27, 64, 65], maternal-infant bonding [27], as well as greater involvement of the father [65, 66]. The experience of a difficult labor as well as early maternal-infant separation decreases rates of breastfeeding [27], and consequently affects timing of introduction of cow's milk. Infant feeding patterns can represent disruptions in maternal-infant bonding [67] and appear capable of affecting infant regulation through multiple routes. Breastfeeding represents a unique form of direct (breast milk) and indirect (proximity) maternal psychobiological regulation and differences in exposure to and duration of breastfeeding may, at least in part, reflect differences in levels of maternal-infant bonding [67].

Prenatal Events

Prenatal Stress

Prenatal stress has a significant impact on the offspring of animals and humans (for reviews, see Verny [68], Nathanielsz [31], Huizink, [69], and Wadhwa [70]). Animal studies assessing the impact of prenatal stress show lower birth size (weight, length, and other measurements), decreased hippocampal size, changes in the HPA axis and cortisol levels, and reduced numbers of glucocorticoid receptors. Prenatal stress also decreases synaptic density and learning ability in the offspring; alters concentrations of neurotransmitters such as dopamine and serotonin; results in faster, larger, and more prolonged responses to stressors, including novelty; affects motor and mental development; increases submissive behavior in social contexts; and differentially affects females, in that female rats demonstrate increased sensitivity to an altered HPA axis as well as differences in maternal behavior. These changes in maternal behavior can have effects over multiple generations [30].

Studies in rhesus monkeys have found that prenatal stress reduces the amount of healthy flora in the neonatal gut, which is further differentiated according to the timing of prenatal exposure (early or late in pregnancy) [71]. Exposure to prenatal stress affects the physiology of the gut wall, increases the number of opportunistic pathogens and infections in the first six months of life, renders the neonatal immune system more reactive, and appears to reduce the duration of immune nonresponsiveness in infants [71]. These factors may all influence immune system reactivity to affect risk for disease.

Obstetric Complications

Prenatal stress in humans is associated with increased risk for preterm delivery and other pregnancy complications [72], affects duration of labor, and increases risk for delivery complications [36]. Dysregulation of the HPA axis is reflected in altered maternal cortisol [73] and other physiological parameters during pregnancy and predicts use of anesthesia at birth, which is suggested to be due to physiological decreases in the ability to regulate pain

[74]. Maternal coping styles also moderate the impact of maternal stress on the outcome of preterm contractions [75].

Prenatal stress alters cortisol levels in the baby at birth as well as the baby's ability to cope with later stressful events, such as vaccinations [76]. The effects of prenatal stressors are not limited to the regulation of mental factors but also influence physiological and metabolic regulation [69]. Studies exploring the duration of the impact of prenatal stress have identified differences in mental and/or motor development at 3 and 8 months [77], during the toddler years [78], at 4 [79, 80] and 6 years of age [81], as well as in puberty [79]. The wide spectrum of consequences of prenatal stress suggest that its effects are not related to a single disease [69].Subjective measures of prenatal stress are more strongly related to birth outcomes than objective measures in some studies [70, 82] and one of the problems with studies of prenatal stress has been the lack of evaluation of individual differences in responses to stress [70].

Birth Weight

As mentioned, prenatal stress increases risk for low birth size [31, 69]. Psychosocial stressors in the first trimester appear to have larger impacts on birth weight than later exposures [70], and incremental increases in life event stress in the third trimester, including pregnancy anxiety, correlate with proportionate reductions in birth weight and gestational age, independent of prenatal complications [74].

The long-term impact of low birth weight has been extensively studied in fetal programming theory [31, 83-85], which was pioneered by David Barker, M. D. [86] and is now referred to as the developmental origins of adult disease [87]. This perspective examines the long-term effects of nutritional stress during critical periods of organ development in prenatal life, and evaluates its impact on birth size and proportion. Research in fetal programming has also studied the relationship between birth size and risk for disease (for reviews, see Nathanielsz [31]; Gluckman and Hanson [85]). Long-term effects appear to begin with altered fetal organ structure and function, and reprogramming of the HPA axis, which can be altered for life [31, 37]. Lower size and proportion at birth has been proposed to reflect suboptimal organ development.

Lower birth size associated with risk for disease is often within the normal range of size for gestational age, and is associated with increased risk for rapid catch-up growth during childhood. Low birth weight and rapid growth in early life, in turn, correlate with an increased risk for adult diseases associated with insulin resistance and the metabolic syndrome. The syndrome includes elevations in blood pressure, cholesterol, and glucose; obesity; and is associated with type 2 diabetes, heart disease, and stroke. In twin studies, the twin who develops symptoms of the metabolic syndrome tends to be the one who was lighter at birth [88]. Low birth weight has also been associated with risk for asthma [89-91], autism [92], celiac disease [93], osteoporosis [94] and osteoporosis fractures [95], among other illnesses.

The timing of nutritional deprivation also has an impact on risk for metabolic disease. Undernutrition during the Dutch Hunger Winter in World War II was associated with obesity in adulthood when it occurred in the first trimester, but not when it occurred in the third [31]. Nutritional stress during pregnancy has also been found to affect birth weight over multiple generations.

The experience of malnutrition as a prenatal stressor represents a psychological stressor, as would clearly be the case in studies of starvation, especially when occurring during a war.

The magnitude of psychosocial stress, however, does not have to be large to have significant and long-lasting effects. Studies by Coe and colleagues [71] demonstrate significant neural, immune, behavioral, and social differences in offspring of rhesus monkeys stressed during pregnancy. Prenatal stressors were designed to be small enough to not affect birth weight and included daily relocation of pregnant monkeys to another area. Relocation occurred during 25% of the pregnancy, lasted for 10 minutes, and was associated with random exposure to three bursts of a horn lasting one second each. Changes in the offspring included reduced sizes in brain structures such as the hippocampus, decreased generation of new neurons in these areas, as well as altered immune function. Many of the changes persisted for the duration of the study, which lasted until puberty.

The Perinatal Period

Birth

The baby appears to trigger labor through activation of its HPA axis, and the effects of prenatal stress on fetal HPA activity and regulation may play an important role in risk for preterm labor [96]. Pearce [97] suggests that the birth process itself is associated with states of high arousal in the baby and that contact with the parent, including the type of sensorimotor cues experienced immediately after birth, are the stimuli that down-regulate the baby's nervous system. This perspective resembles concepts in traumatic stress, in which mobilization in the context of reduced threat is the key to maximizing health after life-threatening situations [38]. Birth is clearly a stressful, and in some cases, life-threatening event, and the enormous changes that occur in organ system functioning during this transition out of the womb likely represent an important critical period for many maturing organ systems, including the respiratory, cardiovascular, digestive, immune, and nervous systems.

Infants are exposed to widely divergent experiences of labor and every labor is different. Variability can be quite significant regarding duration and pacing of labor, type of presentation (vertex, breech, etc), number or type of procedures such as intrauterine monitoring with scalp electrodes, the use of medications for speeding up or slowing down labor or for pain management, and method of delivery, which can involve surgical procedures such as cesarean sections, as well as manual extractions using forceps, vacuum, and other methods. The need for resuscitation or intervention may be related to such factors as maternal medications during labor [98] as well as maternal experiences of stress and support during pregnancy and labor, among other factors [27]. Immediately after birth, routine hospital delivery practices tend to foster parent-infant separation, usually during the first hour postpartum, in order to dry, weigh, measure, prophylacticaly medicate, and dress the infant. All of these events interrupt the onset of early regulation and bonding and may play a critical role in affecting the ability of the infant to self-regulate later in life.

Early Contact

The first days after birth, and the first hour in particular, represent a sensitive period that affects the parent child-bond [27, 57]. Studies of parent-infant contact during the first hours and days postpartum demonstrate the enormous impact of routine early separation between parent and infant associated with hospital practices for managing labor and delivery.

Early Separation

Separation in animals affects autonomic and central nervous system activity and influences regulatory processes to affect the HPA axis. Effects impact heart rate, protein synthesis, enzyme and hormone levels including growth hormones [26], and immune competence [71], among other factors. The extent of dysregulation varies with duration of separation [60].

Rat pups have little physiological response to stressors from days 4 to 14 of life and early separation eliminates this "stress hyporesponsive period" [60] just as prenatal stress appears to alter the early period of immune hyporesponsiveness in monkeys [71]. Early contact differentially influences the development of the HPA axis, among other physiological processes, through multiple regulatory pathways. Early separation predisposes infants to exaggerated, insufficient or otherwise disordered responses to stress later in life, and influences the timing and age at which susceptibility to risk for specific symptoms, such as stress ulcers, occurs [99].Vulnerability to altered patterns of regulation, as well as severity and direction of regulatory patterns influence risk for disease and are dependent on timing of exposure in early life as well as timing of subsequent exposures to other life events [25, 60].

Parent-infant separation also results in withdrawal of psychobiological regulation and can alter the course of development to influence physiologic and behavioral responses of the infant that last into adulthood [25]. Events that directly increase the risk of separation at birth, particularly during the sensitive period, increase the risk for bonding disruptions as do experiences that render the mother or baby less emotionally or physically available to one another. Events affecting risk for bonding disruptions in the mother include maternal illness, pregnancy complications, birth complications including cesarean sections, experiences of pain, exposure to anesthesia, and the use of other medications [27, 100]. Disruptive events affecting the baby's capacity to bond include fetal distress, neonatal illness, effects of anesthesia and other medications, and separation (such as occurs with need for special care in an incubator or intensive care nursery), as well as with pain associated with treatment or illness, among other factors[27, 100].

Buffers

Supportive experiences and relationships decrease the impact of stress and appear to play an important protective role in modulating maternal prenatal stress. Rat studies evaluating potential reduction in the effects of separation stress find that distress is reduced in a dose-dependent relationship according to the number of familiar sensorimotor and other cues present [26]. Social support during pregnancy reduces the impact of stress on HPA dysregulation [74] and the finding that prenatal stress does not inevitably result in obstetrical complications or low birth weight suggests that, as described earlier, prenatal stress can have subtle, subclinical, as well as delayed effects. Stress is also only one of multiple factors that influence risk.

The experience of prenatal social support (for a review see Feldman [101]), especially by mothers who have partners, is associated with increased birth weight irrespective of gestational age or obstetrical risk factors. Birth weight increases with married status and with the presence of multiple supports. Social support has also been associated with fewer pregnancy, labor, and delivery complications, shorter labors, increased gestational age, and higher APGAR scores. The love and attention mothers can give their infants is in direct

proportion to the emotional and physical support they themselves enjoyed during pregnancy, labor, delivery, and the postpartum period [56].

Obstetrical Complications

Although prenatal stress increases risk for obstetrical complications, these events are stressful in and of themselves. Maternal events such as preeclampsia, maternal-fetal blood group incompatability, threatened abortion, and preterm delivery, among others, represent potentially serious or life-threatening events for both mother and baby. Complicated or assisted deliveries may occur because of fetal or maternal distress or illness, and may also be experienced as highly stressful or life threatening. From our understanding of the potential impact of traumatic stress during experience-dependent maturation, illness during pregnancy as well as complications during labor and delivery may represent particularly important exposures that affect risk for disease. Whether obstetrical complications initiate disease or represent secondary events that facilitate an existing disease process, or both, remains unclear. Maternal illness, however, may reflect dysregulation in the mother as well as prior traumatization, and the severity and timing of illness during the perinatal period is likely to be an important factor influencing organ system development and future patterns of regulation in the baby.

Delivery by Cesarean Section

Babies born by cesarean generally experience longer periods of separation from their mothers, especially on the first day after birth, in contrast with babies born vaginally (see meta-analysis in DiMatteo [102]). Cesarean births negatively affect attachment and bonding [27], and mothers who are delivered by cesarean tend to have less positive feelings towards their babies on their initial evaluation of their newborns. Some continue to feel less positivity at 6 weeks [102]. Mothers who deliver by cesarean are also less likely to ever breastfeed, and show less caretaking, stimulation, and play with their children, especially if the cesarean was unplanned [102].

Babies experiencing normal spontaneous vaginal deliveries show better interactive behavior and cuddle significantly more at the initial evaluation 1 to 2 days postpartum than babies delivered by cesarean. At 1 month, vaginally delivered babies are more active, smile more often, cry less, and are better able to quiet themselves, which are all considered signs of better mother-infant synchrony [103]. Following vaginal delivery, mothers also demonstrate greater affectionate behavior initially and at one month follow-up, and are more involved in caretaking activities [104].

Cesarean sections have been associated with psychological trauma (for reviews see Ryding [105] and Fenwick [106]) comparable to the experience of a sudden accident. Emergency cesareans [107], as well as unplanned non-emergency cesareans, are also associated with an increase in maternal depression [105, 108]. Of note, women undergoing elective cesareans have often experienced a previous traumatic delivery by emergency cesarean, and 30% suffer from posttraumatic intrusive stress reactions one to two months after a cesarean section [105]. Elective cesareans are associated with increased risk for respiratory distress in the newborn when performed prior to onset of labor and under 39 weeks gestation [109]. Respiratory distress in the infant results in longer periods of maternal-infant separation, exposure of the baby to painful procedures for treatment and evaluation, and increased risk for continued respiratory symptoms after discharge [109].

Rates of cesarean sections have increased dramatically in the United States (and elsewhere in the world) since the 1960s, when they constituted 4.5% of all births [102]. In 1990, the cesarean rate was 22.7% for all births in the United States [110] and up to 85% of all cesareans were elective [102]. Cesareans represent the most common major surgery in the United States [102] and rates reached 29.1% in 2004 [111], which is the highest level ever reported for women at low risk (singleton, full-term, vertex presentation with no risk factors or complications during labor and/or delivery). Rates are even greater for women who are not at low risk (47.1%), and the rate of repeat cesareans for lower risk women reached 88.7% in 2003 (see Figure 8). Cesareans are performed more frequently for women with diabetes, genital herpes, hypertension, eclampsia, incompetent cervix, and uterine bleeding, suggesting compounding risk with increasing medical as well as labor and/or delivery complications [112].

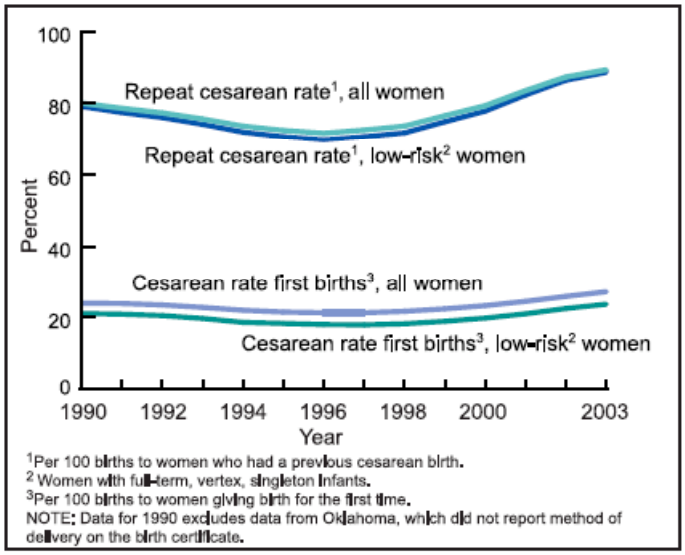

Figure 8. Rates of Cesarean Sections.

> "Cesarean rates for first births and repeat cesarean rates, for all women and low-risk women: United States, 1990–2003." p. 1. Reprinted public document by Menacker, F. (2005). Trends in cesarean rates for first births and repeat cesarean rates for low-risk women: United States, 1990-2003. *National Vital Statistics Reports*. Hyattsville, MD: National Center for Health Statistics.

The increasing rates of cesarean sections are likely to affect risk for long-term psychobiological regulation and may initiate or accelerate states of altered regulation to affect risk for many different kinds of disease. The same may be true regarding other forms of instrumental deliveries, such as those employing vacuum extraction or forceps.

Contact During the Sensitive Period

Bonding Disruptions

Elements in the evaluation of the quality of the maternal-infant bond include a mother's first reaction on seeing her baby after birth (for reviews, see Klaus and Kennell [27] and Madrid [100]).

Table 1 Quick Reference Maternal-Infant Bonding Survey

Physical Separation
Mother was separated from child at or after birth
Mother had a very difficult delivery
Child was sick at birth
Child was twin or triplet
Child was removed to an ICN* or incubator
Mother was anesthetized at birth
Mother was very sick after birth
Mother was separated from child in first month
Child was adopted
Other separation occurred
Emotional Separation
Mother had emotional problems during pregnancy
Mother had emotional problems after birth
Mother had a death in family within 2 years of birth
Mother and father separated before / soon after birth
Mother was addicted to drugs or alcohol at birth
Mother moved before / soon after birth
Severe financial problems
Unwanted pregnancy
Mother miscarried within 2 years of child's birth
New romance in mother's life

Quick Reference Maternal Infant Bonding Survey for identifying events, both physical and emotional, which typically interfere with bonding. Madrid AH, Ames R, Horner D, Brown G, Navarrette L. Improving Asthma Symptoms in Children by Repairing the Maternal-Infant Bond. *Journal of Prenatal and Perinatal Psychology and Health* 2004; 18:221-231. Reproduced with permission from the Association for Pre- and Perinatal Psychology and Health.

* ICN: Intensive Care Nursery

After prolonged separation, some mothers report that they momentarily forgot that they had a baby. In addition, mothers of preterm babies often think of their infants as if they belonged to someone else, such as the doctor or head nurse [27]. These findings do not reflect poor mothering but instead demonstrate the enormous impact of early separation in the formation of parent-child bonds, which can affect future parent-child relationships for years, if not for life [27]. Madrid et al. incorporated information from Klaus and Kennell's [27] research in maternal-infant bonding to design a survey instrument for assessing bonding disruptions. See Table 1 for the quick reference version of this survey.

Parental-Infant Interactions

Mothers with skin-to-skin contact in the first hour after birth show more affection, hold their babies more often and with more bodily contact, and hold them more often in a face-to-face position at 36 hours than do control mothers who first held their swaddled babies at 12 hours as part of routine hospital care [113]. Mothers with early contact smile and cuddle their

infants more at 3 months, and their infants smile and laugh more frequently [114] and cry less [115]. At one year, early contact mothers touch, caress, and comfort their infants more [115], hold their infants with closer body contact, with greater frequency, for longer periods [115], and with more positive empathy [116]. At two years, children exposed to early contact demonstrate greater differences in speech [27], and measurable differences in IQ are evident at 5 years when compared with babies who have been separated according to routine hospital practices [27].

Fathers who are present during delivery also bond more with their infants, and tend to hold, vocalize, and touch them even more than mothers do [117]. Paternal caregiving is greatly increased when fathers have the opportunity to establish eye contact for an hour and to undress their infants in their first 3 days of life [118].

Birth Order

First time mothers (primiparas) experiencing 15 to 20 minutes of skin-to-skin contact with their babies immediately after birth are similar to multiparous mothers in the frequency with which they hold their infants at 36 hours. Frequency of holding is greater than in primiparas with routine contact who are given their swaddled infants for the first time approximately 30 minutes postpartum (after weighing, cleaning, and examination) [119]. Maternal-infant behavior is more synchronized in early contact mothers [115] and first-time mothers with extra contact show behavior patterns similar to more-experienced multiparous mothers [115]. These findings suggest that bonding behaviors are affected by early contact as well as birth order and that attachment behaviors may increase with increasing birth order. This knowledge may provide insights into differences in the role of birth order associated with risk for disease.

Breastfeeding

In a 3 year follow-up of groups with varying durations of early skin-to-skin contact after birth, extended contact of 20 minutes or longer was associated with increases in exclusive breastfeeding [64]. In other studies, higher numbers of early contact mothers breastfed until 3 months [113] and these mothers breastfed for longer than mothers with routine hospital care and early separation [27, 65]. Awareness that increased early contact influences the duration as well as exclusivity of breastfeeding is helpful when considering the many contradictory findings of studies exploring risk for disease in association with breastfeeding practices. Studies linking breastfeeding to risk for chronic illness will be discussed in each of the three explorations of disease.

Employment

Maternal employment status, which is often explored as an independent risk factor for various adult diseases, may be modulated by bonding and vice versa. Early contact mothers experience less frequent return to work outside the home than control mothers [115]. Parental employment status in the early postnatal period may reflect disruptions in parent-infant bonding and may also result in decreased psychobiological regulation.

Neonatal Illness

Neonatal illness is an example of a potentially traumatic event in which psychobiological regulation and bonding are disrupted. These factors, as well as pain from interventions and physiological effects of medications are an example in which factors may be additive in their influence on risk for regulatory disturbances and disease. Infants at highest risk of separation and bonding disruptions due to illness or distress are the ones who are in greatest need of psychobiological regulation, yet they are also the ones most likely to be separated for treatment. Mothers separated from their babies in the early postpartum period, such as when their infants are sick, carry their infants at a greater distance and more in their hands than in their arms [57]. Infections in early life may also reflect loss of or insufficient exposure to psychobiological regulation, as well as changes in immune regulation following stressful or traumatic events.

Early Contact as Treatment

Early contact plays a very important role in facilitating short and long-term psychobiological regulation [27, 57, 119] and incorporating early parent-infant contact provides a powerful and inherently available tool for facilitating optimal regulation.Kangaroo Mother Care (KMC) is a treatment approach initiated by Colombian pediatrician Dr. Edgar Rey Sanabria in order to address a lack of incubator availability for treatment of their pediatric population (for a review, see Charpak [120]). KMC has evolved since 1978 and is used with full-term infants the first day after birth, as well as with preterm and low birth weight babies, mother-infant dyads experiencing breastfeeding difficulties, and in other situations. KMC involves skin-to-skin contact where the baby is placed on the mother's chest and covered with a blanket. Mothers are encouraged to begin as soon as possible and to maintain contact for as long as possible (ideally for 24 hours a day). KMC is associated with a number of positive results, including: increased infant temperature and weight gain; decreased morbidity with respect to infections; higher rates of breastfeeding; decreased crying, quicker settling, quieter sleep and more time in a quiet awake state; greater positive feelings in primary caregivers for their babies; greater adaptation of mothers to the mothering role; more rapid maternal psychological healing from the shock associated with premature birth; greater involvement of the father; the capacity of the baby to respond to the mother's cues and to emit his or her own cues; and earlier discharge than infants in a classical neonatal unit. As with babies exposed to greater early contact [27], long-term studies find that babies with early contact using KMC have higher IQs at 1 year.

KMC is also associated with decreased pain behaviors, decreases in cortisol and HPA activity, and smaller increases in heart rate with venipuncture. Heart rate also increases less with breastfeeding [121]. Findings in studies of KMC support the role of psychobiological regulation and represent an important approach for care for all newborns, including premies.

Transgenerational Transmission

Prenatal Stress

The long-term effects of stressful prenatal events may persevere for multiple generations [31], as found in studies of fetal programming [85], and some of the effects are gender specific. Monkeys who are smaller at birth, for example, have smaller daughters. These females have a smaller uterus and exert "maternal constraint" on the fetus, which reduces the size of her offspring. Other studies find that grandchildren of women exposed to prenatal stress, such as undernutrition during the first trimester of their pregnancies, are of smaller birth size and adult stature, even though their mothers were of normal size at birth. Rat pups born to offspring of rats (third generation) exposed to undernutrition during pregnancy have decreased DNA in their brains as well as perturbed vascular function, even when their parents did not experience nutritional stress in their lifetimes [85].

Maternal Behaviors

Studies show that animals tend to raise their young with maternal behaviors similar to the ones they experienced when they were young [30]. Rat pups are more likely to raise their own offspring in the way they were raised, as measured by behaviors such as licking,grooming, and arched back nursing, which increases availability of breast milk [26]. Greater use of these behaviors, independent of amount of maternal time spent with pups, provides more optimal psychobiological regulation and rat pups raised in these ways demonstrate decreased HPA responsiveness to stress as adults [30]. The frequency of exposure to these behaviors during the first week of life is also significantly correlated with behavioral and neuroendocrine responses to stress in adulthood [30]. Cross-fostering studies further demonstrate that variations in maternal care, rather than genetic cell lines, are responsible for these transgenerational effects on offspring patterns of behavior and regulation.

Studies in humans show similar transgenerational effects. The relationship dynamics observed between a child's mother and grandmother, together with the mother's memories of her childhood, predict patterns of mother-infant attachment at 6, 9, and 18 months. The quality of current and early mother-grandmother relationships also predicts attachment styles between mothers and their infants [122]. Maternal bonding styles in which lack of affection and highly controlling behavior occur are associated with similar parental bonding styles in their daughters, and are independent of socioeconomic status, maternal or child temperament, and maternal or child experiences of depression[122].

Maternal Health

The impact of psychobiological regulation is affected by mothers' states of autonomic regulation. Rat pups genetically predisposed to hypertension, for example, have higher blood pressures in adulthood when reared by mothers with high blood pressure than when cross-fostered with dams who have normal blood pressures [123]. A study in humans examining increasing rates of childhood onset diabetes type 2 in Pima Indians finds that risk is most associated with in utero exposure to maternal type 2 diabetes [124].

Maternal Behavior Affects Genes

Early maternal attachment behaviors modify genes in rat pups, and this process of experience-dependent maturation occurs during a limited window in the first week of life [30]. The fact that maternal behavior modifies genes helps explain the long-lasting impact of early experiences and suggests that these influences may facilitate the transmission of adaptive (as well as maladaptive) strategies over multiple generations. The effect of experience-dependent maturation on genetic expression may therefore also contribute to individual variations in regulatory patterns as well as vulnerability to illness. Given what is known about the positive effects of buffers and the degree to which psychobiological regulation affects infant regulation, it is also interesting to consider the possibility that early maternal behaviors could dampen or reverse the impact of stressful or challenging prenatal events in the infant.

Trauma

As with prenatal stress, traumatic stress has effects that cross generational lines [47, 125-127]. Adult offspring of survivors of the Holocaust are more likely to develop PTSD if their parents have had PTSD, even if the offspring experience no identifiable traumatic life events. This suggests that their symptoms may be related to the severity of PTSD in the parent [125]. Offspring of Holocaust survivors are also more likely to develop PTSD and other psychiatric illnesses, and perceive more life events as stressful even though these events are not of any greater severity than events experienced by controls [126]. Offspring of Holocaust survivors are also more likely to describe non-life-threatening events as their most distressing life event and to develop PTSD as a direct result of these experiences [126].

Cortisol levels have been found to decrease in PTSD, and are even lower following acute trauma in individuals with prior traumatization (for a review, see Yehuda et al. [47]). Cortisol levels are also low in adult children of Holocaust survivors, and have recently been found to be decreased in babies of women who developed PTSD following exposure to the terrorist attacks on the World Trade Center [47]. Levels of cortisol in the offspring varied according to timing of exposure (third trimester) as well as severity of maternal PTSD [47]. Cortisol levels in offspring can also decrease following loss of maternal-infant psychobiological regulation through separation, as found in a study of marmoset monkeys [128]. It remains unclear whether cortisol levels in these infants are low as a consequence of prenatal exposure, or whether they reflect changes in postpartum psychobiological regulation due to altered maternal psychophysiological states or reductions in the ability of mothers to bond with their infants, or all of the above.

Another transgenerational pattern associated with traumatic stress is the finding that children can experience traumatic or stressful events at the same age or on the same dates as traumatic events experienced by their parents [33-35, 129]. This has been referred to as the "anniversary syndrome".

Parenting as a Stressor

In a pilot study of women with a history of exposure to interpersonal violence, such as sexual or physical abuse and/or domestic violence, 90% had a history of PTSD (current or past) [127]. Number of lifetime PTSD symptoms correlated with cortisol levels, which were low. Cortisol levels in these mothers decreased further with the stress of brief separation from

their children. The degree of change in cortisol levels increased with greater severity of maternal PTSD, suggesting an important and overlooked relationship between prior parental exposure to interpersonal traumatic stress and current responses to common and routine activities associated with parenting [127]. Such reactions to stress suggest that the act of parenting, unrelated to the child's temperament or other qualities, can trigger stress reactions in the parent to affect their capacity for psychobiological regulation.

Summary

Findings in traumatic stress and experience-dependent maturation suggest the existence of similar patterns of environmental contributions to the origins of disease (see Figure 9). These patterns involve 1) initiation during critical periods of organ system development, 2) perpetuation of predisposition according to frequency and intensity of exposure to idiosyncratic stressors and buffers, and 3) precipitation of clinically visible symptomatology over variable latency periods following these stressful events. Variability in symptom expression is associated with idiosyncratic stressors, which are influenced by perception and life histories unique to each individual.

Children are particularly vulnerable to traumatic stress because their immature nervous systems are unable to regulate states of high arousal. Brain plasticity and regulatory patterns of other organ systems develop through exposure to gene-environment interactions in which genetically driven behaviors and critical periods of organ development coincide in order to influence one another and optimize development. Many aspects of development of the nervous system and other organs are dependent on, and consequently shaped, by life experiences. Psychobiological regulation is one of the most important features of early parent-child relationships, in which the parents' mature nervous systems help to regulate the infant's immature organ systems.

Psychobiological regulation requires parental proximity and emotional availability, especially in early life, and is fostered by bonding. These early attachment behaviors also influence genetic expression in offspring (at least in animals). Experiences of attachment and traumatic stress, as well as their effects on emotional, psychological, and physiological patterns of regulation in the offspring later influence the second generation and may be perpetuated across future generations. Parental styles of attachment also tend to be transmitted from one generation to the next.

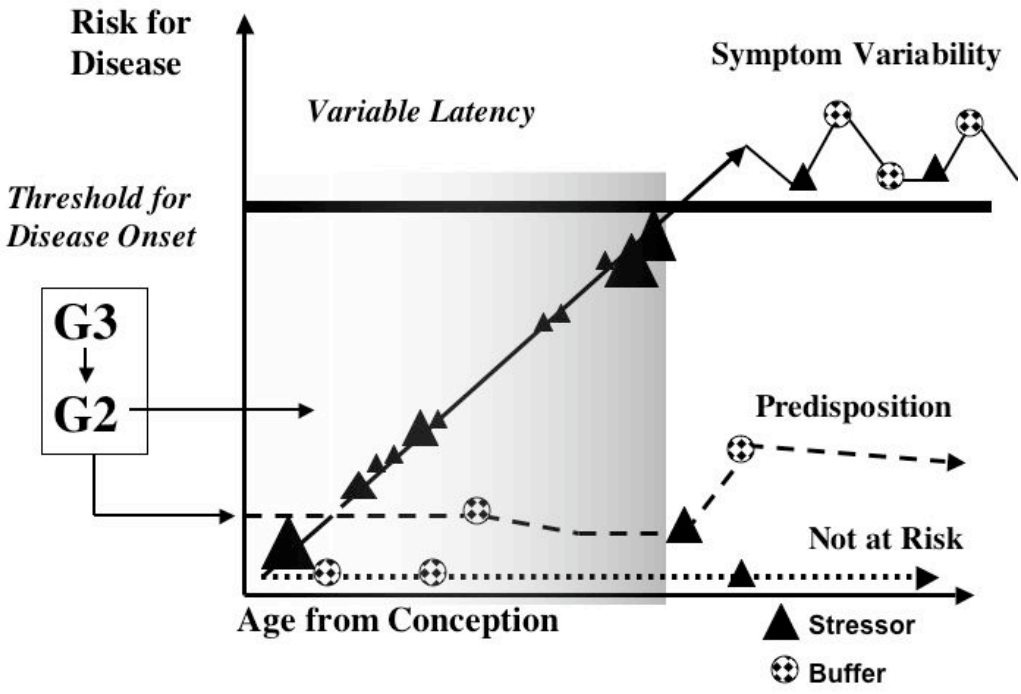

Figure 9. Patterns in origins of disease.

Environmental contributions to the origins of disease appear to follow common patterns involving 1) predisposition to altered states of regulation following exposure to environmental events during critical periods of development in early life, 2) perpetuation of risk following exposure to stressful events or failure to progress if stressor intensity is insufficient and presence of buffers is strong, 3) precipitation of clinically overt symptoms after sufficient exposures to stress, and 4) variations in symptom expression with exposure to idiosyncratic stressors and buffers. Risk is passed on to offspring through transgenerational transmission, such as from grandparents (G3 – generation 3) to parents (G2 – generation 2) to children, which can occur when psychobiological regulation is altered due to disruptions in bonding, lack of proximity, or parental states of altered regulation.

Finally, differences in parental states of psychophysiologic regulation probably impact the younger generation prenatally as well as postnatally and may protect children or predispose them to risk for disease and altered patterns of regulation.

II. A Look at Three Diseases

This section applies data gained from experience-dependent maturation and traumatic stress as a means of exploring, and perhaps understanding, environmental contributions to the

origins of disease. Data from a variety of studies in the epidemiology, physiology, and clinical expression of type 1 diabetes, asthma, and inflammatory bowel disease are examined.

The exploration of environmental contributions to risk for these diseases is presented according to timing of exposures during critical period programming and experience-dependent maturation in early life. Events associated with risk and possible initiation of risk are presented in a time line progressing from prenatal and perinatal events, including mode of delivery, to findings relating risk with birth weight, and early postpartum experiences such as breastfeeding and the need for intensive care. This is followed by a presentation of findings from studies linking stress and traumatic stress to risk and symptom variability, which may be associated with perpetuation of risk or precipitation of disease onset. Variability in age of onset is also discussed where information is available, such as in type 1 diabetes.

Type 1 Diabetes

Environmental factors are believed to account for more than 50% of risk for type 1 diabetes (T1D) [130, 131]. T1D demonstrates tremendous variability in populations of similar genetic and cultural backgrounds, can occur in clusters and epidemics, and varies tremendously by geographic location [132]. Incidence rates vary by a factor of 350 worldwide, with differences in Europe alone varying by a factor of 50 between Macedonia, which has the lowest incidence, and Finland [133], which has the highest incidence rates in Europe and in the world [132]. Incidence of T1D has been increasing since World War II [134, 135], and in some areas this increase appears to be due to a shift to a younger age of onset [136]. An understanding of the relationship between these numerous and seemingly unrelated environmental factors has been difficult to elucidate. Theories presented in section I appear to provide a synthesizing perspective for explaining the complex relationship between risk factors for this disease [137, 138]. Of the group at high genetic risk, 90% of people who are newly diagnosed have no close relatives with T1D, and only 10% [133] will ever develop the disease [139].

T1D appears to have been studied in the most depth regarding the role of initiating and precipitating environmental events in early life. Factors making this a particularly appropriate disease for the evaluation of environmental factors are numerous, and include the fact that T1D 1) is one of the most common diseases in childhood, 2) has a well-identified period of onset in early childhood and adolescence with diagnosis occurring prior to age 21 in 75% of cases [140], 3) is associated with identifiable genetic markers in most individuals, and 4) has clearly identifiable diagnostic signs and symptoms. T1D is also commonly associated with autoantibodies, which are predictive of risk and often detectable for years prior to diagnosis. All of these factors facilitate the use of population-based studies and prospective research designs beginning early in life.

Epidemiology and Patterns of Evolution

T1D has been hypothesized to require three elements in order for clinically evident disease to arise. These elements include genetic susceptibility with initiation by exposure to an exogenous trigger during a critical time in life followed by high subsequent exposure to an antigen that drives beta cell destruction (see Figure 10) [133]. Without all of these

components, it is predicted that T1D will not occur. This hypothesis would help to account for the minority of individuals at genetic risk who never develop the disease [133].

Stressful events have been proposed to be important environmental factors that accelerate the loss of beta cell function through multiple events or "hits" [141] and to eventually precipitate or unmask the disease [134, 142-144]. T1D develops following a prodrome of variable duration, during which diabetes-related autoantibodies develop and beta cell destruction occurs.

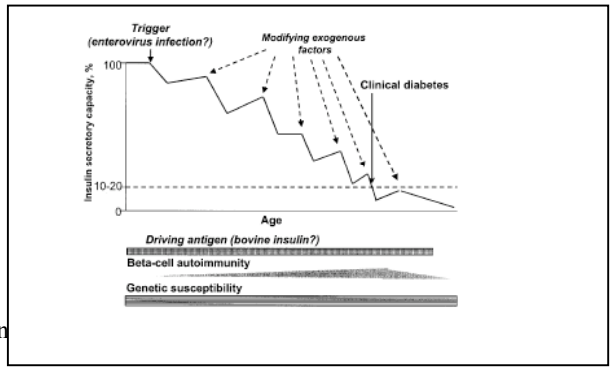

Figure 10. Progression

"According to this model, the disease process is triggered by an exogenous factor, driven by another environmental determinant, and modified by a series of environmental factors in individuals with increased genetic disease susceptibility." p. S127 in Knip M, Veijola R, Virtanen SM, Hyoty H, Vaarala O, Akerblom HK. Environmental triggers and determinants of type 1 diabetes. Copyright © 2005 American Diabetes Association. From Diabetes, Vol. 54, 2005; S125-S136 Reprinted with permission from The American Diabetes Association.

Patterns of Autoimmunity

Risk for T1D is associated with the presence of autoantibodies to islet cells (ICA), insulin (IAA), and glutamate acid decarboxylase (GAD or GAA) [140] even though none of these antibodies are specific for beta cells [143, 145]. The presence of one antibody is common in the general population [133], and only a small number of individuals with autoantibodies progress to type 1 diabetes [146, 147]. In fact, these antibodies remit in up to 78% of individuals, perhaps due to decreased exposure to the triggering factor [144].

Antibody levels fluctuate [144] and exhibit transiency [148, 149], and risk for T1D rises with increasing level [150], persistence [148], sequential progression [151], and presence of multiple antibodies [147, 152]. The incidence of autoantibodies appears to decrease with age [144] and conversion to autoantibody positivity is rare over the age of 10 [140, 141, 144]. Diabetic twins tend to have higher levels of antibodies than their nondiabetic co-twins, which cannot be accounted for by genetic factors alone [150]. Furthermore, when one twin develops diabetes, the co-twin usually follows within 5 years, after which risk decreases [150].

Perinatal Risk Factors

Important environmental risk factors for type 1 diabetes appear to originate during a limited period of exposure [153, 154] in early life [131-133, 143, 155-158] and are proposed to be factors to which only children are exposed [154]. Environmental factors are believed to affect risk during prenatal life [131, 134-136, 153, 154, 156, 159-162], and this hypothesis appears to be supported by the recent finding that diabetes-related antibodies have been identified at birth in infants of nondiabetic mothers [163].

Prenatal Risk Factors

Prenatal risk factors associated with increased risk for T1D include maternal infection [134, 160, 164], placenta previa [165] and nonspecific pregnancy complications [166]. Prenatal procedures such as amniocentesis have also been associated with risk although the reasons for the procedure, such as concern for the baby or older maternal age, were not described [162]. The process of amniocentesis can be a stressful experience for both mother and infant [68].

Common factors linking perinatal factors associated with risk for T1D appear to be that they are stressful [167] and increase risk for maternal-infant bonding disruptions through exposure to events such as medical illness, pain, stress, and/or early separation. Some early risk factors, such as preeclampsia and blood group incompatability, also involve states of altered maternal physiological regulation.

Preeclampsia

Preeclampsia is associated with increased risk for T1D in most [157, 162, 167, 168], although not all [158] studies. Any exposure to preeclampsia has been found to reduce the age of onset to under 15 years of age [167], and exposure in the first or second trimester increases risk for T1D [162].

Preeclampsia represents a state of increased maternal sympathetic activity [169-173] and can be life-threatening to both mother and fetus. As presented earlier, exposure to maternal states of altered regulation during critical periods can predispose the growing child to disease [2]. Preeclampsia has been associated with increased blood pressure in 12-year-old children and the impact of preeclampsia on children who were small for gestational age is even larger, with associated changes in cortisol levels [174].

Maternal-Child Blood Group Incompatibility

Maternal-child blood group incompatibility has been associated with T1D in the Swedish Childhood Diabetes Study [157, 167], and increased severity requiring phototherapy, which is a procedure that separates mother and infant for the treatment of infant jaundice, is associated with greater risk for onset before 5 years of age. Blood group incompatability was not associated with risk for T1D in one study [175] or for antibody development in another [176].

Labor and Delivery Complications

Increased risk for T1D has also been associated with labor complications [162] and oxytocin [165], which is a medication generally used to facilitate uterine contractions to initiate or facilitate labor. Assisted delivery involving forceps, vacuum, and breech extractions has been associated with increased risk for the development of autoantibodies and

T1D [176]. Cesarean deliveries, which are associated with risk in many [158, 162, 167] but not all [157, 165, 176-178] studies, have been found to increase risk for onset prior to 15 years of age [167]. Risk also varies by the type of cesarean, and higher risk has been associated with elective cesareans in one study [158] and with emergency sections with near statistical significance in another [162].

Size and Gestational Age at Birth

Size and gestational age at birth show conflicting results. An increased risk for T1D has been associated with smaller birth weight [157], as well as **s**hort [167] and prolonged gestation [166]. In another study, poor intrauterine growth and small size for gestational age decreased risk. Risk increased with large size for gestational age and with increasing birth weight in mothers who do not have type 2 diabetes, as well as with excess growth postpartum [179, 180]. High birth weight has been found to be associated with risk only in children who develop the disease before 10 years of age in one study [180] and risk for T1D within a limited window may explain why most studies find no association with birth weight [158, 161, 178, 181] or gestational age [158, 161, 162, 178, 179, 182]. Given that T1D is higher when a parent has type 2 diabetes and that birth weights are higher in babies born to mothers who have diabetes during pregnancy [183], it is also interesting to speculate that increasing risk with higher birth weights could reflect exposure to subclinical states of maternal physiological dysregulation.

Rapid growth in infancy is associated with increased risk for T1D, and may at least in part precipitate onset due to an increased demand on insulin production [184]. As we have seen, timing of prenatal stress can increase risk for smaller birth size and shorter gestational length and can also affect the baby's HPA axis. Since the baby appears to play an important role in initiating labor [96], contradictory findings regarding risk with gestational age may reflect variability in prenatal patterns of fetal regulation. Cascading effects may be further compounded by growth-related demands on insulin to facilitate progression to diabetes.

Neonatal Events

Increased risk for T1D is associated with neonatal events such as the need for postpartum intensive care [166], as well as infection and respiratory difficulties associated with fetal distress, such as birth asphyxia [162] and respiratory disease [157, 167]. Low APGARS (< 6 at 5 minutes) were not associated with risk in the one study known to have assessed impact [167].

Postpartum Events

Jaundice

Jaundice is associated with increased risk for T1D regardless of association with maternal blood group incompatability [185], and greater severity requiring phototherapy further augments risk [167]. In an exploratory study in mice predisposed to risk for T1D-related disease, maternal-infant separation, rather than the treatment of phototherapy per se, was the factor identified with risk for diabetes [167]. These findings suggest a role for bonding disruptions, traumatic stress, and loss of psychobiological regulation in risk for T1D.

Breastfeeding

Exclusive breastfeeding, even when only measured at postpartum hospital discharge [162], has been associated with a decreased risk for T1D, and duration of exclusive breastfeeding for more than 4 months is associated with decreased risk of autoantibody positivity in genetically at-risk individuals [186]. Earlier onset of weaning [175], as well as lack [161, 187-189] and shorter duration [175, 182, 189, 190] of breastfeeding are also more likely in individuals with T1D than in controls. Shorter duration of breastfeeding is also associated with increased risk of autoantibody development [186], perhaps due to the early introduction of cow's milk and other foods, although this is not the finding in every at-risk study population [191, 192]. Interestingly, a few studies have found that longer duration of breastfeeding is associated with trends [192, 193] as well as statistically significant increases [194] in T1D. The study authors [194] suggest that the small number of study participants may account for this finding as may the fact that risk of ever breastfeeding was not evaluated.

Formula feeding with soy products has been associated with higher risk of T1D as well as the development of thyroid antibodies [195], which are common in T1D [139]. The early introduction of supplementary milk [166] such as cow's milk formula before 3 [175, 184, 196] and 4 [186] months of age is also associated with increased risk for seroconversion to antibody positivity [186, 196] as well as T1D [175, 184], although use of cow's milk is not associated with risk in all studies [193, 197].

Incidence of T1D has been found to fluctuate with variations in breastfeeding patterns in Scandinavian populations of similar genetic makeup [188] and breastfeeding is proposed to be protective [188, 189], whether by enhancing the infant's immune response [189], reducing the number [188] or severity of early infections [198], or by delaying the early introduction of other foods [189]. Because breastfeeding facilitates slower growth, it has also been proposed to reduce risk because higher weight gain early in life is associated with increased risk for T1D [184]. Another possible role of early feeding practices is the finding that bottle feeding and nonexclusive breastfeeding are associated with greater infant sympathetic nervous system reactivity to stress than exclusive breastfeeding [62], suggesting that breastfeeding may be protective or delay onset, whereas bottle feeding may increase or perhaps even contribute to initiating risk.

Latency and Age of Onset

It has been proposed that variation in age of onset reflects differences in timing, sequence, and levels of exposure [199] in early life, and that these factors influence rates of disease progression [141, 144]. Diabetes-related autoantibodies develop over a period of months to years [151] and there is evidence for a long preclinical period. The variable duration of a preclinical phase in T1D has been documented through decreases in insulin levels and the presence of autoantibodies, which have been identified as long as 7 [200], 11, [141] and 13 [150] years prior to the onset of diabetes. Furthermore, the presence of antibodies has been found as early as three months of age in children who develop T1D by age five [146]. Accordingly, T1D probably does not occur solely as a consequence of exposure to environmental events in the period immediately preceding onset.It is hypothesized that patterns of antibody fluctuations [144] and transiency [148, 149] reflect exposures to environmental triggers and that decreasing age of onset in Sweden relates to factors such as increased exposure to stressful life events [136].

Stress

It has long been suggested that stress is an important risk factor for T1D [143, 156, 201-204] and its role has been affirmed in the past decade [135]. Stressful events have been proposed to influence risk over the life span, beginning in utero [161, 167].

Stressful events occurring early in life have been proposed to initiate the disease process [167] whereas stressful events such as cold climates, life event stress, infections, and high growth rates [156] occurring later in life have been hypothesized to accelerate beta cell loss to eventually precipitate the disease, perhaps through a process of increasing insulin requirements [142, 156]. It has been suggested that progression from autoantibody positivity to T1D depends on sufficient exposure to environmental pathogens or "multiple hits" [141, 205], which is similar to concepts of cascading of effects during experience-dependent maturation and to self-perpetuating patterns that foster kindling following traumatic stress.

When assessing history of exposure to life events in individuals recently diagnosed with T1D, negative events occurring in the first two years of life carried a near twofold increase in risk for T1D [206]. Stressful events in the first year of life have also been found to increase risk for diabetes-related autoantibody positivity in a general population studied prospectively from birth [207], and risk was associated with a higher degree of family chaos with no difference found in access to the potential buffers of social support [206].

Stress in the days, weeks, and years preceding diagnosis occurs in 75% of individuals developing T1D compared with 30% of individuals in control groups [208]. Risk is associated with a higher number as well as greater severity of stressful life events in the three years before diagnosis [209], and stressful events affect risk for T1D whether they are real or perceived [161, 210]. In children, greater number of events in the year before diagnosis has been associated with increased risk in 5- to 9-year-olds [161, 210] and 10- to 14-year-olds [161], and life event stress in the year before diagnosis has been found to be the only factor affecting age of onset in children [190]. Severity of stress is associated with increasing risk in a dose-related response [161, 166, 211], and is particularly evident with exposure to high stressors in the context of low buffers [211]. Increases in dose-related risk have also been related to onset in the 10- to 14-year-old age group [161].

Stress, Symptoms, and Complications

Although glycemic responses to stress in individuals with T1D are contradictory [212-214], they have been found to reflect differences between individual responses to stress rather than a lack of impact of stress on the disease [215, 216]. Glucose responses to stress, which may increase, decrease or remain unchanged following exposure to stress, are idiosyncratic and are based on subjective perceptions [215, 216].

Although good glycemic control is associated with reduction in risk for long-term complications [217], complications can vary despite similar intensity, duration, and cumulative dose of exposure to diabetes-related fluctuations in glucose and cholesterol levels, among other factors [199]. Recent severe stressors are associated with poorer glycemic control and positive life events with fair or improved glycemic control [218]. Stressful life events also affect risk for long-term complications and individuals who commenced anti-

hypertensive therapy during a four-year study had had a greater number of severe life-events and long-term difficulties than controls in the five preceding years.

Traumatic Stress

The onset of diabetes has occurred within days or weeks of intense emotional events [219-221] and traumatic stress was once believed to be an important risk factor for type 1 diabetes [204]. Daniels describes specific examples of onset following traumatic events, such as in a prisoner after his brother was shot in his sleep [222], in a child soon after being rescued from drowning, and not long after another person's steering wheel came apart while in heavy traffic [204]. In his 1948 article, Daniels referred to similar examples scattered in the literature of the previous fifty years [204]. During this period, stressful life events were suggested to "reactivate infantile neuroses and primitive anxiety patterns", which were later "indirectly expressed through altered patterns of autonomic regulation" [202, 221, 223] and dysfunction of the HPA axis [221]. These patterns were thought to represent intelligent, albeit maladaptive, attempts to adapt to a challenging environment [224], expressed solely through the body as a metabolic version of an exaggerated stress response [221].

Transgenerational Transmission

Maternal experiences of violence and divorce occurring since the birth of their 2 1/2 year-old children were associated with a threefold higher rate of diabetes-related autoantibodies in the toddlers [207]. This was found in a general population not at increased genetic risk for T1D. Maternal experiences of other severe life events, including serious diseases, accidents in the family, and loss of relatives, as well as unemployment in either parent, showed a similar, albeit nonsignificant, trend toward increasing risk for antibody positivity.

Exposure to stressful life events, which can affect parental and consequently infant physiology, may affect risk for T1D through transgenerational transmission [207]. In the study mentioned above, a mother's experience of violence was associated with existence of T1D in the maternal or paternal grandparents, even though T1D in the extended family was not itself associated with antibody status in the grandchildren. The authors [207] speculated that the mothers' experiences of psychological stress were transferred to their children through a process of psychobiological regulation, which induced or initiated, rather than precipitated, autoimmune processes associated with T1D.

The finding that maternal exposure to violence is a factor linking grandparents and their diabetic grandchildren raises intriguing questions regarding transgenerational effects of traumatic stress. Individuals exposed to domestic violence or abuse are likely to have been exposed to interpersonal traumatic stress earlier in life, perhaps in their own families [34]. Given that offspring of parents exposed to traumatic stress appear to be more vulnerable to PTSD [47], perhaps grandchildren and later generations are also vulnerable to altered states of regulation or perhaps even more easily predisposed to risk for diseases such as T1D.

From this point of view, traumatic stress may have played a role in the lives of grandparents who had T1D as well as in the lives of their grandchildren. The grandchildren could be affected through direct or indirect exposures to traumatic stressors, including the witnessing of parental violence or by experiencing bonding disruptions associated with the

secondary effects of parental traumatic stress on emotional availability for psychobiological regulation.

Summary

In summary, T1D follows patterns of evolution similar to what has been seen in PTSD (see Figure 11).

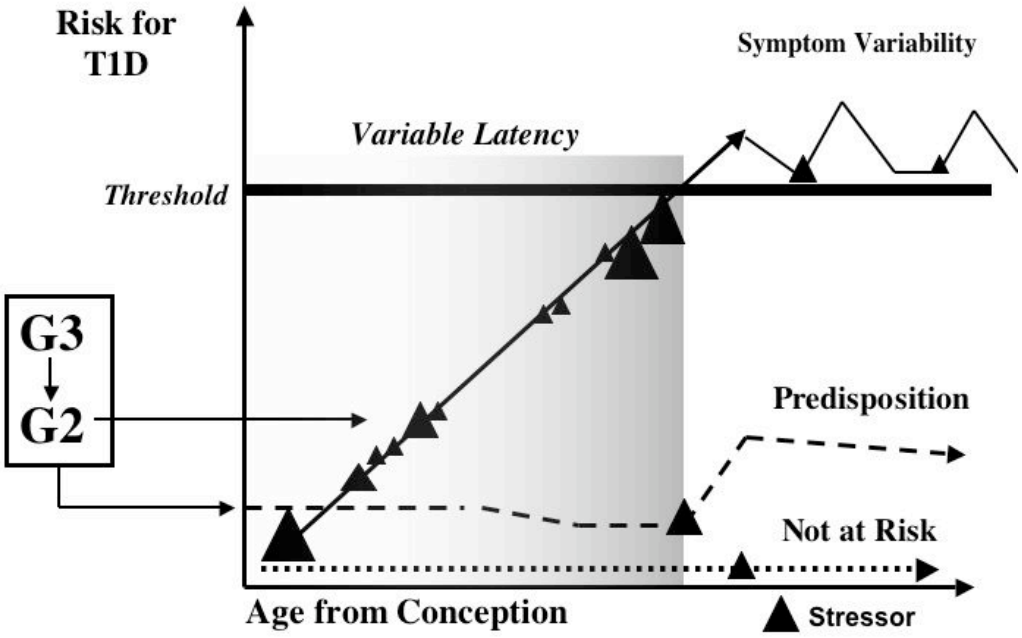

Figure 11. Environmental origins of type 1 diabetes.

Predisposition to risk for T1D is associated with presence of T1D in first degree relatives such as parents (G2 – generation 2). Risk increases following stressful events in early life as demonstrated by the presence of antibodies, and clinical symptoms are precipitated following stressful events in the period preceding onset. Antibodies resolve spontaneously in many individuals who then appear to no longer be at risk. The latency period is variable and age of onset in children appears to be reduced by exposure to stressful events. Patterns of symptom exacerbations as well as some complications are influenced by idiosyncratic stressors.

Risk factors in early life appear to initiate or predispose an individual to risk and may occur during critical periods of development relevant to risk for T1D. A common link between these events is that they are stressful. Predisposition can often be identified through the presence of autoantibodies, which fluctuate and can progress or spontaneously resolve. T1D is unmasked or precipitated following a variable latency period, the duration of which is influenced by exposure to stressors prior to onset. Symptom variability is influenced by idiosyncratic stressors, and risk for some complications is also influenced by stress.

Asthma

Asthma is a disease that can begin at any time in life, although approximately 50% of cases develop in childhood [143]. The biggest stimulant of asthma symptoms is allergy (atopy), and a positive family history also influences risk. A large percent of individuals have no family members with the disease, however, and many individuals have normal responses to allergy testing [143]. Environmental factors clearly play a role in affecting risk for asthma, and because of its predominance in childhood, it is hypothesized that risk is affected by events in early life [91, 225-227].

Three primary characteristics comprise asthma: bronchial hyperirritability, airway obstruction that is at least partially reversible, and airway inflammation [143]. Of the three, bronchial hyperirritability fits a pattern consistent with our understanding of long-term reactivity to context-related cues following traumatic stress. This is demonstrated by the finding in asthma that bronchi are highly reactive to many kinds of stimuli, respond rapidly and in a dose-related manner to these stimuli, and return only gradually to pre-exposure levels, which can take weeks [143]. Airway hyperresponsiveness is also an indicator of severity of asthma, and is associated with greater impairment of lung function, risk for persistent asthma lasting into adulthood, and risk of relapse after remission [228]. In contrast, although intensity of the inflammatory response affects bronchial reactivity, inflammation bears no relationship to disease severity or *level* of airway reactivity, and similar populations of inflammatory cells are found in people without symptoms, suggesting that they are nonspecific markers of atopy [143]. Markers of inflammation could, on the other hand, reflect predisposition to risk.

Experience-Dependent Maturation

Critical Periods

Lung development occurs over a lengthy period lasting from very early in pregnancy to adolescence [21]. The bronchial tree begins to form in the first weeks of prenatal life, and bronchi gradually develop radially into smaller and smaller bronchioles [12]. The newborn respiratory system is far from mature at birth, and postpartum lung growth consists of increasing numbers of developing respiratory bronchioles and alveoli [12]. As previously mentioned, nervous system regulation of respiration, including the HPA axis [229], as well as immune system patterns of regulation [71] are also immature at birth.

Large changes in lung function occur at birth as the neonate transitions from the irregular, episodic breathing movements of prenatal life, to the regular, rhythmic, and functional respiration patterns of postnatal life [229]. Alterations occurring at birth involve shifts from maternally-regulated oxygen delivery and a fluid environment, to a centrally-regulated respiratory drive, which affects breathing in response to differing concentrations of oxygen and carbon dioxide. This transition is supported by structural shifts in cardiac and pulmonary blood flow as well as psychobiological regulation [25, 229, 230]

Maternal-Infant Separation

Early maternal-infant separation in rats affects multiple aspects of respiratory function, including tidal volume and breathing frequency [229, 230]. Early separation has been proposed to affect risk for respiratory disorders such as asthma [231] and sudden infant death syndrome (SIDS), as well as sleep disorders [229, 230] and chronic obstructive lung disease [232], among others.

Perinatal Complications

Asthma is increased with maternal mental and physical health complications during pregnancy [225, 233], labor and delivery, and neonatal illness or health problems in the first week of life [225]. Risk is also increased with preterm delivery [89, 225, 234-238], threat of early labor [225, 233], and malposition or malpresentation of the baby [225], perhaps because irregular fetal position is associated with an increased risk for assisted delivery or represents an existing problem in the prenate. All of these risk factors are associated with risk for greater asthma severity in adulthood [225], perhaps because of fetal programming changes occurring during critical periods [225, 233]. Hyperemesis in pregnancy [233] and antenatal hemorrhage [239] are also risk factors for asthma.

Asthma risk increases with APGARS less than 9 and 10 at 1 and 5 minutes in one study [91], and less than 7 at 5 minutes in another [89]. Respiratory effort and evidence of good oxygenation and circulation are important parts of the APGAR score, which reflects levels of fetal wellbeing at birth. The use of supplemental oxygen or the need for positive pressure ventilation at birth, which mechanically assists respiration in fetal distress, are also associated with increased risk for asthma [89].

Assisted Delivery

Risk for asthma is increased with assisted deliveries such as vacuum extraction, forceps, breech extraction [91], and cesarean section [91, 233, 240, 241]. In a population based study of 8000 cohorts born in Finland in 1966, cesareans were associated with a 40% increase in risk for onset of asthma by age seven [91, 241] as well as doctor-diagnosed persistence or recurrence of asthma at 31 years of age [240]. These relationships suggest an association between cesarean delivery and asthma severity [240].

In a Norwegian study, asthma progressively increased over time. From 1967-75 the incidence per 1000 individuals was 1.5; between 1976-1984 the rate was 3.31, increasing to 6.9 from 1985-1993 [233]. The strongest association between asthma and pregnancy complications (such as cesareans) was found in the youngest cohort, suggesting greater importance of pregnancy-related complications with earlier age of onset. The increasing incidence of asthma was proposed to be influenced by exposure to risk factors that were

changing over the study period [233]. Xu et al. [240] have suggested that increasing incidence of asthma coincides with rates of cesarean deliveries, which increased from 5% in 1966 to 25% in 1997 in neighbouring Finland and which have changed by similar amounts in other countries, such as the United States [110].

Cesareans have been proposed to affect risk for asthma because of functional and structural changes that occur in the lungs at birth [236]. Cesareans are also known for their association with increased respiratory problems in the newborn [236, 242]. These respiratory problems may be due to differences in physical mechanisms associated with mode of delivery, such as the fact that fluids are gradually squeezed out of the baby's lungs during the process of vaginal delivery, which does not occur with abdominal deliveries [236]. It has also been proposed that cesarean delivery affects risk for asthma by altering intestinal microflora, thereby influencing immune system development (for a review see Bager [236]).

Birth Weight

Risk for asthma is higher with low birth weight [89, 91, 226, 238, 243, 244] and increases with decreasing birth weight [90]. Low birth weight has been associated with reduced lung function in adults, but not with wheeze [245]. In addition, low birth weight appears to have a larger effect on risk for asthma onset prior to 5 years of age [226].

Bonding Disruptions

A series of serendipitous events led one researcher to explore the role of bonding disruptions in risk for asthma [100, 231, 246]. When hypnotherapy was unsuccessful in reducing symptoms of severe asthma in an 8-year-old girl who was on multiple medications, including multiple annual steroid bursts, and who had frequent emergency room visits, her mother asked to continue counseling for herself [100]. After admitting she felt shame because she did not feel love for her daughter, the mother described a series of difficult events during pregnancy and birth. Brief hypnosis helped the mother process her residual feelings about the pregnancy and birth and to imagine a corrective birth experience. Three months later, the mother reported that her daughter's severe asthma had resolved the day of the reparative session, when she also stopped needing medications as well as emergency room visits. The mother also said that she now felt love for her daughter [100].

Following this event, Madrid [231] began exploring the association between asthma and disruptions in maternal-infant bonding, finding that bonding failures were three times more frequent in asthma than in controls [247]. Bonding disruptions that were found to be predictive of asthma included a) prenatal factors such as emotional problems during pregnancy, b) early separation at birth, such as delay in holding the baby, and c) stressful life events in the first year of life, including maternal emotional problems, and death in the family. A survey was developed, which draws from existing research [27] to assess risk for bonding disruptions (see Table 1) [231].

Madrid and colleagues then conducted two studies evaluating the efficacy of hypnosis as a means of address bonding disruptions as a potential new treatment for asthma. In the first study, asthma resolved completely or nearly completely in five of six asthmatic children aged 6 months to 12 years [231]. The two infants achieved complete remission. All mothers were treated, along with brief hypnotherapy with the four older children, and improvement was found on each of 18 variables studied. As with the initial case, asthma resolution either occurred on the day that the mother's emotional issues were addressed, or did not occur at all.

Case studies identify factors contributing to bonding disruptions in Madrid et al.'s research. Risk factors included preeclampsia, preterm labor followed by newborn intensive care with delayed discharge occurring after the mother went home, abandonment by the father during pregnancy, separation from the father after birth of the child, relationship and financial stressors, difficult labor, teen pregnancy, consideration of abortion early in one woman's pregnancy, and lack of emotional support. Two mothers who had stressful pregnancies bonded with their babies at birth only to experience bonding disruptions when relationships with their partners became distressing. Although a few children experienced brief recurrences of their symptoms, these events appeared to be related to emotional or physical separation, such as when the 8-year-old with severe asthma visited her father (who was separated from her mother) [100]. Symptoms resolved with reunions or with an additional treatment session.

In a second study [248], 12 of 15 children aged 1-14 years improved with treatment of the mother alone. Ten of these children had complete remissions, and eight of them stopped needing medications. As with the first study, asthma resolution occurred on the same day as maternal recovery. The five children who did not experience complete remission were the older children aged 9 years or older, and the authors hypothesized that older children may have experienced additional stressors in their lifetimes to perhaps render treatment of bonding disruptions at birth insufficient as a form of treatment. Citing Klinnert [249], Madrid et al. speculate that the influence of bonding disruptions on asthma may relate to factors involving stress or quality of maternal caregiving during development of the HPA axis or immune system [231]. Events associated with non-bonding in this second study included recent miscarriages, marital problems, cesarean deliveries, illness in the mother or child, physical separation at birth, homelessness, and emotional problems. In both studies, experiences of maternal emotional distress far outweighed instances of physical separation [231, 248].

In these studies, hypnotherapy appeared to help the mothers resolve their anger, grief, despair, and other emotions regarding events surrounding their nonbonding experiences in childbirth. One possible mechanism for this effect is that hypnotherapy fosters states of altered consciousness [250], which can provide different routes for accessing and altering the intensity of traumatic procedural (unconscious) memories and their context-related cues [33]. Given the improvement in most of the children, treatment may have resolved maternal emotional states associated with disruptions in maternal regulation that originally prevented bonding, and/or allowed the innate maternal-infant drive for bonding to occur, which improved and increased psychobiological regulation for the child while simultaneously removing the sources threat. Reasons for decreased responses in the older children could include a) lack of efficacy in addressing all nonbonding related events, b) lack of success in addressing the impact of other stimuli that had become additional perpetuating factors for altered regulation, such as exposure to additional stressful or traumatic events, c) childhood experiences of traumatic stress outside of the bonding relationship (painful procedures, accidents, etc), d) initiation of symptoms during a critical period other than birth, or e) decreasing dependence on maternal psychobiological regulation with age.

Breastfeeding

Decreased risk for asthma has been associated with having ever been breastfed [227, 244], as well as with longer duration of exclusive (> 4 months) [251, 252] or any breastfeeding (> 6 months) [243]. Longer duration of breastfeeding conveys increasing protection in a dose-response relationship [237, 238] and delays the age of onset of asthma

[237] as well as early but not late onset transient wheezing [243]. Longer duration of exclusive breastfeeding [253] and ever breastfeeding appear to be protective for asthma in the first 2 years of life, and breastfeeding may buffer risk to delay onset [238] or reduce severity in individuals with existing predisposition to risk. Duration of breastfeeding for more than 6 months has also been found to reduce the probability of developing asthma in individuals who are at low risk due to a lack of family history [254]. In addition, any breastfeeding also reduces the risk for development of asthma in children exposed to tobacco smoke [244]. Increased risk for asthma is also associated with shorter duration (< 4 months) of breastfeeding [251].

Contradictory findings have also been identified, however, in which longer durations of breastfeeding have been associated with increased risk for late-onset wheezing [243], and asthma [228, 255]. Longer duration of exclusive breastfeeding has also been associated with greater risk of wheezing and asthma in the small percentage of older children (6 to 13 years old) with allergic asthma whose mothers also had asthma [253]. In one of these studies [228], however, the authors explain that although they referred to their findings as "exclusive breastfeeding", most babies were probably given formula prior to discharge from the maternity hospital as part of a routine practice in the nursery. This may be the case in other studies as well.Although control subjects appeared to be protected from risk through shorter exposures to breastfeeding in the above study, it is not known which subjects nor how many were actually exposed to supplemental feedings. Increased risk for asthma is associated with bottle feeding [226], the introduction of nonhuman milk before 4 months of age even with continued breastfeeding [237], and absence of exclusive breastfeeding [252]. It would be interesting to explore whether there were differences in exposure to formula feeding in the nursery between groups in this study [228]. Time spent in the nursery would be more likely to occur with pregnancy, labor, and delivery complications, poor initial health of the baby (requiring nursery care), and other potentially stressful perinatal events.

Differences in study outcomes regarding the effects of breastfeeding on risk for asthma appear to reflect complex interactions between multiple environmental events, which may include maternal physiological states and psychobiological regulation. Possible contributions to risk for asthma with increases in breastfeeding include the finding that infants who are bottle-fed have higher autonomic lability, as demonstrated by greater sympathetic reactivity during stress and higher vagal tone after stress. Exclusive breastfeeding, on the other hand, buffers the sympathetic response to stress [62]. Breastfeeding is also associated with increases in maternal baseline levels of parasympathetic activity, as documented by measures of vagal tone on heart rate, and these effects are dose-related [62]. Sympathetic tone mediates bronchodilation whereas vagal tone facilitates bronchoconstriction [256], suggesting the possibility that breastfeeding may in some cases accentuate pre-existing states of predisposition to high vagal or low sympathetic tone in individuals at risk for asthma. Psychophysiologist Stephen Porges proposes that up-regulation of parasympathetically mediated immobility responses facilitates bronchoconstriction as a means of maximizing energy conservation in the face of extreme threat [257-259].

Other means by which breastfeeding may influence risk include the possibility that breast milk and breastfeeding represent context-related cues, which may soothe or trigger infant responses to stress according to the nature of the experience that occurred when breastfeeding was initiated. Elements in breast milk may also influence risk for asthma, either as context-related cues or due to direct physiological effects. Breastfeeding in the first days postpartum

provides antibodies and other factors affecting the immune system (in colostrum), and breast milk differs according to mode of delivery, parity, time of day, meal times, maternal smoking [242], as well as with maternal disease such as asthma [253]. Maternal illness and use of medications may also influence infant physiology and immune function [253].

Latency and Age of Onset

Individuals who eventually develop asthma demonstrate preclinical symptoms of airway inflammation and remodeling in infancy [260]. This is especially evident in individuals who have persistent and relapsing asthma, suggesting that outcomes are determined early in life [228]. Age of onset of asthma is variable, and subclinical alterations in physiology appear to be unmasked following exposure to stressful events, such as parental separation [231]. Onset prior to age 4 has been associated with increased severity of asthma [252], and risk for relapse after "outgrowing" asthma is higher with earlier age of onset [228], suggesting that exposure during early critical periods may be important in determining risk as well as severity [228]. Evidence also exists for ongoing physiological dysregulation between asthma flares [261].

The Role of Stress

Responses to stress in asthma are paradoxical, and different individuals respond to similar study stressors with increases, decreases, or lack of change in bronchial reactivity (for a summary see Ritz [262]). Emotionally stressful stimuli are associated with changes on functional magnetic resonance imaging (MRI) in individuals with asthma, demonstrating involvement of the nervous system in stress-related airway reactivity [263]. Changes on MRIs in response to stress have been noted in the insula and anterior cingulate, which are areas that influence perception. In addition to bronchoconstriction, emotional stressors also affect non respiratory physiology and accounted for over 40% of immune responses identified on blood testing in this study (eosinophils in sputum, glucocorticoid responses, peripheral blood lymphocytes, etc.) [263].

A wide variety of stressors can stimulate bronchoconstriction in asthma, including emotional stressors associated with positive as well as negative valence [262]. Responses to study stressors persist longer following exposure (slower recovery), and asthmatics show greater stress responses to passive coping than do controls [262]. Stress in the caregiver has also been associated with increased risk for asthma [253] as well as changes in the immune system in a population predisposed to atopic asthma [264].

Traumatic Stress

Respiratory regulatory patterns are altered following early exposure to stressful environments in animals. A single exposure to immobilization stress in young rats, for example, affects the plasticity of the respiratory system by altering respiratory responses to carbon dioxide. These changes last into adulthood [229].

Wright [265] describes four case studies of children whose asthma worsened following violent events. One had an exacerbation beginning the night she heard gunshots and learned that a peer had been killed, another worsened after witnessing domestic violence between her parents, and a third, whose symptoms had recently stabilized, worsened following an assault

by an older student on the school bus. After further threats from these students, the boy refused to board the school bus and subsequently developed symptoms severe enough to require emergency treatment. A fourth case describes a 15-year-old with a history of severe asthma since infancy who experienced an exacerbation following an assault by classmates at the end of the school year. The following year, this adolescent experienced asthma exacerbations requiring steroid bursts on Sunday nights, prior to returning to school every week. She pressed charges, and her symptoms worsened after being threatened by her assailants in court. Symptoms, including the need for all medications except albuterol as needed, remitted completely during the 15 months in which the students were incarcerated. She was then hospitalized twice in two months for her asthma after their release [265].

Madrid, whose work suggests that asthma is related to prenatal and perinatal traumatic events resulting in disruptions in maternal-infant bonding, describes the onset of asthma in a one-year-old boy whose first asthma attack occurred the day his mother experienced a physical assault [266]. The son's asthma appeared to be related to a disruption in the maternal-infant bond as a consequence of his mother's experience of extreme stress, which affected her ability to stay emotionally connected to him. The child's asthma, which was still present at 7 years of age, resolved when his mother's PTSD was successfully treated [267].

Transgenerational Events

Multigenerational effects on respiratory function have been found in neonatal rats. These rats develop respiratory instabilities such as apnea following exposure to intermittent hypoxia during sleep and their symptoms last into adulthood. Their offspring demonstrate equally high episodes of apnea during sleep, despite lack of exposure to conditioning events in their own lives [229]. This intergenerational pattern suggests that a mother's respiratory behavior is transmitted to her young [268].

Risk of asthma has been found to be higher in children whose grandmothers smoked when pregnant with their mothers [234], even if the mothers had not smoked during their own pregnancies and did not have asthma. Risk was further increased, however, if mothers also smoked during their pregnancies [234], suggesting independent and additive effects across three generations. It is notable that individuals are two to four times as likely to smoke if they have grown up in an environment in which they were exposed to violence [53].

Summary

The evolution of asthma appears to follow patterns seen in PTSD and T1D (see Figure 12). Predisposition and risk are influenced by maternal behaviors over two generations, as well as by maternal-infant bonding disruptions and maternal stress.

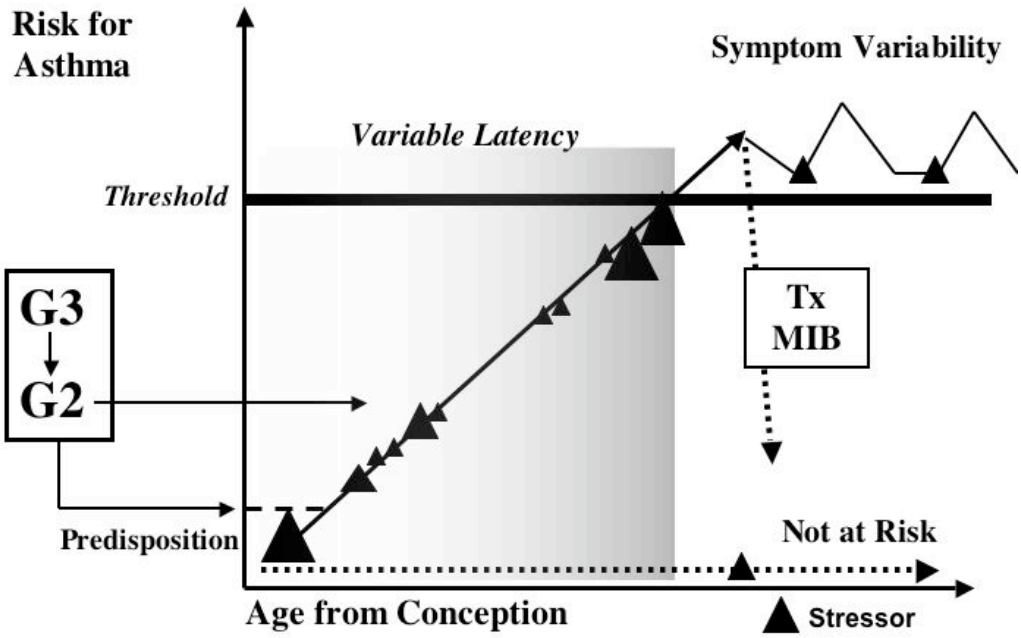

Figure 12. Environmental origins of asthma.

Predisposition for asthma is associated with behaviors in the grandmother (G3 – generation 3) and mother (G2 – generation 2) and risk for asthma increases with a variety of stressors in early life. Age of onset is variable. Symptoms are influenced by idiosyncratic stressors, and resolution of asthma symptoms occur when maternal-infant bonding disruptions are resolved (Tx MIB).

Events in early life are associated with risk and may occur during critical periods of development relevant to asthma. A common factor linking environmental risk factors for asthma may be that they are stressful and asthma is unmasked or precipitated following exposure to stressful events, including bonding disruptions, among other factors. Symptom variability is influenced by idiosyncratic stressors and immediate resolution of asthma has been found to occur following resolution of maternal-infant bonding disruptions.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by chronic over-responsiveness and dysregulation of the intestinal lining [143, 269]. This overreactivity appears to be an inappropriate response to environmental stimuli, such as to normal microbial flora that live in the gut, as well as to other contents within the gut lumen [143, 270]. IBD is characterized by

remissions and exacerbations and is associated with symptoms such as diarrhea, abdominal pain, bloody stool, weight loss, and fever [143]. Ulcerative Colitis (UC) and Crohn's disease (CD) comprise the two forms of IBD. UC involves the mucosal lining of the rectum and can extend to all parts of the colon. CD, on the other hand, may affect any part of the gastrointestinal tract from the mouth to the anus, including the liver and pancreas, and is associated with changes in the deeper layers of the intestinal wall as well as the mucosa. The rectum is often spared in CD [143].

IBD runs in families, and risk of having the disease increases from 10% when one parent has IBD to 36% when both parents have the disease. Although antibodies are detectable in many individuals with IBD, they are not present in everyone and also occur, although to a significantly lesser extent, in the general population [143].

Experience-Dependent Maturation

Critical Periods

About two thirds of the immune system is organized in the intestines [22]. Structural development of the gastrointestinal system begins in the first month of pregnancy [21] and early exposure to microbes in the intrauterine and early postpartum environment appears to play a vital role in the development of long-term immune system responsiveness (for a review, see Herz and Petschow [22]). Biologically active components in breast milk, for example, as well as products from bacterial colonization of the intestine after birth stimulate the mucosal immune system to promote long-term patterns of immune system responsivity and reactivity [22]. In humans, breastfeeding stimulates the release of 19 different gastrointestinal hormones in response to touch on the mother's nipple and on the inside of the infant's mouth [56]. In animals, suckling during the first 24 hours increases the mass of intestinal mucosa by 45% in piglets and by over 80% in puppies. Furthermore, DNA content in the intestinal mucosa increases by 60% in suckled puppies in contrast with a control group fed simulated milk [271]. Protein content, which contains antibodies believed to be important in the development of immune regulatory processes [22], is increased by 90% in these puppies. These differences are said to be due to colostrum intake [271], which is the first fluid expressed with postpartum breastfeeding in days one to three. Because the impact of suckling on intestinal mucosa varies with time and in different animal species, it is believed that influences on intestinal development occur only within a limited window of time [272].

Prenatal stress has been found to predispose to the presence of pathological microflora in the gut in the first weeks of life, and to increase the risk for asymptomatic as well as clinical infections in rhesus monkeys. This appears to represent a shift toward increased immune system reactivity in early life, which contrasts with normal neonatal levels of low immune reactivity [71]. Early maternal-infant separation in animals also affects intestinal mucosal immunity by increasing gut permeability in all regions of the gastrointestinal tract and by predisposing to increased susceptibility to inflammation as well as severity of inflammation and/or hypersensitivity of the colon [273]. These effects last into adulthood.

Perinatal Events and IBD

The occurrence of any health event in the perinatal period is associated with an eightfold increase in risk for CD and a threefold increase in risk for UC, and may also confer risk in

40% of cases of IBD in one Swedish study [274]. Risk was highest with neonatal infections in the first 10 days of life, and was also independently associated with pre and postnatal maternal and neonatal infectious as well as noninfectious events. Risk was associated with any infectious event in the third, but not the first or second, trimester of pregnancy [275]. Events associated with risk included preeclampsia, threatened miscarriage, low placental weight, and jaundice, as well as factors such as difficulties in neonatal temperature regulation, among others [274]. In this study population, one mother developed UC 10 years after the birth of her child, who also developed UC [274]. An international multi-center study found no difference in risk with birth weight, gestational age, or birth in the home or at the hospital [276].

Citing hypotheses for environmental contributions to type 1 diabetes [199], Ekbom et al. [274] propose that perinatal events alter the developing immune system in genetically predisposed individuals, and that the disease is later precipitated by immunologically stressful events such as infections, pregnancy, or emotional trauma.

Breast Feeding

A meta-analysis found that breastfeeding is protective for UC and plays an even greater protective role in CD [277]. Two of the studies cited [278, 279] identify a dose-response relationship showing higher risk with shorter duration of breastfeeding [277]. Since studies were not specific regarding exclusivity of breastfeeding, it was not possible to assess whether increased risk was due to an absence of breastfeeding or the presence of bottle-feeding. Klement et al. [277] further explain that the protective role of breastfeeding may be underestimated because some of the studies evaluated only the presence or absence of breastfeeding prior to hospital discharge.

Changes in Age of Onset and Expression

The peak ages of onset of IBD occur between 15 to 30, and 60 to 80 years of age [143]. The incidence of IBD increased dramatically after World War II [275, 280, 281] and was followed in many, although not all, studies by a plateau [282, 283] or a decrease in incidence [275] (see Figure 13).

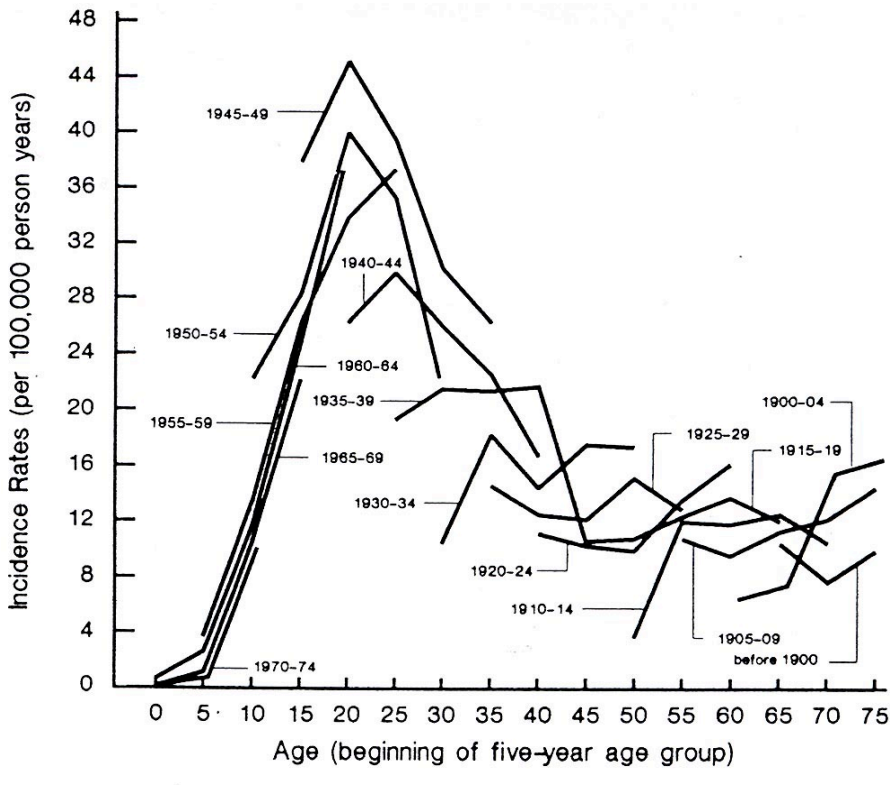

Figure 13. Incidence Rates of IBD.

"Age specific incidence rates for ulcerative colitis and Crohn's disease combined, by 5-year birth cohort, Uppsala, Sweden, 1965-1983" p. 356. Reprinted from Ekbom A, Helmick C, Zack M, Adami HO. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. Gastroenterology. 1991; 100(2):350-8, with permission from American Gastroenterological Association.

A dramatic rise in incidence has been noted in individuals born between 1945 and 1954, with evidence for progressively decreasing age of onset beginning in the decade leading up to World War II [282]. An earlier age of onset has also been found following hospital births in comparison with home births and deliveries in small community centers (onset at 25 vs. 28 years of age) [274]. Prior to 1960, CD only affected parts of the small intestine (the ileum) and severity of the disease increased in the second half of the century when it also began to manifest in the colon for the first time [143].

Stress

Stress appears to contribute to initiation and/or aggravation of IBD-related inflammation [284] (for reviews see Levenstein [285, 286] and Maunder [287]) as well as disease severity [287], and animal studies have found that restraint and noise stress potentiates the effects of subthreshold chemical exposures to foster exacerbations of IBD-like disease [288]. The role of stress is believed to be due to interactions between the nervous, immune, and gastrointestinal systems and the manner in which stress is perceived [284, 289].

Although findings regarding the role of stress in IBD have been contradictory, higher disease activity has been associated with greater perceived stress [290, 291] and increasing number of stressful events [291, 292], including life events such as divorce and the loss of a loved one (see summary in Sewitch [291]). Drossman [293] describes the case of a woman experiencing an exacerbation of CD with symptoms that were new for her in the 15-year course of the disease. These symptoms, which included nausea, vomiting, and epigastric pain, were discovered to have begun eight weeks prior to hospital admission after onset of recurring dreams on the first anniversary of her father's death from alcohol-related cirrhosis. Her father had had symptoms of pain, nausea, and vomiting prior to dying. Her parents had divorced 15 years earlier [293].

Risk for exacerbation has been found to be highest in subjects with greater long-term general stress, and brief increases in stress affect risk for exacerbation of UC 8 to 11 months later only when events have a prolonged influence on perceived stress [290]. Subjects with IBD demonstrate exaggerated vagal responses to passive coping stressors (cold pressor test), as well as a greater degree of intestinal inflammation and oxidative injury than controls [284]. Individuals with IBD are also more overwhelmed by minor stressors [291].

The experience of satisfying support networks buffers the impact of moderate to high perceived stress and has been associated with reductions in psychological stress and IBD activity [291]. In an unexpected finding, one prospective study found that levels of stress decreased with the number of questionnaires filled out over the period of the study [292]. This response could reflect an experience of increased perceived support. Writing and telling others about emotional events have been associated with reductions in experiences of stress and physical symptoms [294].

Traumatic Stress

Geographical Distribution of IBD

The incidence of IBD shows a trend toward a higher incidence in northern European countries (for a review, see Binder [280]) and North America [143], and varies by national rather than natural boundaries [295]. Greece is an exception in that incidence rates are higher there than in other southern European countries and are similar to those of northern Europe [296].

IBD Is More Common in Ashkenazi Jews

Epidemiological studies demonstrate that incidence of IBD is two to four times higher in Jewish populations in Europe, the United States, and South Africa and that prevalence within the Jewish population is twice as high among Ashkenazi Jews [143]. Jews were persecuted in Europe in the late 19th and early 20th century and were exposed to risk of violence and mass

murder through pogroms. 2 million Jews emigrated in this time period, mostly to the United States, Canada, and Western Europe [297, 298]. Most of the 8.8 million Jews living in Europe at the beginning of World War II were Ashkenazi [299], and the estimated 6 million Jews who were systematically murdered during the Holocaust constituted 67% of the European Jewish population [300]. Most Jewish communities with extended histories from Europe are Ashkenazi [299].

The geographical patterns of the persecution of Jews during World War II are similar to the patterns of geographic distribution of IBD. Approximately 90% of Jewish populations were decimated through systematic murder in northern Europe including in Poland (91%), the Baltic States (90%), the Protectorate (England, Scotland, and Ireland: 89%) and Germany/Austria (88%), and there were significant losses in other northern European countries as well [300]. Greece was the only country in which communities of non-Ashkenazi Jews experienced degrees of decimation during World War II similar to Ashkenazi Jews [299]. It has been proposed that environmental factors affecting risk for IBD occur through transient exposure to a common agent, which then triggers the disease process [301]. While this hypothesis has been directed at infection as an etiologic agent, exposure to war also represents a "common event" to which a significant portion of the Jewish population was directly, or indirectly exposed.

Although the literature makes no identifiable reference to a possible connection between the tragedy of the Holocaust and risk for IBD, higher incidence in the Ashkenazi population and large changes in incidence of IBD in the middle of the 20th century suggest that this hypothesis warrants further exploration. IBD may well reflect states of altered regulation associated with global exposure of a specific population to traumatic stress. Jews have been persecuted for centuries, and these actions were high in the decades prior to World War II [297, 298]. The period of exposure to potentially traumatic stressors during World War II covers a well-defined period of events leading up to the War, including the establishment of the first concentration camps in 1933, social isolation of Jewish populations beginning in the early 1940s, the prohibition of many staple food items for years prior to onset of the War, the existence of life-threat and starvation both in and outside of concentration camps, and the fact that camps for displaced persons (such as concentration camp survivors) existed until 1957 [302]. Many of the individuals who did survive experienced the added loss of their immediate and extended families during this War.

When we consider that traumatic stress may have played a role in influencing patterns of incidence and geographical distribution of IBD, the possibility introduces questions regarding how such experiences influenced the health and lives of other groups affected by World War I and II, including soldiers, individuals risking their lives to shelter and evacuate Jews and other refugees at great personal risk, innocent civilians, and relatives or loved ones connected to any of these groups. The second highest prevalence of IBD is seen in non-Jewish Caucasians [143].

Differences in patterns of geographical distribution and incidence (increasing in some areas, plateauing in others) are potentially useful for exploration from a perspective that considers a role for trauma in the initiation and precipitation of IBD. Variability in incidence could, for example, reflect differences in transgenerational transmission in some groups in whom PTSD unmasked a predisposition to the disease in specific geographical areas, such as areas of high activity during World War II. Incidence could similarly decrease or remain low in areas associated with lesser degrees of PTSD, as well as reduced exposure to triggers and

reminders of events associated with the War or lack of exposure to these stressors. Given the long history of persecution, prohibitions, and forced exile in Jewish history, an event such as World War II could have represented a massive re-exposure to a recurring pattern of traumatic stress uniquely experienced by the Jewish population.

Evidence for decreasing age of onset and increasing incidence in the period leading up to World War II could also suggest that World War I, which also targeted the Jewish population in Europe, may have represented an initiating traumatic stressor for many individuals. The short period between the two events may have contributed to increased World War II stress responses.

Transgenerational Transmission

Although research assessing the impact of the Holocaust on survivors and their children has been somewhat contradictory, most studies find mental health disturbances in the offspring [126, 303]. In a review of this literature, Kellerman [303] finds that risk for clinical symptomatology is higher following events such as a) being born soon after parental exposure to trauma, b) being the first or only child, c) having two parents who are survivors, or a parent who is highly disturbed following extraordinary suffering and loss, and d) being conceived as a "replacement" following the loss of a previous child. These characteristics are consistent with the proposal that risk for disease is affected by alterations in psychobiological regulation, early parent-child relationships, and exposure to traumatic stress.

Children of Holocaust survivors also demonstrate increased levels of reactivity to non life-threatening events and have higher lifetime rates of PTSD [126]. Risk for PTSD in these children is increased when the parent has chronic PTSD or intrusive memories of the Holocaust [125], whether or not offspring were exposed to traumatic stress [126].

Approximately half of individuals with CD in one New York City study were of Ashkenazi descent and there was clearer evidence of transgenerational transmission in this population, including younger age of onset in 90% of children and relatives of Ashkenazi Jews with CD [304]. An interesting area to consider in this group when evaluating the role of traumatic stress would be to learn about family histories and the nature of their experiences during World War I and II. It may also be relevant that although patterns of intestinal distribution of IBD are highly variable among individuals, anatomic distribution and clinical type tends to be similar within families [143].This would be another area worthy of study to evaluate whether similarities in disease expression varied according to ethnicity or commonalities in life experiences, including early life events and experiences of World War II.

Summary

In summary, IBD follows patterns of evolution similar to what has been seen in T1D, asthma, and PTSD (see Figure 14). Risk is increased with IBD in other family members and is not limited to first-degree relatives.This familial pattern is higher in Ashkenazi Jews than in other groups with high incidence for IBD. It is hypothesized that risk for IBD was initiated following prolonged persecution and unmasked in World War I and World War II, and this hypothesis is based on: increased incidence in the Jewish population; dramatic changes in incidence, severity, and age of onset in the 20th century; and geographical patterns of distribution of IBD, among other factors.

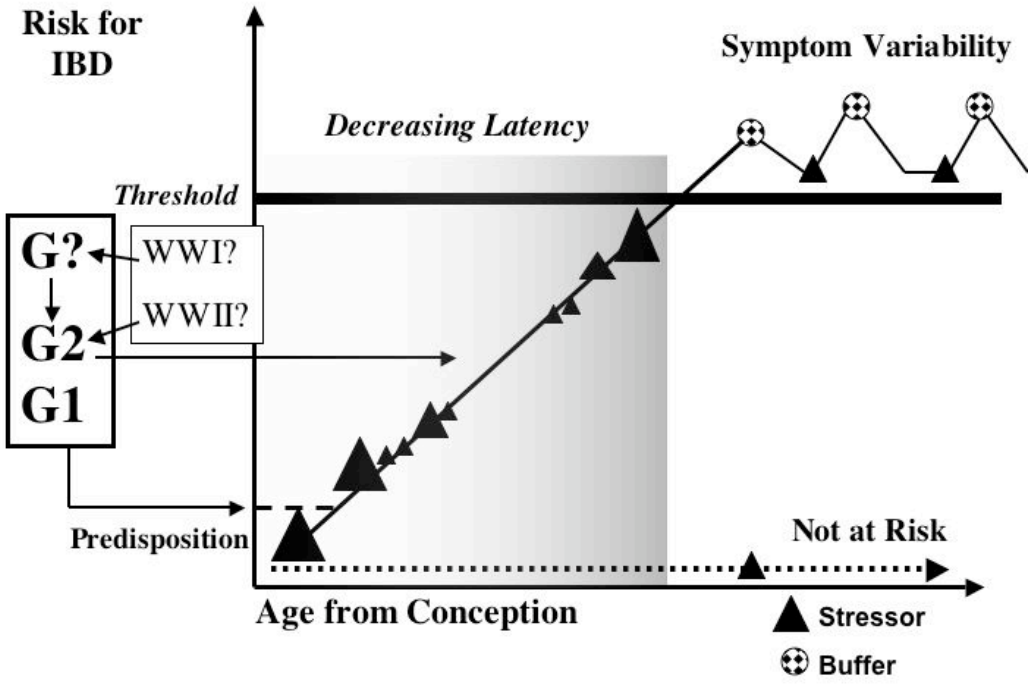

Figure 14. Environmental Origins of IBD.

Incidence of IBD is higher in the Jewish population, particularly in Ashkenazi Jews. Predisposition for IBD is associated with IBD in relatives (first [G1] and second generation [G2], perhaps also in earlier generations [G?]), especially in Ashkenazi Jews, and is hypothesized to have increased following the traumatic stress of World War I and II. Risk for IBD increases with a variety of events in early life, which appear to be stressful. These events may occur during critical periods of development relevant to IBD. Age of onset is variable and has been decreasing, especially in children of Ashkenazi Jews with IBD. IBD has been precipitated by stressful life events in the period immediately preceding onset, and symptoms are influenced by idiosyncratic stressors and buffers.

Risk is increased in association with exposure to events in early life, which appear to initiate or perpetuate risk, and these may occur during critical periods of development relevant to risk for IBD. A common link between these early events is that they are stressful. Age of onset of IBD is variable and has been decreasing, and IBD appears to be precipitated by stressful events, such as parental divorce. Symptom variability is influenced by idiosyncratic stressors and buffers.

CONCLUSION

Early life events appear to initiate or perpetuate risk for a wide variety of diseases and affect susceptibility both for psychopathology [5, 69] and physical disease [2, 26, 32] . Common elements among risk factors for disease include that they may 1) be experienced as stressful or traumatic, 2) increase risk for maternal-child separation, bonding disruptions, and alterations in psychobiological regulation, and 3) influence risk according to timing of exposure during critical periods of organ system development.

Attachment experiences and traumatic stress affect risk for altered regulation in the child and later in the adult, and parental states of regulation shape the second generation's psychological, physiological, and socioemotional development through psychobiological regulation [2, 25]. Heritability of disease, furthermore, is influenced by these parent-child interactions [30] and maternal attachment behaviors in one generation tend to influence genetic expression [30] as well as future attachment behaviors [58] in the second generation. Future generations also appear to be influenced in what appears to be a perpetuation of risk through psychobiological regulation and its effects on behavior and genetic expression.

Research in experience-dependent maturation and traumatic stress, along with findings from case studies of type 1 diabetes, asthma, and inflammatory bowel disease, suggest the existence of identifiable and predictable patterns of environmental events in the evolution of disease. Such patterns, if they truly exist, differ from our current view that specific diseases are each caused by unique and unrelated events. Instead it is proposed that the timing of exposure and the manner in which events are perceived are the more important denominators determining specificity and risk. Information regarding environmental contributions to origins of each disease further informs an iterative process of understanding the role of environmental risk factors for other diseases.

The following paragraphs review some of the complex interactions between early life events and risk for additional diseases not previously discussed, and also summarize the role of stress and traumatic stress in risk for disease. Implications for treatment and prevention, as well as suggestions for future research, are also discussed.

Timing

Relationships between prenatal exposure to teratogens and easily recognizable congenital defects, such as occurred with thalidomide, have demonstrated a connection between exposure to toxins during specific periods of prenatal life and structural deformities in corresponding organ systems. Evaluations of artificial reproduction technologies have also found that the environment of culture media in which embryos are fertilized and grown exerts important effects on embryo quality, blastocyst development, rate of cleavage, and gene regulation, among other factors [305]. These studies demonstrate that abnormalities in the fetus or baby are not limited to genetic or other pre-existing defects in the embryo or fetus, but are also influenced by the quality of the intra- and extra-uterine environment as well as exposure to environmental events. If the timing of early events influences cellular and structural development, it is logical to suspect that timing also influences function, and that

such changes can affect specific organ systems to influence patterns of regulation and risk for disease.

Prenatal Stress

Pre- and perinatal events, as well as experiences in early childhood, probably influence risk for disease through complex interactions. Exposure to prenatal stressors has been associated with obstetrical complications during pregnancy, labor, and delivery [36, 72], low birth weight [31, 69, 70, 74], and risk for bonding disruptions [27, 306] as well as with an astonishing array of functional as well as structural abnormalities [69], some of which have also been found to vary with timing of exposure [69-71, 126, 307]. It is noteworthy that subjective maternal perceptions of prenatal stress are more predictive of outcomes than objective measures [70, 82].

Prenatal Obstetrical Complications

Obstetrical complications are not limited to increased risk for T1D [157, 158, 162, 165, 167, 176], asthma [89, 91, 226, 238, 243, 244] and IBD [274, 282], but are also associated with greater risk for autism [92, 308-310], eating disorders [311], multiple sclerosis [312], and schizophrenia [313, 314], among others. Prenatal obstetrical complications associated with risk for disease include preeclampsia [157, 162, 167, 168, 274, 315], bleeding during pregnancy [239, 274, 308, 315], threat of early labor [225, 233], preterm delivery [89, 225, 234-238, 315], maternal-child blood group incompatability [157, 167, 315] and even nonspecific pregnancy complications [166, 225, 233, 309]. These alterations in maternal regulatory function may interact with prenatal stress to initiate or perpetuate risk for disease. They also represent a cascade of stressful events, and frequently represent life-threatening experiences for both mother and baby.

Prenatal procedures such as amniocentesis are also associated with risk for disease such as T1D [162]. Greater awareness of the potential impact of different aspects of this procedure will help gather more detailed information in the future, such as whether the procedure was performed because of concern for the baby, suggesting the possibility of a pre-existing abnormality, or as a routine evaluation because of older maternal age, or for other reasons. A foundation of knowledge now exists demonstrating the need for caution regarding the application and performance of such procedures, which can be highly stressful for baby and mother [68].

Birth Weight

Low birth weight is associated with risk for a lengthening list of diseases including autism [92], celiac disease [93], altered lung function in adults [232], osteoporosis [94], and osteoporotic fractures [95] as well as increases in risk for high blood pressure, high cholesterol, elevated glucose, obesity, type 2 diabetes, heart disease, and stroke (all components of the metabolic syndrome) [31, 83-85]. Women exposed to the terrorist attacks

on the World Trade Center during pregnancy had smaller babies than nonexposed controls and will be followed as part of a prospective study to evaluate long-term effects of exposure to this traumatic event [126].

Interventions during Labor and Delivery

Complications during labor [162] as well as assisted delivery [91, 176, 312] and delivery by cesarean section [91, 92, 158, 162, 167, 236, 240-242, 308, 315] are not only associated with risk for disease but also for precursors to disease, such as diabetes-related antibodies [176]. This suggests that we may be underestimating contributions of early risk because some at-risk individuals never progress to clinical expression of disease.

Investigators debate whether early events initiate disease or compound pre-existing prenatal factors to influence risk for obstetrical complications and the need for interventions during labor and delivery. Cesarean sections are performed when the mother or baby's life is in danger, such as can occur with preeclampsia or when the baby is experiencing distress [112]. Risk associated with the use of oxytocin in T1D [165], as another example, might result from the effect of induction of labor prior to natural onset of contractions, but could also reflect abnormalities in the progress of labor associated with a pre-existing problem with the uterus, in the baby or mother, in some regulatory process affected by exposure to the medication, or other factors. The use of routine interventions and the active management of labor and delivery, including the dramatic rise in elective cesarean sections in women at low risk [102, 111], however, are indications that these events are risk factors independent of prenatal events. Twin studies further demonstrate the importance of the pre- and perinatal environment in risk for disease in that the twin with the larger number of obstetrical complications [308, 310] is at greater risk for developing a specific disease than is his or her co-twin.

Routine separation at birth is another ongoing practice in many hospital settings that represents a greatly underestimated intervention. Separation is increased with procedures such as cesarean sections, compounding their effects by increasing risk for bonding disruptions and suboptimal exposure to psychobiological regulation. An understanding of the importance of early contact, loss of psychobiological regulation, and traumatic stress are helpful in explaining the impact of early risk factors, and suggest that we need to value the role of other natural events such as spontaneous vaginal delivery. This awareness may be helpful in identifying and exploring the context in which such events occur in order that they may be addressed.

Fetal Distress and Postpartum Events

Fetal distress, as reflected by low APGARs [91, 92, 316] and the need for oxygen or positive pressure ventilation in the baby [89], are also associated with risk for disease, as are postnatal procedures such as phototherapy for neonatal jaundice [157, 167]. Gastric suctioning at birth is related to a threefold increase in functional bowel disease in adults [317, 318] and exposure to painful procedures in the postpartum period influences subsequent

physiologic and behavioral responses to novelty, stress, as well as pain [319], including increased pain responses to immunizations [320].

Implications

Data presented in this chapter strongly indicate that we have been grossly underestimating the degree to which brain plasticity responds to environmental events. We have consequently failed to recognize the potentially enormous impact of early events in the initiation, perpetuation, and precipitation of disease as well as in the possibility for recovery from chronic illness. The implications of research in bonding, critical periods, and traumatic stress are far-reaching and the impact of prenatal stress on even one aspect of psychophysiological regulation, such as cognitive function, has large societal implications [5, 97]. As we have seen, these effects also continue through multiple generations. Cognitive ability and intelligence, as one example, affect the capacity of a population to positively contribute to society through work, creativity, independence, and health, among other factors [5].

Stressor Intensity

Environmental events and life experiences appear to perpetuate risk as well as to precipitate or unmask disease. Increased number and frequency of stressful or negative life events occur in individuals who have developed disease in contrast with controls. The effects of stressful life events are dose related [161, 166, 211, 311, 321] and additive [1, 141, 205, 309], are associated with subjective perceptions of stress [82, 161, 210], and influence rates of progression to affect age of onset of disease [161, 167, 237, 252, 274, 311, 316, 322, 323]. They also appear to influence risk during two periods, with the first exposure period occurring in early childhood and the other in the time frame preceding onset of disease [156, 167, 206-209, 211, 284-287].

If sufficient exposure to stressful events fails to occur early in life, risk for disease in predisposed individuals appears to decrease, further supporting the concept that a threshold in exposure to environmental events is needed for progression from predisposition to clinical expression to occur. This is supported through observation of patterns of antibody positivity in individuals at risk for T1D, in whom conversion to antibody positivity is rare over the age of 10 years [140, 141, 144].

Traumatic stress occurring prior to disease onset has been frequently documented in Parkinson's disease [324], and a particular pattern of disease onset has also been noted to occur in the limb injured during the traumatic event [325, 326] [326]. Stressful events are also more frequent in patients who develop multiple sclerosis, and location of disease-related lesions has also been found to correlate with injury site [327] although this does not appear to be due to direct physical damage [328].

Stressor Idiosyncrasy

The knowledge that stressful experiences are idiosyncratic and relate to context and an individual's unique set of life experiences appears to explain paradoxical reactions to stress in individuals with chronic disease. The importance of differences in perception and life experience provides a broad perspective from which to understand and explain the role of stress, not only in perpetuating and precipitating disease, but also in influencing symptom expression and risk for long-term complications of disease following diagnosis. Among the many factors influencing perception, as well as intensity and frequency of exposure to stressors, are class, ethnicity [329], and ethnic density [330]. Findings described in the case exploration of IBD suggest that war and other globally traumatic events may affect large populations in diverse geographic, ethnic, or cultural groups. Drawing also from studies of Holocaust survivors and their offspring, it appears that these effects can have significant long-term consequences on risk for physical as well as psychological health.

Stress is associated with exacerbations in many diseases, including multiple sclerosis [327, 331] and type 2 diabetes [214], and idiosyncratic stressors are believed to play an important role in syndromes such as multiple chemical sensitivity [332]. Models similar to the one proposed here have also been suggested for origins of psychopathology such as schizophrenia, in which early stressors are followed by latency periods of variable length and the disease is unmasked after stressful life events [313]. Early life events are also proposed to affect risk for the dementias, such as Alzheimer's, according to the developmental origins of adult disease hypothesis [333]. Risk for Alzheimer's disease is affected by transgenerational events and is increased with negative life experiences [333]. In addition, it is also interesting to note that syndromes such as multiple chemical sensitivity [334], fibromyalgia, and chronic fatigue have been proposed to represent models of sensitization similar to PTSD [32].

Societal Trauma

Diseases such as IBD, which are influenced by both genetic and environmental events, may provide important clues toward gaining a better understanding of the role of environmental events in the origins of disease. Arguments supporting the genetic origins of IBD, for example, may in fact reflect environmental contributions or interactions between genes and environment. The hypothesis that IBD risk is influenced by events leading up to and occurring during World War I and II appears to be helpful in explaining some findings, such as increased incidence in multiple family members with wide differences in geographical location as well as large differences in time and age of onset. Also, there is a younger age of onset in the children of parents with IBD, and different incidence rates of IBD within Jewish populations from disperse geographic origins.

Other findings consistent with a history of common exposures to an environmental event such as war come from differences in incidence and risk in genetically-based symptoms and diseases known to be more common in the Jewish population, such as lactase deficiency and Tay Sachs disease. Incidence patterns of lactase deficiency, for example, are remarkably consistent in different geographic areas, whereas incidence patterns of IBD vary tremendously [281]. Siblings of individuals with Tay-Sachs disease, as another example, carry a 25% risk of developing the disease whether or not they are Jewish [335]. This reflects a common pattern of genetic inheritance, and recent increases in exposure to traumatic stress

in the Jewish population appears to an equally elegant and simple means for understanding patterns of expression seen in some populations with IBD.

Transgenerational Effects

Patterns of environmental contributions to disease in individuals also appear to apply to patterns of risk across multiple generations. In the case of IBD, repeated exposure to traumatic experiences such as persecution, threat of mass murder, loss of loved ones, expulsion from home lands, and forced relocation may have predisposed the Jewish population in particular to specific patterns of dysregulation resulting from changes in genetic and/or behavioral expression modified over centuries. Such a predisposition may have been perpetuated across multiple generations, to eventually be precipitated following exposure to contextually relevant and particularly severe traumatic events to which the majority of this population was exposed, such as the Holocaust. That the effects of trauma can be increased over generations is supported by the existence of greater stress reactions in children of Holocaust survivors, who are at greater risk of developing PTSD despite apparent differences in exposure to traumatic events [126], and the finding of younger age of onset of IBD in the second generation of Ashkenazi Jews who have IBD [304]. Jewish children with IBD more frequently have a positive family history for the disease than the non-Jewish population with IBD, and family history is greater in children than in adults with the disease [336]. This supports the proposal that exposure to a recent precipitating event in the population with IBD influences incidence rates and expression of the disease.

Type 1 Diabetes

Hypotheses regarding the role of traumatic stress in the origins of IBD may provide clues in the exploration of contributing environmental events to origins of T1D. T1D is most common in Caucasians, has tremendous geographical variability including greater incidence in Northern countries and highest incidence in Finland and Sardinia [132], can occur in epidemics, has been increasing since World War II [134, 135], and is shifting to a younger age of onset in some countries, such as Sweden [136]. Might exposures to traumatic events such as World War I and II also be influencing patterns of incidence and expression of this disease?

The Metabolic Syndrome

While it is commonly believed that type 2 diabetes and other symptoms of the metabolic syndrome are directly caused by changes in diet and increases in sedentary lifestyles, the astronomically high rates of the metabolic syndrome in Native populations suggest that such factors may be precipitants of disease rather than initiating or causal events. Native populations all over the world have been forced to accommodate to ways of life imposed by others, altering their nomadic and natural lifestyles, evacuating their lands, transferring to government or other types of housing not of their choosing, and submitting to educational

environments prohibiting the use of their languages, cultures and other well-established ways of life. These experiences of imposed change have increased exposure to real and perceived life threat while simultaneously removing these populations from access to buffers of social support such as long-established traditions and sense of community. Type 2 diabetes is also more common in African Americans and Hispanic Americans and occurs at an earlier age than in non-Hispanic whites in all three of these populations [143].

Other Diseases

Systemic lupus erythematosus is more common in African-Americans, Hispanics, Asians, and women than in non-Hispanic whites. Might this disease also represent long-term effects of social and cultural disenfranchisement? Perhaps this is also at least partly the case with diseases that are more common in women, such as autoimmune illness and syndromes such as chronic fatigue, fibromyalgia, and multiple chemical sensitivity. Women are also affected over multiple generations by factors such as prenatal exposure to maternal stress. Findings from IBD suggest that these are valuable hypotheses to explore.

Prevention

As we begin to realize how prenatal and perinatal stressors influence regulation and bonding to affect risk for disease in a dose-related manner, we gain the knowledge necessary to modify our health care practices as well as our social support systems. Such knowledge emphasizes the need to facilitate opportunities for bonding and bonding repairs between parents and their children.

The benefits of touch, proximity, and emotional support are already evident, and can be immediately implemented by informed parents and health care professionals. Kangaroo Care [120] is an important example of an existing intervention that capitalizes on the innate drive for psychobiological regulation and bonding. Even seemingly small interventions can be effective, such as the finding that availability of educational and emotional support by midwives in a high risk inner city population reduced the risk of low birth weight even though these women were exposed to high overall stress [101]. The presence of emotional support during labor, such as with trained personnel known as “doulas”, also provides buffers that significantly reduce the number of obstetrical complications such the use of cesareans (rates reduced by 50%) and forceps (by 40%), as well as duration of labor (by 25%). Doula support was also associated with decreasing needs for pain medication (by 30%) and epidurals (by 60%) [337].

The ability to understand the impact of stressful prenatal and perinatal events also provides markers for the identification of infants at high risk for emotional, psychological, and physiological patterns of dysregulation, including risk for disease. Obstetrical complications, APGAR scores, and bonding assessments, for example, provide immediately available data for identifying infants at greatest need for early interventions, even when these infants appear to be healthy and normal in standard newborn evaluations. Number of obstetrical complications, need for treatment and other events, including subjective perceptions of prenatal maternal stress, may also provide useful information regarding

exposure levels as indicators of "dose". Easily identifiable markers of fetal well-being, such as fetal activity at 36 weeks gestation, can predict fetal responses to labor as well as outcomes in temperament at 2 years of age [338]. All of these examples provide opportunities for the development of risk assessment tools using existing and accessible parameters that also happen to be non-invasive.

Treatment

As demonstrated in asthma [231, 248], interventions that address the impacts of traumatic stress and bonding disruptions offer promising opportunities that should be evaluated further in the prevention and treatment of physical and psychological symptoms as well as disease. Treating parental trauma may be another important means of addressing symptoms in the child, which may be occurring because of parental dysregulation and lack of emotional availability for psychobiological regulation.

Chronic disease, like PTSD, is extremely resistant to resolution once established [34]. Therapeutic approaches addressing interactions between mind, brain, and body, however, appear to be effective in the treatment of PTSD [32, 33, 35, 39, 40, 339, 340] and are among a variety of existing therapeutic modalities that might offer effective new interventions for treatment of chronic disease. The types of interventions mentioned above and used by Madrid and colleagues [231, 248] appear to be successful because they access the body, procedural memory, and other unconscious processes rather than focusing exclusively on cognitive function and factors available only to conscious awareness. Traumatic memories are stored in procedural memory in the hippocampus and other parts of the brain, tending to remain outside of conscious awareness and unavailable to conscious recall or verbalization [32, 33]. This may be a component of the pathophysiological process linking early life events with disease.

Therapeutic approaches for working with trauma that could be evaluated in the prevention and treatment of disease include Somatic Experiencing [35, 38, 39], Sensorimotor Psychotherapy [40, 341], and EMDR (Eye Movement Desensitization and Reprocessing) [339], among other modalities [32, 33, 340, 342]. Integration of data from multidisciplinary fields may help explain and validate the potential for such approaches to provide effective solutions as well as to facilitate their integration into more common usage in the treatment of chronic symptoms and chronic disease.

Future Research

Data from the fields of traumatic stress and experience-dependent maturation provide new insights and questions for research and study designs. Drawing from studies in attachment and experience-dependent maturation lead one group of researchers, for example, to identify transgenerational influences linking maternal experience of violence to diabetes-related antibodies in the child [207]. For others, the realization that perinatal events influenced risk for autism lead them to recognize the need for better documentation of indications for procedures such as cesareans [308]. Asking whether a cesarean was a repeat event, as well as exploring the conditions in which prior cesareans had been performed and

were experienced, helped another group understand links between cesareans and traumatic stress [106].

Qualitative Research

The importance of qualitative data and individual case studies is becoming more evident, as demonstrated in asthma, where it was possible to understand the role of bonding, trauma, and stress in the initiation and resolution of the disease, as well as in relation to exacerbations [231, 248, 265, 343]. The inclusion of qualitative data in descriptions of spontaneous recoveries may also be helpful in providing information relevant for understanding how such events occur. Spontaneous recoveries [344] were initially regarded with great skepticism because we had no paradigm for comprehending resolution of chronic disease, and investigators had to provide detailed objective documentation in order to demonstrate that a disease had truly existed prior to its resolution. New knowledge can now guide the selection and documentation of social, psychological, and other contextual data related to onset and recovery from disease. As we begin to better understand the role of gene-environment interactions in the initiation and perpetuation of disease, we are also in a position to better understand the long disregarded role of behavioral, psychological, and emotional factors relevant for recovery as well as prevention.

Findings from One Disease Informs Others

Although some scientists have applied theories from one disease as a means of helping to explain patterns of initiation and precipitation in another, most of the focus of chronic illness research tends to be limited to a specific disease, such as T1D, asthma, or IBD. Potentially relevant studies that may facilitate the identification of environmental risk factors more readily in one disease may be invaluable sources of data contributing to a better understanding of environmental origins in other diseases. This appears to be the case with diseases associated with childhood onset, where a significant body of literature indicates the influence of prenatal and perinatal risk factors.

The presence of diabetes-related antibodies in T1D provides evidence for the existence of a latency period of variable duration preceding overt clinical expression. Changes in number and levels of antibodies suggest that some individuals seem to be predisposed to risk, and to then experience complete resolution without progressing to overt disease. The early presence of antibodies in toddlers of mothers exposed to violence [207], as well as increases in diabetes-related antibodies in children exposed to obstetrical complications at birth [176] are also suggestive of a role for traumatic stress in the evolution of predisposition for T1D. This appears to be the case in other diseases as well.

Antibodies have been found to precede the onset of systemic lupus erythematosus by up to 7 years, and presence of these antibodies suggests earlier onset, more variable course, and greater severity of the disease [345]. Early changes associated with Parkinson's disease are believed to begin in adolescence or earlier [346], and a latency period has been proposed to exist some 30 years prior to the onset of Alzheimer's disease [347]. The existence of latency periods in multiple diseases lends further support to the hypothesis that the process leading to

disease is neither linear nor fixed. The existence of preclinical windows also provides the opportunity for the identification of risk for particular diseases even if genetic and antibody markers do not exist or are not associated with the disease. Such periods may also be useful for evaluating the role of risk factors and their additive effects, especially with respect to prenatal and perinatal events. These are also valuable periods needed for the evaluation of prevention strategies. Branching from these findings, studies could also explore factors that buffer vulnerability to disease and long-term prospective studies could evaluate threat to offspring of these individuals.

A greater understanding of the role of traumatic stress provides helpful insights for re-examining its role in diseases where it has been eliminated as a potential risk factor. Elimination of traumatic stress as a risk factor in chronic illness resulted from hypotheses that traumatic stress affected risk only through direct and localized biological damage and that its effects could occur only within short periods of time following the traumatic event. These were among the reasons that trauma and stress were eliminated as potential triggers in multiple sclerosis [328]. In Parkinson's disease, the role of traumatic events was discarded because latency periods existing between time of exposure to stressful events and onset of disease were highly variable and could not be explained. These decisions to eliminate traumatic stress occurred despite findings in both MS [327] and Parkinson's [348, 349]that onset of the disease frequently began in the area where trauma had occurred. The impact of traumatic stress was also eliminated from theories of causation in T1D when the hypothesis that incidence would significantly increase in those serving in World War II was not supported [1, 204]. Interestingly, incidence rates of T1D have been increasing in epidemic proportions since World War II [134, 135], and diagnosis appears to be occurring at a younger age in the same time frame [136].

Summary

Increases in incidence of many diseases since World War II has suggested that Westernization (not to mention traumatic stress) plays an important role in the environmental origins of disease. Westernization, however, is not limited to changes in diet and lifestyle, but also includes significant changes in prenatal and perinatal care, and may also involve decreased availability of buffers such as the loss of proximity to our multi-generational communities and decreases in emotional and physical availability to ourselves, our partners, and even moreimportantly to our children. Our increasing use of, and complacency with, technological birthing practices such as the performance of cesarean sections "on demand" is perhaps a particularly concerning example of the possible impacts of our underestimation of brain plasticity. A progressive understanding of the role of factors such as perception, contextual memory formation, and triggers associated with idiosyncratic cues following traumatic stress appears to be useful in clarifying the role of life events in the initiation, perpetuation, and precipitation of disease and in symptom exacerbations. From our understanding of the long-term consequences of traumatic stress, we have a basis from which to *anticipate* health problems. Accordingly, we can implement prevention and early treatment or remediation in individuals and populations who have been specifically exposed to trauma, such as following natural disasters as well as traumatic stress imposed by humans, including torture, imprisonment, forced exile, and discrimination. From this perspective, identification

of specific disease processes in different geographic, racial, ethnic, cultural, religious and other groups may provide important clues to understanding the role of traumatic stress, as well as timing, in environmental origins of physical as well as psychological disease.

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