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The Pre & Perinatal Origins of Childhood and Adult Diseases and Personality Disorders

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Abstract: This paper will explore the effects on the unborn and newborn child of psychological stress, depression, and other relevant maternal factors in the pre and perinatal period. Particular attention will be paid to the effects of stress on the organization and function of the fetal brain, on neurohormones, the immune system, personality evolution, as well as on the development of many childhood and adult diseases.

Keywords: Pregnancy, Prenatal, Stress, Neuroscience, Fetal Development

Introduction

Stress refers to both the internal and external demands that we face to accommodate change. Stress becomes negative when adaptation or coping mechanisms fail. The primary hormonal mediators of the stress response are glucocorticoids (hormones secreted by the hypothalamus, pituitary gland, and the adrenal cortex) and catecholamines (secreted by the inner core of the adrenal gland). These hormones have both protective and damaging effects on the body. When they act for short periods of time they serve the functions of adaptation, homeostasis, and survival “allostasis" (McEwen, 2000). However, if the stress becomes chronic, associated hormones exact a cost, referred to as “allostatic load” that can accelerate disease processes. The concepts of allostasis and allostatic load center around the brain as interpreter and responder to environmental challenges and as a target of those challenges. Stress can be caused by a variety of factors such as:

- Exposure to chemical toxins, electromagnetic fields, ionizing radiation, etc

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- Anxiety
- Depression
- Smoking and alcohol
- Undernutrition
- Disease, infection
- Physical trauma
- Birth complication

In this paper we shall focus almost entirely on psychological factors. Before we do, we need to take a brief look at the developing brain.

A Brief Introduction to Neuroscience

The last twenty years have produced more knowledge about the brain and how it develops than scientists had gleaned in the previous centuries.

In the past we learned about the brain through animal studies, autopsies, physical size and appearance of different brains, microscopic examination of brain tissue, and electrical stimulation of various parts of the brain, e.g. Wilder Penfield and EEG's. Also, observation of prenates with fiber optics - plus EEG leads demonstrated that the unborn child experiences REM sleep. In other words, he/she is most probably dreaming while asleep.

Current Neuroscience

- Ultrasound imaging - echoes produced by sound waves
- Magnetic Resonance Imaging - MRI - (exposes the body to a magnetic field)
- Functional MRI (magnetic field - computers - detailed images)
- Positron Emission Tomography-PET scan-we can observe brain structure and activity levels of various parts of the brain; it shows how the brain uses energy. A person is injected with a tracer chemical similar to glucose which produces color coded X-sectional images
- Correlating EEG's with videotapes, e.g. REM sleep studies
- Analysis of saliva for cortisol. Measures stress hormone levels.

In view of recent brain research the nature vs. nurture controversy is dead. It is the dynamic relationship between nature and nurture that shapes human development. While genes play a role in determining temperament, the intrauterine environment that reflects what the mother is eating, drinking, inhaling, and experiencing has

decisive influence on fetal development including temperament.

The brain develops from the outward-most layer, the ectoderm, of the very early embryo. The ectoderm forms a neural tube and this structure gradually gives rise to the cerebral hemispheres and the central and peripheral nervous system.

At birth we have 100 billion neurons, roughly as many nerve cells as there are stars in the Milky Way. Forming and reinforcing neural circuits are the key processes of early brain development.

Also in place are a trillion glial cells, named after the Greek word for glue. Axons hook up with dendrites as a result of stimulation resulting in synapses. Each individual neuron may be connected to as many as 15,000 other neurons forming brain wiring or circuitry. Those synapses that are reinforced by virtue of repeated experience tend to become permanent; the synapses that were not used often enough tend to be eliminated.

Brain development is a "use it or lose it" process, in which respect it is like a muscle.

- 0 – 3: In the first 3 years production of synapses outpaces elimination
- 3 – 10: The next 7 years - production and elimination are roughly balanced
- 10+: After age 10 - elimination is the dominant process

The pruning process is largely confined to the cerebral cortex while the hard-wired areas of the brain such as the brain stem are left intact. At birth, the human brain weighs 25 percent of its eventual adult weight. In comparison, our closest primate relation, the chimpanzee, is born with about 45 per cent of its brain weight already developed and its brain growth slows down shortly after birth. Seventy five percent of the human brain develops after birth, in direct relationship with the external environment.

By the age of two, toddlers' brains are as active as those of adults and the number of synapses reaches adult levels. A three year old has 1,000 billion synapses - about twice as many as her pediatrician - and her brain consumes twice as much energy. This suggests that young children - particularly toddlers and infants - are biologically primed for learning.

The cerebral cortex of higher forms is made up of six cell layers. Each layer has its distinct pattern of organization and connections. During the developmental phase the cells initially move from the neural tube to form the deepest or sixth layer (figure 1a). Each

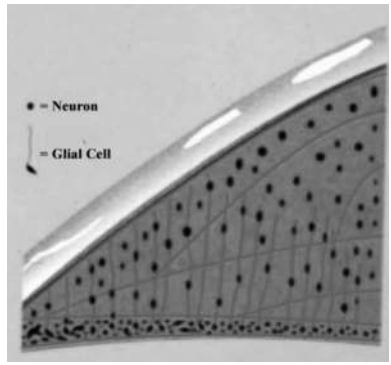

Figure 1a. *Cortical Cell Migrations.*

successive migration ascends farther, progressively forming more superficial (fifth, fourth, third, second, and first) layers beyond the layer that was initially laid down. Thus each group of migrating cells must pass through the layers already laid down by the earlier arrivals, thereby following an inside-out sequence of development.

The later arriving cells migrate along the same radial glial guide cells or cortical ladders (Figure1b) used by the earlier immigrants.

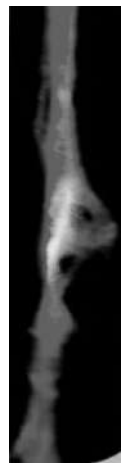

Figure 1b. *Cortical Ladder.*

It is, accordingly, very important that the earlier groups succeed in "getting off" the glial ladder before the next wave of immigrant cells tries to come up and through. Unless they do release their hold, the next wave of cells coming up the ladder may not be able to get by on

their way to a more distant destination. When this happens, the ensuing traffic pile up produces developmental anomalies, which can lead to abnormal neuronal connections and disturbed behavior (Scheibel, 1997).

Mustafa Sahin, Assistant Professor of Neurology at Harvard Medical School, sees autism as a developmental disconnection syndrome—there are either too many connections or too few connections between different parts of the brain. In mouse models, Nie et al (2010a; 2010b) found an exuberance of connections, consistent with the idea that autism may involve a sensory overload and/or a lack of filtering of information.

This study adds to growing evidence that autism is caused by a miswiring of connections in a child's developing brain, resulting in impaired information flow. Furthermore, as a cell climbs along the cortical ladder it comes in contact with other neurons. This passing acquaintance activates various genes that define the cell's identity, location, and mission. However adverse environmental conditions e.g. too much cortisol, nicotine, or other neuro-toxin can interrupt this journey. Imagine a neuron, let us call it Neuron A, that is genetically programmed to move to point X in the cerebral cortex. If there is too much cortisone, nicotine, or other brain toxic substances in the maternal blood, Neuron A may end up not at X but at Y. Or, if there is a very high concentration of these toxins, the neuron will be actually destroyed. Since this would be happening to thousands of neurons not just one, this child would be born with a miswired brain. He would be handicapped from the beginning. This process also reminds us once again that genes provide the blueprints. But the environment determines how the blueprint is executed.

Stress Pathways

The stress response can be subdivided into rapid and slow response. Rapid Response (Figure 2) occurs through the sympathetic system (one part of the autonomic nervous system) by way of increased adrenaline and nor-adrenaline production. This is often referred to as the flight/fight response. Signals from the hypothalamus activate the adrenal medulla, which responds by producing adrenaline and nor-adrenaline. Also, the hypothalamus activates the locus coeruleus, which produces nor-adrenaline. Adrenaline and nor-adrenaline stimulate the vagus nerve, which supplies the heart, lungs, and gastro-intestinal tract and is part of the para-sympathetic system.

The activation of this system will result in increased heart rate,

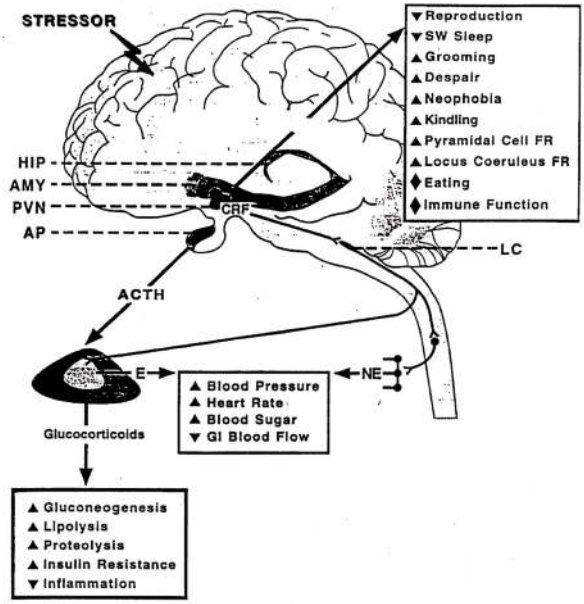

Figure 2. *Fight/Flight Response*.

blood pressure, blood sugar, and insulin resistance. Also, because the body is being readied for fight or flight, blood is diverted from the internal organs such as the GI tract to the large muscles. But the GI tract is not the only organ that is affected this way. Blood is also diverted from the uterus and what that means for a pregnant woman is that her baby is getting less than optimal oxygen and nutrients. If this state persists, the consequences can be quite dire.

It should be added that stimulation of the sympathetic system is accompanied by inhibition of the parasympathetic system that leads to inhibition of sleeping and eating. This response is wonderful for a person being chased by a lion but not so great for a pregnant mother.

Slow Response is mediated through the HPA axis (Figure 3) and results in increased concentrations of cortisol. Stimuli associated with danger activate the amygdala. By way of neural pathways from the amygdala to the paraventricular nucleus of the hypothalamus (PVN Hypo), corticotrophin-releasing factor (CRF) is sent to the pituitary gland, which, in turn, releases adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH then acts on the adrenal cortex, causing it to release steroid hormones (CORT) into the bloodstream. CORT

freely travels from the blood into the brain, where it binds to specialized receptors on neurons in regions of the hippocampus and amygdala, as well as other regions. Through the hippocampus, CORT inhibits the further release of CRF from the PVN. However, as long as the emotional stimulus is present, the amygdala will attempt to cause PVN to release CRF. The balance between the excitatory inputs (+) from the amygdala and the inhibitory inputs (-) from the hippocampus to PVN determines how much CRF, ACTH and ultimately CORT will be released.

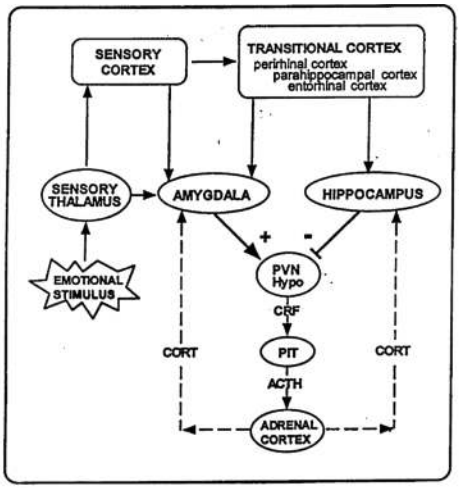

Figure 3. *HPA Axis*.

This system works beautifully under normal conditions. It is "designed," for lack of a better term, to preserve homeostasis or, at times of stress, to restore homeostasis as quickly as possible. It is a closed system similar to the heating systems of most apartments or houses where a thermostat is set at a certain temperature. When the temperature in the room falls, let us say, three degrees below the set temperature, the thermostat will send an electrical signal to the furnace, the furnace will respond by producing heat. After a little while the heat reaches three degrees above the set temperature and the thermostat will kick in and tell the furnace to shut down. Everything is quiet for a while and then the whole process is repeated.

However, should this be winter and you live in Canada and you left the window open in the room where the thermostat is, no matter how hard the furnace works the temperature in the room will not rise. So

the thermostat keeps sending information to the furnace – it is cold – and the furnace keeps pumping heat into the house. If this continues long enough, the furnace will break down. Similarly, with the body, if a pregnant woman runs to catch a streetcar, she will experience stress but after she has reaches the streetcar and sits down, her system will quickly return to normal. No harm was done. On the other hand, if this pregnant woman is a single mother, unemployed, suffering of several addictions, undernourished, and constantly worried about how she will support this child that she is carrying – she will be in a chronic state of stress. And like the house with the open window, her glands and CNS will be responding to the stress she is experiencing by an overproduction of cortisone, adrenaline, and nor-adrenaline.

Needless to say, everything that the mother experiences, everything she eats, drinks, or inhales is passed to her unborn child through the umbilical circulation in the same way her hormones are passed. A study of 100 mothers at Queen Charlotte's Hospital, at 32 weeks' gestation demonstrated a strong correlation between plasma levels of the stress hormone cortisol in the mother and in the fetus (Glover, 1999; Teixeira, Fisk, & Glover, 1999).

Effect of Maternal Stress on the Unborn Child

As we have already shown large concentrations of cortisol will lead in the brain to:

1. Cell migration to the wrong destination resulting in the formation of wrong circuits
2. Destruction of neurons
3. Destruction of synapses - when this occurs in the amygdala and hippocampus it will interfere with memory - when this occurs in the hypothalamic and reticular activating system it will interfere with internal states such as sleep and digestion
4. Inhibition of dendritic branching

Figure 4 shows neurons from unstressed (control) and stressed (subordinate) tree shrews, a mammalian species related to early primate evolution. The stress in this experiment involved exposing subordinate males to a dominant male. Repeated social stress of this type reduced the branching and length of dendrites. Compare the top half of the cell from the unstressed control and from the stressed subordinate (Magarinos, McEwen, Flugge, & Fuchs, 1996).

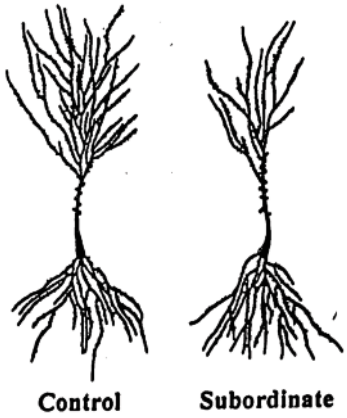

Figure 4. *Dendrites Shriveled by Social Stress*

Returning now to the effects of cortisol on the brain, we discover:

5. Gene regulation. Although we do not have space here to discuss it, it is an important part of the picture. The new science of epigenetics teaches us that genes get turned on or off by the environment. (Lipton, 2005.)
6. Decreases brain corticosteroid receptor
7. Sensitizes certain receptor sites
8. Decreases serotonin (5-HT1A) in the brain.

Serotonin is anxyolitic and may buffer aversive events. It is a known contributor to feelings of well-being. Stress, anxiety, and depression decrease receptors for serotonin. In animals, in addition to trophic properties, serotonin participates in most biological functions, especially those associated with limbic and brainstem circuits. The ability to change morphology, stimulate neurogenesis and differentiation, or promote cell survival is influenced by acetylcholine, GABA, catecholamines, EAAs (glutamate and glycine), and neuropeptides. However, only serotonin has the evolutionary and anatomical properties to serve as a global regulator unifying the whole brain into a cohesive biological system (Pasternak, Potters, Caubergs, & Jansen, 2005; Kolar & Machackova, 2005). Serotonin has an important function in prenatal development, where its expression pattern is tightly regulated, and in adult neurogenesis.

In the human brain, serotonin neurons are more numerous

(>250,000) than in other species and form a tight, small cluster along the midline of the brainstem (Tork & Hornung, 1990). Serotonin is manufactured in the brain using the essential amino acid tryptophan, which is found in foods such as bananas, pineapples, plums, turkey, and milk. Modulation of serotonin at synapses is thought to be a major action of several classes of pharmacological antidepressants. The dual role of serotonin as a neurotransmitter and a neurotrophic factor has a significant impact on behavior and risk for neuropsychiatric disorders through altered development of limbic neurocircuitry involved in emotional processing, and development of the serotonergic neurons, during early brain development (Nordquist & Oreland, 2010). Low serotonin contributes to increased risk for depression and violence in men. It also regulates respiration, heart rate, body temperature, and arousal from sleep. Hypothesis: The precursor of serotonin is tryptophan that adults obtain from certain foods and convert to serotonin. 5-HT from maternal blood begins to bathe the developing fetus from conception, providing a very early start to its functioning as a homeostatic regulator in the dynamic emerging connections of the brain. (Azmitia, 2007). But what happens when the pregnant mother is low in 5-HT because of depression? I believe this may lead to a deficiency in serotonin in her unborn child. This is, at the moment, only a hypothesis that needs to be either proved or disproved.

Continuing now our discussion of the effect of maternal stress on the unborn child:

9. Increases neuronal irritability
10. Reduces brain weight because of destruction of neurons and dendrites.
11. ANS becomes overcharged. This results in health risks and pathological personality traits as will be demonstrated subsequently.
12. Suppresses immune and inflammatory response
13. Inhibits development of the corpus callosum. This structure is a communication channel between the left and right brain. The corpus callosum is larger in women than men. This variance is given as one explanation for the different ways women and men see and relate to the world. There are other small but significant differences between male and female brains. (Brizendine, 2006).
14. Inhibits development of the cerebellum, which may be related to autism. In the past the cerebellum was considered involved

only in postural balance. Today, there is evidence that it may also be involved in emotional balance.

15. Decreases production of oxytocin. Oxytocin produces uterine contractions during parturition and ejection of milk when the baby latches onto the breast. However, it also increases male and female social and sexual responsiveness, caretaking in both sexes, in males it energizes gentler aspects of male behavior and, finally, as recent observations have shown, it increases trust. Therefore, it is not surprising that Michel Odent (1999) has referred to oxytocin as the "Love Hormone."
16. Increases production of vasopressin. Vasopressin, on the other hand, is largely a male hormone, although also present in women but to a lesser extent. It increases male sexual persistence, such as in courtship. (Please observe how tactful this science scribe can be on occasion.) In females it energizes the more aggressive aspects of maternal behavior, e.g. protecting their young from perceived harm.
17. Males tend to become feminized, females masculinized. More of this later.
18. Decreases capacity to learn. This is due to the loss of neurons in the amygdala and the hippocampus.
19. Inhibition of prefrontal cortex, thereby favoring instinctual responses over more complex intellectual functions.
20. Facilitates the encoding of aversively charged emotional memories starting at the amygdala.

Representative Research on the Effect of Maternal Emotions on Fetal Behavior

Animal Studies

Stress and Personality. Hutchings & Gibbon (1970) reported on research done by Thompson in 1957 and Ader and Belfer in 1962. Female rats were trained to avoid shock when a conditional stimulus (CS), a loud buzzer, was presented. After training they were mated. During their pregnancies the CS, but no shock, was presented. Therefore, these animals, every time they heard the buzzer, expected to be shocked. Consequently, they were stressed psychologically without the physical stress of shock. Another group of pregnant rats were exposed to the sound of the buzzer also. However, since they did not have the previous experience of associating the sound with an unpleasant experience, they were not made anxious by the buzzer. After birth half of pups from the trained - anxious mothers were given

to be reared by the non-anxious mothers and vice versa - a procedure known as cross fostering. What they found was:

- Regardless of which mothers they were reared by, pups from anxious mothers were more anxious; measured by the fact that when placed in an open field they demonstrated increased defecation and decreased activity.
- Stressed mothers demonstrated a different parenting style, eliciting more negative reactions in the pups they raised.
- Stressed pups elicited more negative maternal behavior from unstressed mothers.

Consider the implications of this and similar studies on the practice of adoption.

Stress and Testosterone. Paanksepp (1999; 2004) found that in a normal unstressed male rat litter there are 80 percent what he called sexual studs and 20 percent sexual duds. In a stressed litter there were still 20 percent duds but the number of studs fell to 20 percent and 60 percent of the litter turned out to be bi or homosexual. Generally, he found the male rats became more nurturing and female rats less nurturing.

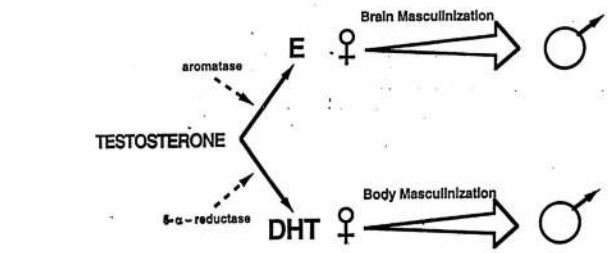

Figure 5. The Effect of Testosterone on Brain and Body.

According to Paanksepp (1999; 2004) both the brain and body of mammals are initially organized according to a female characteristic plan. Maleness emerges from two distinct influences of testosterone on body tissues - masculinization of the brain being mediated by estrogen (E) and of the body by dihydrotestosterone (DHT). Different tissues can convert testosterone to different products because of the enzymes

they contain. DHT is manufactured in cells containing 5 -a-reductase, and E is manufactured in those that contain aromatase.

Paanksepp's model suggests that stress can interfere with the enzymes 5-a-reductase and aromatase. Depending on when during gestation the stress is experienced and on the degree of stress, a man can develop a more stereotypically female brain in a stereotypically male body or vice versa or any combination of these.

Human Studies

Project Ice Storm. Project Ice Storm was designed to study the effects of in utero exposure to varying levels of prenatal maternal stress (PNMS), resulting from an independent stressor on the children's development from birth through childhood. In January 1998, the Quebec Ice Storm left millions of people without electricity for up to 40 days. In Project Ice Storm researchers at McGill University (LaPlante, Barr, Brunet, Galbaud du Fort, Meaney, et al, 2004; LaPlante, Brunet, Schmitz, Chiampi, & King, 2008) were able to separate the "objective" stressors (days without power) from the "subjective" reactions (post-traumatic stress symptoms) and physiological reactions (cortisol over 24 hours), and maternal personality factors of 178 pregnant women exposed to the disaster. Child follow-ups at ages 6 months, and 2, 4, 5.5 and 6.5 years show significant effects of objective and subjective PNMS on temperament, parent- and teacher-rated behavior problems, motor development, physical development, and IQ, attention, and language development. The majority of these effects have persisted as of November 16, 2011 (King, Laplante, Brunet, Dancause, Grizenko, et al, 2011-ongoing).

The researchers conclude: the more severe the level of prenatal stress, the poorer the outcome. The difference of an average of 15 IQ points between the high and low stress groups were largely maintained as of 2009, that is for eight and a half years (Laplante, Villiancourt, & King, 2010).

Stress and Brain Morphology. In a parallel study, at UC Irvine, researchers evaluated the influence of stress during human pregnancy on brain morphology (Buss, Davis, Muftuler, Head, & Sandman, 2010). The study included 35 women for whom serial data on pregnancy anxiety was available at 19, 25, and 31 weeks gestation. When the offspring from the target pregnancy were between six-to-nine-years-of-age, their neurodevelopmental stage was assessed by a structural MRI scan. With the application of voxel based morphometry, the

researchers found regional reductions in gray matter density in association with pregnancy anxiety after controlling for total gray matter volume, age, gestational age at birth, handedness, and postpartum perceived stress.

Specifically, independent of postnatal stress, pregnancy anxiety at 19-weeks gestation was associated with gray matter volume reductions in the prefrontal cortex, the premotor cortex, the medial temporal lobe, the lateral temporal cortex, the postcentral gyrus as well as the cerebellum extending to the middle occipital gyrus, and the fusiform gyrus. High pregnancy anxiety at 25 and 31 weeks gestation was not significantly associated with local reductions in gray matter volume.

This is the first prospective study to show that a specific temporal pattern of pregnancy anxiety is related to specific changes in brain morphology. Altered gray matter volume in brain regions affected by prenatal maternal anxiety may render the developing individual more vulnerable to neurodevelopmental and psychiatric disorders as well as cognitive and intellectual impairment (Buss et al, 2010).

Stress and Low Birth Weight. Low birth weight (Nathanielsz, 1999) increases risk for adult mental health disorders according to a study in which 4,627 subjects were tracked from birth to age 53 (Coleman, 2005; Wysong, 2005). An additional kg of body weight was associated with a 17 percent reduction in the likelihood of a mental disorder. Being born small isn't necessarily a problem. It is a problem if you were born small because of adverse conditions in the womb.

Coleman reported, "We found that even people who had just mild or moderate symptoms of depression or anxiety over their life course were smaller babies than those who had better mental health. It suggests a dose-response relationship. As birth weight progressively decreases, it's more likely that an individual will suffer from depression and anxiety later in life" (Coleman, 2005; 2007).

Low birth weight babies also tended to have shorter height and lower body weight at ages six and 11 years, and did poorly on cognitive tests at ages eight and 11 years. Even when other factors known to contribute to mental health were taken into account, such as major stressful life events and parental divorce, low birth weight was still associated with increased risk.

Low Birth Weight and ADHD. Researchers from Michigan State University analyzed data from low–birth weight and normal-weight children born from 1983 through 1985 in two major hospitals in

Detroit. The investigators discovered that among the teens living in the disadvantaged urban community, those with a low birth weight had an approximately threefold greater risk of having attention problems. Notably, the increased risk was greatest among teens whose birth weight was 1500g (3.3 lb) or less. By comparison, teens living in the middle-class suburbs had no significant increased risk for attention problems associated with low birth weight. Children with low birth weight also appear to be at higher risk for psychiatric disturbances than normal-birth-weight children (Bohnert & Breslau, 2008).

Prematurity and IQ. A study of 18,000 children at McGill University by Seungmi Yang, Robert Platt, and Michael Kramer (2010) of babies born before 39 weeks found that at age six-and-a- half they showed slightly lower IQs compared to babies born at 39-40 weeks, increased mortality in infancy, and increased risk of neonatal seizures. This is troubling because an increased number of births are induced at 38 or 37 weeks.

Extreme Prematurity and Behavior Problems. Children born extremely premature (at or before 25 weeks of gestation) may be at significantly higher risk for behavior problems by age six, with boys particularly vulnerable. The investigators found that overall, 19.4 percent of the extremely preterm children had behavior problems, but just 3.4 percent of the control children did. Notably, boys were twice as likely as girls to suffer behavioral problems, the team discovered. (Verrips, Vogels, Saigal, Wolke, Meyer, et al, 2008)

Maternal Asthma. A study of 16,000 children in Manitoba (Liem, 2006) has shown that mothers who had asthma going back 5 years gave birth to children born prematurely 6.3 percent of the time as compared to 2.8 percent of non-asthmatic mothers. Asthmatic mothers had 4.9 percent low birth weight babies compared to non-asthmatic mothers who had 3.0 percent low birth weight babies. Why is this study relevant to our exploration of the effects of stress on the unborn? There are two factors at play here. One, asthmatic sufferers when they experience an attack have huge difficulty in breathing. Panic ensues with its outpouring of cortisol, adrenaline, and all the other neurohormones of stress. Two, what do asthmatics do to prevent or treat asthma? They take cortisol sprays.

Maternal Stress and Autism. Autism risk doubles in babies born prematurely and low birth weight, according to a study by D. Schendel

and T Karapurkar Bhasin (2008) at the National Center on Birth Defects. Baby girls born < 2.5 kg (5.5 lb) had 3.5 times increased risk of autism. Baby girls born more than 7 weeks early had a 5.4 times increased risk. Five hundred and sixty five boys and girls with autism were studied. The researchers discovered that boys had less than a twofold increased risk of autism if they were born at low birth weight, but the low birth weight girls had a threefold, or higher, risk. For all low birth weight children, the risk for autism accompanied by other developmental problems, such as mental retardation, was higher than the risk of developing autism alone.

Maternal Stress and Schizophrenia. A new study (Malaspina, Corcoran, Kleinhaus, Perrin, Fennig, et al, 2008) discovered pregnant women who endure the psychological stress of being in a war zone are more likely to give birth to a child who develops schizophrenia. Research supports a growing body of literature that attributes maternal exposure to severe stress during the early months of pregnancy to an increased susceptibility to schizophrenia in the offspring.

For example, according to Dolores Malaspina, Anita Steckler, and Joseph Steckler at the NYU School of Medicine (Nauert, 2008)), "The stresses in question are those that would be experienced in a natural disaster such as an earthquake or hurricane, a terrorist attack, or a sudden bereavement." Malaspina and her team examined data from 88,829 people, born in Jerusalem from 1964 to 1976, collected from the Jerusalem Perinatal Study that linked birth records to Israel's Psychiatric Registry.

The NYU authors discovered that the offspring of women who were in their second month of pregnancy during the height of the Arab-Israeli war in June of 1967 (the "Six Day War") displayed a significantly higher incidence of schizophrenia over the following 21-33 years. The study also showed that the pattern was gender-specific, affecting females more than males.

"It's a very striking confirmation of something that has been suspected for quite some time," said Malaspina. "The placenta is very sensitive to stress hormones in the mother," explains Malaspina, "these hormones were probably amplified during the time of the war."

Summary of Health Effects of Maternal Stress

Once again, it should be emphasized that we are referring here to excessive and sustained stress.

- Low birth weight
- Prematurity
- Congenital malformations: cleft lip, cleft palate, and spina bifida
- SIDS serotonin defects in the brain stem
- Heart disease
- Hypertension (Barker 1992)
- Cancer

Using mice as a model to study human breast cancer, researchers have demonstrated that negative social environment (in this case, isolation) causes increased tumor growth. This interdisciplinary research illustrates that the social environment and a social animal's response to that environment can indeed alter the level of gene expression in a wide variety of tissues including the brain (Conzen, 2009).

- Dyslipidimia
- Osteoporosis (Gluckman & Hanson,2004)
- Type 2 diabetes
- Susceptibility to seizures
- Inhibition of the immune system
- Decreased ability to deal with stress
- Premature Aging

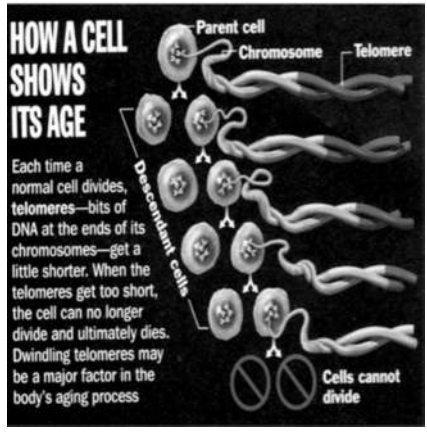

Figure 6. *How a Cell Ages.*

Stress shortens telomeres, leading to premature aging. Elissa Epel and colleagues (2004) and Naomi Simon and colleagues (2006) showed that each time a normal cell divides, telomeres - bits of DNA at the ends of chromosomes - become a little shorter. When the telomeres get too short, the cell can no longer divide and ultimately dies. Dwindling telomeres may be a major factor in the body's aging process.

Exhaustion of the adrenals leads to deceased cortisol which overcharges the immune system which then may turn against its own body as seems to be the case in:

- Rheumatoid Arthritis
- Multiple Sclerosis
- Fibromyalgia
- Chronic Fatigue Syndrome

Effect of Maternal Stress on Personality

Excessive and sustained stress may predispose to personality disorders as a result of poor academic performance and poor capacity to learn from past mistakes (because of decreased neurons in the amygdala and prefrontal cortex) and antisocial behavior (more hostile because of decreased oxytocin, decreased serotonin, increased vasopressin, dominance of lower brain centers over prefrontal cortex). In addition, the amygdala plays a major role in fear recognition. If impaired, a person tends to take abnormal risks, does not learn from past mistakes (Dadds, Perry, Hawes, Merz, Riddell, et al, 2006; Marsh, Finger, Mitchell, Reid, Sims, et al, 2008).

1. Depression (Nemeroff & O'Connor, 2000)
2. Schizophrenia
3. ADHD, HKD (Markussen, Obel, Bonde, Hove-Thomsen, Secher, et al, 2006) Adult ADHD respondents reported poorer function on:

    - Quality of childhood experiences
    - Academic achievement
    - Relationships

They had higher rates of arrests, impairment in the workplace - the average household income among the ADHD group was almost half of the non-ADHD group (Biederman, Spencer, & Mick, 2007).

Also noted were:

- Autism
- Decreased intellectual and language function
- Males tend to become feminized, females masculinized
- Microchimerism (This refers to fetal-maternal cell swapping that may be involved in both the cause of and response to various diseases such as juvenile idiopathic inflammatory myositis and juvenile dermatomyositis [Hampton, 2004].)

If we consider all of the above factors it becomes crystal clear that the old adage about "Adversity makes you stronger," is simply not true. It may build character but it does not do much for your brain or the rest of your body. The more you are exposed to stress, the more vulnerable you become to all forms of illness and stress. This applies to all living creatures from conception on.

Maternal Depression

According to the American Pregnancy Association, approximately 10 to 20 percent of pregnant women will have some symptoms of depression, and as many as half of them will suffer from major depression. Women need to be aware that depression in pregnancy is common, might affect the baby, and can be treated. However, one must balance the effect of untreated depression against treatment with antidepressants. Each course has it upside and downside. Space limitations do not permit me to say more on this important subject.

Effect of Depression on the Fetus

Twenty five percent of infants of depressed mothers were born prematurely compared to 7 percent of non-depressed mothers. Thirty four percent of infants of depressed mothers were low birth weight compared to 14 percent of non-depressed mothers.

Higher maternal depression during pregnancy results in elevated cortisol and norepinephrine levels, prematurity, and low birth weight (Field, Diego, Hernandez-Reif, Schanberg, Kuhn, et al, 2004).

Researchers at Kaiser Permanente's Division of Research in Oakland, CA, found that depressed pregnant women have twice the risk of preterm delivery than pregnant women with no symptoms of depression. The more severe the women's depression is, the greater their risk of delivering preterm (Li, Liu, & Odouli, 2009).

Depression and Inflammation

In depression there is an increase in:

- Tumor necrosis factor-alpha(TNF-a)
- Interleukin (IL)-6
- TNF-a activates cytokines and prostaglandins
- IL-6 activates immunoglobulin-secreting B-lymphocytes

In the brain these substances inhibit:

- hippocampal neurogenesis and activate
- the HPA axis

Due to the above reactions stress exacerbates inflammatory diseases such as diabetes and coronary heart disease (Dowlati, Herrmann, Swardfager, Liu, Sham, et al, 2010).

Effect of Maternal Depression on the Newborn

- Irritability
- Excessive crying
- Increased need for resuscitation
- 40 percent showed reduced brain activity
- 75 percent showed reduced left frontal cortex activity, which impacts one's ability to experience joy, following one's interest or express anger (Dawson, Glasson, Dixon, & Bower, 2009).
- Babies born to depressed mothers are more likely to have chaotic sleep patterns (Armitage, Flynn, Hoffmann, Vazquez, Lopez, et al, 2005).

Researchers from the UK's Cardiff University found that women who were depressed while they were pregnant were four times as likely to have children who were violent by the age of 16 as the control group of mothers. (Hay, Pawlby, Waters, Perra, & Sharp, 2010).

Other Factors

Maternal Prenatal Smoking

There appears to be a dose response relationship between index crime rates for male offspring and maternal prenatal smoking. The same applied to female offspring to a lesser extent. Maternal smoking

during the 3rd trimester was related to higher rates of hospitalization for substance abuse in both sexes. There was a dose related response for substance abuse. In female offspring criminal arrest was related to an increased risk for substance abuse (Brennan, Grekin, Mortensen, & Mednick, 2002).

Boys born to women who smoked are double the risk for early onset oppositional defiant disorder (ODD) compared to boys whose mothers did not (Weaver, Campbell, Mermelstein, & Wakschlag 2007). Children whose mothers had smoked were 20 percent more likely to suffer psychotic symptoms, such as delusions and hallucinations. The link was 84 percent more pronounced if 20 or more cigarettes a day were smoked. The investigators suggested tobacco exposure in the womb might affect the child's brain development (Zammit, Thomas, Thompson, Horwood, Menezes, et al, 2009). Also, see excellent paper by Markussen, et al, 2006.

Prenatal Alcohol

Ethanol decreases neurogenesis and causes cell death (Crews, 2008). Excessive imbibitions of alcohol lead to Fetal Alcohol Spectrum Disorder. Babies so afflicted may be born tiny and stay quite small. They usually develop more slowly than children without FASD.

Children with FASD may have trouble:

- speaking well
- learning at school
- dealing with change
- controlling their temper (increased impulsivity).

Prenatal Maternal Undernutrition

Increases risks for:

- Hypertension
- Diabetes
- Cardiovascular disease (Roseboom, van der Muelen, Osmond, Barker, Ravelli, et al, 2000).

Some of the body's "memories" of early undernutrition become translated into pathology and, thereby, determine disease in later life (Barker, 1998).

Birth Complications and Autism

Birth complications may join with other factors to cause autism.

Increased risk factors are:

- Older maternal age
- Threatened miscarriage
- Labor induction
- Labor duration of less than one-hour
- More likely to have experienced fetal distress
- C-sections
- Apgar score of less than six at one minute
- More likely to be first born.

Birth Complications Combined with Early Maternal Rejection

Four-and-one-half percent of subjects had both birth complications and early maternal rejection. This small group accounted for 18 percent of all violent crimes in Denmark (Raine, Brenman, & Mednick, 1994).

Fetal Hypoxia and Schizophrenia Risk

Tyrone Cannon and colleagues (2008) of the University of California, Los Angeles, examined 70 individuals with schizophrenia and 333 control individuals drawn from the Philadelphia cohort of the National Collaborative Perinatal Project. Fetal hypoxia appears to contribute to the risk for schizophrenia in later life by disrupting neurotrophic signaling in developing neurons in individuals with an underlying genetic or prenatally induced vulnerability.

Among controls, birth hypoxia was associated with a significant 10 percent increase in BDNF (brain-derived neurotrophic factor) in cord samples. Among schizophrenia cases, hypoxia was associated with a significant 20 percent decrease in BDNF.

The Good News

Coping with intermittent social stress is an essential aspect of living in complex social environments. Coping tends to counteract the deleterious effects of stress and is thought to induce neuroadaptions in corticolimbic brain systems. These studies support recent indications that stress coping stimulates hippocampal neurogenesis in adult rodents. Psychotherapies designed to promote stress coping may well have similar effects in humans with major depression (Lyons, Buckmaster, Lee, Wu, Mitra, et al, 2010).

Healthy physical exercise is known to increase neurogenesis

(Fulton Crews Carolina). Hands on contact can reverse nerve cell deficit. Experiments with rats handled 15 minutes per day by Djoher Nora Abrous at the Francois Magendie Institute in Bordeaux Cedex, France have shown that an environment enriched by handling reverses the damage caused by prenatal stress (Arehart-Treichel, 2006). Therefore, be sure to hug someone you love at least once a day!

Points to Remember

1. Psychological stress during pregnancy produces lasting undesirable changes in both mothers and their children.
2. The cumulative impact of health risks from modest dysregulations in multiple systems can be substantial, even if they individually have minimal and insignificant health effects.
3. In the brain hardware and software is constantly changing as a result of the dynamic interaction between genes and environment.
4. Experience changes the organization and function of the brain. To quote Daniel J Siegel (2012), "Human connections create neural connections from which the mind emerges."

Summary

This paper explored the effects on the unborn and newborn child of psychological stress, depression, and other relevant maternal factors in the pre and perinatal period. Particular attention was given to the effects of stress on the organization and function of the fetal brain, on neurohormones, the immune system, personality evolution, as well as on the development of many childhood and adult diseases.

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