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MYSTERIES OF THE HUMAN FETUS REVEALED

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Abstract

The impressive program of research from the DiPietro laboratory succeeds in its aim to document the ontogeny of human fetal neurobehavioral development. From studies of great depth and breadth, and wielding creative methods of assessment, DiPietro et al open a window into the largely inaccessible developing human fetal brain. This commentary, with reference to the seminal cardiovascular studies of the Lacey's, supports the measures of the fetal heart to index fetal well-being and to provide evidence of stimulus processing. A separate case is made that the DiPietro program provides unique and invaluable information for assessing the influential Developmental Origins of Health and Disease or Fetal Programming Models. The goal of these models, to predict or understand the influences of early experience or response patterns on later postnatal life, is identical to the ultimate goal of the DiPietro program. Because human fetal behavior is uncontaminated by socialization or parenting or peers, it may be the best reflection of fetal exposures. The remarkable neurobehavioral profiles generated by the DiPietro program can make a critical contribution to the Fetal Programming Model in terms of sensitive and critical periods of nervous system vulnerability and to specify gestational periods of neurobehavioral risk..

We do not laugh because we are happy

We are happy because we laugh.

William James

As a freshly minted PhD in 1971, who had resolved (in my mind) the James-Cannon “debate” in my dissertation and converted to radical neo-Jamesianism while also benefitting from remarkable pre-doctoral experience in the endocrine laboratory of Abba Kastin and the soon-to-be Nobel biochemistry laboratory of Andrew Schally, I accepted a position in the clinical psychology department of The Ohio State University. I had discovered the research of John and Beatrice Lacey while conducting my psychophysiological dissertation investigation of human emotion, thanks largely to the influence of my mentor, Lyle Miller. The Lacey's stood alone among the researchers in the technically challenging field of psychophysiology. From the 1950's to the 1970's their studies elevated the status of the study of the autonomic nervous system (ANS) with empirical findings and theoretical concepts that still are current. I have been heard to argue that there are no new concepts in psychology than those in William James, “Psychology” and after attending several

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psychophysiology meetings in the past ten years, that there are no new ideas relating the ANS and the brain from those proposed by the Lacey's. These undertones and a peripatetic research career form part of the basis of my perspective about the contribution of the DiPeitro et al monograph to developmental issues specifically and to psychology and science generally. In my blind review of the DiPietro article, I predicted (and still do) that it will be an instant classic. I will elaborate, but first, a little more context.

Although I had never met the Lacey's, I was aware when I accepted the position at Ohio State University that they were about 50 miles west of Columbus, Ohio, in Yellow Springs at the Fels Research Institute. After setting up my own psychophysiology laboratory and getting settled, I made plans to make pilgrimages to the Lacey's. Periodically I would pile my 1974 Pontiac Grandville convertible full of graduate students and head west to visit John and Beatrice. They graciously allowed us to observe ongoing studies and hear first-hand about the law of initial values (Lacey and Lacey, 1962), response stereotypy (Lacey and Lacey, 1958) and specificity (Lacey, Bateman and Van Lehn, 1953). Of greatest interest was to learn about their theory of how the dynamics of the cardiovascular system affected the brain and behavior (Lacey and Lacey, 1978). Based on the elegant studies of Bonvallet, Dell and Hiebel (1954) the Lacey's proposed that activation of the baroreceptors in the wall of the carotid sinus would exert predictable influences on brain activity. They knew that nerves from the carotid sinus and aortic arch join the vagas and the glossopharyngeal nerves which terminate in the lower brainstem providing homestatic control of blood pressure. But there were other consequences of baroreceptor activity. In a classic study, Bonvallet et al (1954) mechanically distended the carotid sinus in cats (an analogue of increased pressure) and discovered that electrocortical activity shifted from low-voltage fast activity to high-voltage slow activity. There are qualifications (Sandman, Walker and Berka, 1982), but the general conclusion was that there is a direct pathway between peripheral cardiovascular activity (heart rate, transient pressure changes with each ventricular contraction and baroreceptor activation) and cortical activity. John allowed us to watch in his animal model how carotid sinus distention in real time altered cortical activity.

The findings that changes in cortical activity were related to peripheral stimulation and autonomic activation had obvious implications for behavior. With the Lacey's as sources of inspiration and encouragement, students (e.g. Tom McCanne, Barbara Walker, Don Kaiser, John Cacioppo, Marcia Ward, Jane Veith, Pat Zingheim and Chris Berka) and I began a series of studies to test the limits of the Lacey theory. Tasks requiring attention to the environment were associated with heart-rate deceleration but tasks requiring “mental effort” or “rejection of the environment” were associated with heart-rate acceleration (Kaiser and Sandman, 1975; Cacioppo and Sandman, 1978). We pushed further by observing that behavioral performance varied during episodes of operantly conditioned heart rate increases and decreases (Cacioppo, Sandman, and Walker, 1978; McCanne and Sandman, 1974; 1976). In a series of studies that John Lacey said to us were the most convincing test in humans of his theory (he may have said that to others), we found that presentation of stimulation either during normally fluctuating heart rate or during discrete periods of the PQRST cardiac cycle not only was related to performance (Sandman, McCanne, Kaiser and Diamond, 1977) but also to evoked potentials of the brain (Walker and Sandman, 1979; Sandman, 1984).

There are several intersections between the DiPietro et al monograph and the foregoing. The Monograph is an instant classic in part because it reflects classical scholarship. There is genuine reverence presented for past and present contributions to the impressive body of research collected by the DiPietro team and reported in this Monograph. What is most unusual and greatly appreciated was the linkage between the pioneering (and largely forgotten or ignored) work of Lester Sontag and the current studies of the human fetus by Janet DiPietro. But before considering the science, there is an irony that previously I had not considered. Lester Sontag was director of the Fels Research Institute from 1929 to 1970. He overlapped at Fels with the Lacey's for at least 20 years. I wonder if the pioneering studies of fetal heart rate conducted by Sontag ever were discussed with the Lacey's? There is no evidence I could find that they collaborated. In any case it is ironic that these two pioneering and inspirational scientists were at the same small (but highly productive) facility for many years studying different aspects of a similar question. If they discussed their ideas, there is no evidence, and if they did not, why not? If they had, we might have an advanced understanding of the significance of fetal heart rate.

WHY STUDY THE HUMAN FETUS?

Before considering why it is important to study the human fetus, it is worth recognizing how difficult it is to study the behavior of the human fetus. DiPietro et al remind us that access to the human fetus is complicated by the obvious inability to have physical contact. In addition, there are ethical restrictions and medical limitations as to what can be done. There are also problems of logistical access. Developmentalists typically are not welcome to intrude on the territory of obstetrics and approach women for consent to research when they first learn they are pregnant. It can be a time for women of great joy, fear or anxiety and many times all three. All of these issues conspire to discourage the study of the human fetus and contribute to the fact that there are few laboratories that have made the human fetus a focus of their research and none with the depth and breadth demonstrated in the DiPietro et al Monograph. The remarkable and impressive collection of studies presented here are a tribute to the sensitivity and competence of the DiPietro research team.

DiPietro et al clarify that obstetric monitoring of fetal heart rate has a different purpose than observations of the fetal heart by a developmentalist. The obstetrician is interested in fetal heart rate as a general index of fetal well-being. The developmentalist uses fetal heart rate to document neurobehavioral development (aim 1 of the DiPietro research program). It is equally important to distinguish the interest of the developmentalist in fetal heart rate from those of a cardiologist. In contrast to clinical studies of the fetal heart and circulation, which may use exotic measures (magnetocardiograms) of cardiac function (Schneider et al, 2009: Fukushima, Nakai, Kanasugi, Terata and Sugiyama, 2011), most studies of fetal behavior rely on relatively crude assessments of heart rate. (Fetal movement also is assessed with sensitive but even less precise metrics.) But this is not a criticism because it is clear from the studies of the DiPietro team that these measures are a window into fetal behavior and the intimate relationship between mother and fetus.

It is unclear from the DiPietro laboratory if directionality of fetal heart has the same behavioral currency as it does in the adult. In the Monograph, heart rate deceleration is

referred to as “ominous.” I would imagine that the Lacey's would be curious about the conditions associated with episodes of acceleration and deceleration and the ontogeny of autonomic nervous system balance. Does the human fetal baroreceptor system respond to these changes in transient pressure and impact the activity of the brain? Answers to these questions come primarily from studies of the preterm infant. There is evidence that sometime between 26 and 37 weeks gestation, the preterm infant has a fully developed baroreceptor reflex with clearer evidence that it is present by 33 weeks (Andriessen, Oetomo, Peters, Vermeulen, Wijn and Blanco, 2005). Studies in lambs and non-human primates indicate that the fetal brain responds to variability in heart rate. Both fetal measures of the electroencephalogram and electrooculogram show increased activity in association with variability of heart rate and body movements. When, activity slows and fetal heart rate variability decreases, brain activity is consistent with fetal sleep (Parer, 2008). This is evidence that there is an association between fetal cardiac activity and the central nervous system most likely mediated by the baroreceptor reflex.

DiPietro et al discuss that fetal heart rate is determined by both neural and non-neural influences. Autonomic nervous system balance (between sympathetic and parasympathetic) increases as gestation advances. Major changes in ANS function (i. e. maturation) occur around 28 weeks gestation (Fukushima et al, 2011). This is roughly the same time frame for development of the human fetal baroreceptor reflex and suggests that directional heart rate influences on the central nervous system are unlikely before ~28 weeks gestational age (GA). However, it is unknown and untested if the consequences for cortical activity of transient cardiac activity observed in adults are possible in the human fetus even after 28 weeks GA. Assessment of the directionality of the fetal heart rate response could be best tested by acoustical or vibratory stimulation. The Monograph does not present data from the DiPietro laboratory that included fetal stimulation but does review several studies that have. In addition to those reviewed in the Monograph, the sophisticated studies of Lecanuet, Granier-Deferre and Busnel, (1995) indicated that the human fetus by at least 33 weeks GA (and maybe before) exhibits differential heart rate responses to various sources of (*nonstartling*) stimulation. We used group based trajectory analysis in response to a *startling* vibroacoustic stimulus (VAS) at 30 weeks GA that resulted in five distinctive fetal heart rate patterns (Sandman, Cordova, Davis, Glynn, & Buss, 2011; Sandman, Glynn and Davis, in press). Two of the patterns were significantly associated with subsequent birth weight. The group of fetuses with an immediate heart rate deceleration to the VAS followed by an immediate acceleration that persisted for over 30 seconds had the lowest birth weight. A group characterized by immediate and fast acceleration to the VAS followed by a slow recovery to baseline was associated with the highest birth weight. Thus, it is unclear if fetal heart rate deceleration is an “ominous” indicator or evidence of higher levels of stimulus processing. It may be both depending on the gestational age of the fetus and the level of stimulation.

One primary aim of the DiPietro research program is to document the “normal ontogeny of fetal neurobehavioral development between and within individuals.” Among the several implicit assumptions required to assess this aim the most salient assumption is that there must be a method of assessing the fetal brain. It can be safely concluded from the evidence

provided in the Monograph that assessment of fetal heart rate (and movement) provides an index, although indirect, of fetal nervous system activity. There is evidence from several laboratories cited in manuscript that the human fetus can orient to stimulation, habituate and even dishabituate (Sandman, Wadhwa, Hetrick, Porto and Peeke, 1997). There is a discussion of more direct measures of fetal brain activity with 3- and 4D ultrasound scanning approaches. There also are magnetic resonance imaging (MRI) scans of the fetal brain that have been used in high risk cases (Andreas, Wedegartner, Tchirikov, Hecher and Schroder, 2006; Glenn, 2009) and an MRI atlas developed from postmortem cases (Zhan et a, 2011). At this point in time, however, elective use of MRI for research of the fetal brain carries unknown risk for mother and fetus because of the presence of a strong magnetic field and the high decibel environment.

Magnetoencehpalography (MEG) is a non-invasive method that is low risk and can provide high temporal resolution of fetal brain activity (Lowery, Govindan, Preissl, Murphy and Eswaran, 2009). It has been used to assess visual and auditory evoked potentials of the fetal brain. In a remarkable study, MEG recordings were synchronized with the ventricular contraction of the maternal heart and compared with fetal MEG responses linked to external auditory stimulation (Pocaro et al, 2010). The tracings for three representative subjects are presented in the publication as evidence that the human fetus between 36-40 weeks GA exhibits strong evoked responses to both maternal ventricular contractions and a known provocative external stimulus. This study illustrates several relevant issues for the DiPietro research program. First, there are more direct, admittedly exotic, measures of fetal neurobehavior than measures of fetal heart rate. Certainly the DiPietro team know this and cited several papers including the Pocaro et al paper in the Monograph. Second, the Pocaro et al paper provides strong evidence that the human fetal brain is synchronized with maternal signals. The human fetus is exposed to 25,000,000 maternal heart beats over the course of gestation and still responds (does not habituate) to each ventricular vibroacoustic episode near term (after at least 20,000,000 exposures). Spatial maps of the fetal evoked response suggest that there is the potential for localizing fetal brain activity. Second, this is strong evidence for on-line synchronization of mother and fetal physiology. The interesting twist that the DiPietro team propose is not that the mother influences the fetus but if and how the fetus influences the mother.

Before discussing this latter issue (fetus affecting mother), it is important to acknowledge another reason to venerate the research described in the Monograph. This additional reason broadens the potential impact of the DiPietro contributions to the area of research which focuses on the influences of maternal adversity on the fetus. The ultimate goal of this area of research is identical with the DiPietro team to examine “the degree to which fetal neurobehavioral measures are associated with postnatal temperament, regulatory processes, and developmental outcomes.” The advantage of studying the human fetus is that the programming consequences of maternal signals associated with adversity on postnatal development can be detected before environmental and postpartum influences such as parenting and general socialization can contribute to outcomes (Sandman, Wadhwa, Chicz-DeMet, Porto, Garite, 1999; Sandman, Glynn, Wadhwa, Chicz-DeMet, Porto and Garite, 2003;. Class, Buss, Davis, Gierczak, Patillo, Chicz-DeMet and Sandman, 2008). The application of the careful metrics, methods and designs of the DePietro research program

provides for the first time in the human fetus developmental timetables for neurobehavior and has the potential to add significance to the rapidly expanding field of Fetal Programming or more generally the area described as the Developmental Origins of Health and Disease.

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE AND FETAL PROGRAMMING MODELS

Early in my research career I exercised parallel interests in psychophysiology and the psychobiology (mostly endocrinology) of stress. However, part two of my perspective of the DiPietro research program is shaped by the past twenty years or so, during which I have focused on endocrine/stress research with a special emphasis on early development.

With animal models I had observed that neonatal and fetal exposure to stress peptides and hormones resulted in permanent effects on the brain and behavior but exposure in adults resulted in acute and reversible consequences. I was curious if similar, long term consequences would be observed after human fetal exposures to changes in endocrine profiles related to stress. I was aware that the fetal period in the human life cycle is unmatched by any other in growth and development and it is the stage in the life span that is most vulnerable to both organizing and disorganizing (programming) influences. The human fetal nervous system is a primary target for these circulating programming influences because it is undergoing dramatic growth over a prolonged period of time. For instance, radial neuronal cell migration begins in the human brain around 42 days GA (Takahashi, Folkerth, Galaburda and Grant, 2012) and by 16 weeks GA, form the subplate zone. Concurrently, cells accumulating in the outer cerebral wall form the cortical plate which will become the cerebral cortex. By gestational week 20, axons form synapses with the cortical plate and there is an exponential increase in cortical thickness (Huang et al, 2009) and by gestational week 24, cortical circuits are organized (Kostovic, Judas, Rados and Hrabac, 2002). The human fetal brain is forming secondary and tertiary gyri, and exhibiting neuronal differentiation, dendritic arborization, axonal elongation, synapse formation and collateralization, and myelination by gestational week 28. Near term the fetal human brain contains billions of neurons and is 40% greater in number than in the adult (Huttenlocher and Dabholkar, 1997). The rate of synaptogensis reaches an astonishing peak so that at gestational week 34 through 24 months postpartum, there is an increase of 40,000 synapses per minute (Levitt, 2003).

Awareness of the timing of these events is critical for understanding fetal neurobehavior. It prescribes what the fetus can do, when it can hear, feel and learn. It also is important because fetal exposure to maternal adversity during discrete periods of neurological development may produce specific disruptions in neurogenesis or in the sequence of neuronal events that result in permanent consequences in the nervous system (Sandman, Buss, Head and Davis, 2014). The Fetal Programming Model shares with the DiPietro team the goal of answering the “ultimate” question of how early experience shapes later systems. Both approaches require longitudinal studies during and after pregnancy. The neurobehavioral database generated by the DiPietro team in both its depth and breadth is unique and could be an invaluable tool for examining the fetal programming model

especially in terms of the issues of sensitive and critical periods of nervous system vulnerability.

When my studies of the human pregnancy began, I was not aware of the Fetal Programming or Developmental Origins of Health and Disease Models. It was not widely announced until Barker's book (1998) was published (cited by the Lancet as “books that will shake the foundations of medical thinking are rare, but this is one”). Although this model has become influential in the medical sciences, it has not penetrated mainstream thinking in psychology. The back-story of the Barker model is a first rate medical detective story. Briefly, in Britain, at the turn of the last century, there was a decline in population. Birth rates were low and infant mortality was high. Two thirds of the young men who volunteered to fight in the British colonies were unfit. In response to this potential calamity, one district enlisted midwives to interview and assist all women during and after pregnancy. This intervention was intended to improve the health of mothers and their children, but a secondary consequence was meticulous record keeping of pregnancy histories and birth outcomes. These early-life-history records, combined with national health records from later in life, formed the basis of the Barker hypothesis or the fetal programming model.

The Fetal Programming model predicts that early or fetal exposures to maternal signals of threat or adverse conditions have lifelong consequences for health outcomes. A basic assumption of this model is that developing organisms play a dynamic role in their own construction (Sandman & Davis, 2010; Sandman, Davis, Buss, & Glynn, 2011a; Sandman, Davis, Buss, & Glynn, 2011b). To accomplish this, a remarkable fetal surveillance and response mechanism has been conserved across species to acquire information about the maternal (or host) environment. If a stress or a threat to survival is detected, a complex series of adjustments are made to decrease the risk of morbidity and mortality. One example of this conserved mechanism is the adjustment made by the tadpole in response to environmental stress. The desert-dwelling Western Spadefoot toad lays its eggs in pools of rainwater. If the tadpoles detect that the conditions for normal development and survival are unfavorable (e.g., rapid evaporation of the pool), stress hormones including corticotrophin-releasing hormone (CRH) and corticosterone (glucocorticoids) are released. These hormones accelerate metamorphosis, so that the tadpole can escape the desiccating environment. If the biological stress response is blocked during this life-threatening stress, the rate of development is arrested, and the tadpole's survival is compromised. There are penalties for the tadpole that survives under these conditions, however, because it is smaller at maturity and is at a disadvantage when competing with a normally developing toad for food and reproduction (Denver, 1997; Boorse and Denver, 2002). In a similar way, the human placenta collects information from the maternal environment and responds with a complex series of signals to the host. If the prenatal environment is perceived to be stressful or hostile, the fetal-placental signals to the mother may promote accelerated developmental trajectories, such as preterm birth permitting fetal escape from an inhospitable environment and ensuring short-term survival. In parallel, the fetus incorporates this bidirectional information to adjust its developmental program in preparation for survival after birth. The information may cause (or program) the fetus to modify its nervous system to adapt to an expected postpartum environment.

THE JAMESIAN PARADOX AND THE FETAL INFLUENCE ON THE MOTHER

An obvious and significant consequence of human pregnancy is the profound, but normative, alteration of the maternal "fight or flight" system (Sandman & Davis, 2012; Sandman, Davis, & Glynn, 2012a; de Weerth & Buitelaar, 2005; Glynn, Dunkel-Schetter, Hobel, & Sandman, 2008). William James (1892) suggested that the "fight or flight" response was a product of visceral and autonomic input the brain. He proposed that sensations developed perceptual qualities as a result of the context in which they were experienced and that the peripheral nervous system contributed to this context. Perceptions acquired unique qualities that corresponded to distinctive patterns of physiological response. For example fear in the "flight" response was "we are afraid because we run." During human pregnancy the maternal pituitary gland doubles in size increasing by several fold the synthesis, and release of pituitary (stress) peptides into the maternal circulation. Production from target tissues, such as cortisol from the adrenal gland also increases over the course of pregnancy. But it is the growth and development of a *new fetal organ*, the placenta in primates that is primarily responsible for the profound changes in the maternal/fetal stress systems. The human placenta and amniotic membrane express the genes for the major stress hormones, CRH (hCRH mRNA) and proopiomelanocortin, by the seventh week of gestation. All of the HPA and placental *stress* hormones increase as pregnancy advances, and the increase in placental CRH in maternal plasma is especially remarkable, reaching levels observed only in the hypothalamic portal system during physiological stress (Sandman & Davis, 2012; Sandman, Davis, & Glynn, 2012). Despite this biological context consistent with extreme stress as gestation advances, women paradoxically become less responsive to external stimulation and exhibit a decrease in anxiety (Glynn and Sandman, 2011; Glynn et al, 2008). Contrary to predictions from William James, during human pregnancy, the autonomic and visceral signals typically associated with high stress do not translate into the experience of extreme emotional distress.

The placental release of hormones into the maternal circulation is a powerful route of communication between the fetus and mother with long term and profound influences for both fetus and mother. There is compelling evidence for the effects of placental actions on the fetus (Sandman and Davis, 2012) and it is believed that high levels of placental CRH circulating in the maternal blood stream down-regulates *maternal* corticotrophs blunting the communication between the hypothalamus and pituitary gland and affecting her response to the environment. This not only explains the decrease in maternal responses to stress as pregnancy advances but also has been proposed as a mechanism for postpartum depression (Glynn and Sandman, 2014). In this way, the fetus exerts a profound and lasting influence on the mother. This is not the pathway between the fetus and mother that the DiPietro team have examined but it is solid evidence that the fetus can and does effect the mother.

Dipietro et al briefly mention the reciprocal sharing of cells between mother and fetus as another potential route of mutual influence. It has been established that foreign cells cross back and forth through the placenta and invade the fetus (maternal microchimerism) and mother (fetal microchimerism). These cells survive in both mother and the offspring for decades and perhaps forever (Bianchi, Zickwolf, Weil, Sylvester, & Demaria, 1996; Hall, 2007). Moreover, cells present in maternal blood from earlier born children may appear in

later born offspring establishing a linkage among siblings (Hall, 2007). There is evidence that these cells migrate to areas of tissue damage (Adams & Nelson, 2004) and are found in many target tissues including the brain (Kaplan & Land, 2005) of the developing fetus. The potential for maternal cells to influence the risk for health outcomes has been suggested (Hall, 2007) but the precise "programming" influence of this intimate relationship between mother and fetus and among siblings is unknown at this time.

CONCLUSION

The Monograph was extensively reviewed prior to publication so this commentary is not a review. This piece was intended to provide a perspective about where the research described in the Monograph fits into past and present and perhaps even future renderings of the science of human development. It was tempting to muse about the significance of the Monograph 75 years from now. Will some enterprising young Janet DiPietro *revisit* this manuscript, *renew* the scholarship and *reimagine* the science? Although I have been accused of writing science fiction (meant to be a criticism) my cloudy crystal ball obscures a clear look at the future. However, because we already have exotic methods for direct assessment of fetal neurological function, it is reasonably certain that there will be safe and readily available methods for assessing and *revealing* the mysteries of the human fetal brain and brain function in the future. Development of these procedures for research and clinical application may well have as their foundation in the studies reported here.

I resisted the temptation to take a forward look and instead sited the DiPietro research program in the past and the present. I believe that the influence of this impressive program of research is greater than the DiPietro team realize. My commentary is meant to broaden the influence by linking the findings to earlier theories of heart/brain interactions and by consideration of contemporary mechanisms of action. And because evidence unequivocally supports the conclusion that exposure to early life stress, especially during the fetal period, exerts profound and persisting consequences for human neurobehavioral development, there is a natural contribution of the DiPietro research program to the Fetal Programming Model. Evidence from prospective and retrospective studies that adverse birth phenotype and fetal exposures to maternal signals of psychobiological stress both result in increased risk for emotional and cognitive disorders and in alterations in brain structures in children and adults (Sandman, Class, Davis and Glynn, in press). Although there may be different consequences related to the timing of exposures to stress and there is some indication that prenatal stress exposure affects males and females differently, it is remarkable that a range of early life exposures exerts relatively similar consequences on neurobehavioral development. There is a significant opportunity for the DiPietro program of research to provide new critical information about the ontogeny of these consequences during the fetal period and to pinpoint specific gestational periods of neurobehavioral risk.

Acknowledgments

Curt A. Sandman is Professor Emeritus at the University of California, Irvine and currently is Principal Investigator of a project in a five year Conte Center award from the NIMH to examine Brain Programming of Adolescent Vulnerabilities. Professor Sandman has maintained an NIH funded research program for over twenty-eight consecutive years and has published over 300 scientific papers. He has been Principal Investigator for a consecutive series of NIH-supported studies that examined the "programming" effects of stress and activation of the HPA /

placental axis on the human fetus, birth outcomes infant and child development. The findings from Professor Sandman's projects include over 800 mother/fetal/infant/child dyads and have contributed to the growing acceptance that prenatal stress has consequences for neurological development and is a risk factor for poor postnatal outcomes.

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REFERENCES

Adams KM, Nelson JL. Microchimerism - An investigative frontier in autoimmunity and transplantation. Journal of the American Medical Association. 2004; 291:1127–1131. doi: 10.1001/jama.291.9.1127. [PubMed: 14996783]

Andreas T, Wedegartner U, Tchirikov M, Hecher K, Schroder HJ. Fetal brain volume measurements by magnetic resonance imaging. Ultrasound and Obstetrics and Gynecology. 2006; 27:588–589.

Andriessen P, Oetomo SB, Peters C, Vermeulen B, Wijn PFF, Blanco CE. Baroreceptor reflex sensitivity in human neonates: The effect of postmenstrual age. Journal of Physiology. 2005; 568:333–341. [PubMed: 16051623]

Barker, DJ. Mothers, babies and health in later life. Churchill Livingston; Edinburgh, UK: 1998.

Bianchi DW, Zickwolf GK, Weil GJ, Sylvester S, DeMaria MA. Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum. Proceedings of the National Academy of Sciences, USA. 1996; 93:705–708. doi: 10.1073/pnas.93.2.705.

Bonvallet M, Dell P, Hiebel G. Tonal sympathetique et activitie electrique corticale. Electroencephalography and Clinical Neurophysiology. 1954; 6:119–144. [PubMed: 13141926]

Boorse GC, Denver RJ. Acceleration of Ambystoma tigrinum metamorphosis by corticotropin-releasing hormone. Journal of Expimental Zoology. 2002; 293(1):94–98.

Cacioppo JT, Sandman CA. Physiological differentiation of sensory and cognitive tasks as a function of warning, processing demands and reported unpleasantness. Biological Psychology. 1978; 6:181–192. [PubMed: 667241]

Cacioppo JT, Sandman CA, Walker BB. The effects of operant heart-rate conditioning on cognitive elaboration and attitude change. Psychophysiology. 1978; 15:330–338. [PubMed: 693741]

Class QA, Buss C, Davis EP, Gierczak M, Pattillo C, Chicz-DeMet A, Sandman CA. Low levels of corticotrophin-releasing hormone during early pregnancy are associated with precocious maturation of the human fetus. Developmental Neuroscience. 2008; 30:419–426. [PubMed: 19127063]

Denver RJ. Environmental stress as a developmental cue: corticotropin-releasing hormone is a proximate mediator of adaptive phenotypic plasticity in amphibian metamorphosis. Hormones and Behavior. 1997; 31(2):169–179. [PubMed: 9154437]

de Weerth C, Buitelaar JK. Cortisol awakening response in pregnant women. Psychoneuroendocrinology. 2005; 30:902–907. doi: 10.1016/j.psyneuen.2005.05.003. [PubMed: 15970390]

Fukushima, A.; Nakai, K.; Kanasugi, T.; Terata, M.; Sugiyama, T. Comparison of normal pregnancy and intrauterine growth restriction.. Journal of Pregnancy. 2011. http://dx.doi.org/10.1155/2011/218162

Glenn OA. Normal development of the fetal brain by MRI. Seminars in Perinatology. 2009; 33:208–219. [PubMed: 19631082]

Glynn LM, Dunkel-Schetter C, Hobel CJ, Sandman CA. Pattern of perceived stress and anxiety in pregnancy predicts preterm birth. Health Psychology. 2008; 27:43–51. doi: 10.1037/0278-6133.27.1.43. [PubMed: 18230013]

Glynn LM, Sandman CA. Prenatal origins of neurological development: A critical period for fetal and mother. Current Directions in Psychological Science. 2011; 20:384–389. doi: 10.1177/0963721411422056.

Glynn LM, Sandman CA. Evaluation of the association between placental cortiocotrophin-releasing hormone and postpartum depressive symptoms. Psychosomatic Medicine. 74 in press.

Hall JG. The importance of the fetal origins of adult disease for geneticists. Clinical Genetics. 2007; 72:67–73. doi: 10.1111/j.1399-0004.2007.00842.x. [PubMed: 17661809]

Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. Journal of Comparaitve Neurology. 1997; 387:167–78.

Huang H, Wue R, Zhang J, Ren T, Richards LJ, Yarowsky P, Miller MI, Mori S. Anatomical characterization of human fetal brain development with diffusion tensor magnetic resonance imaging. The Journal of Neuroscience. 2009; 29:4263–4273. [PubMed: 19339620]

James, W. Psychology. Henry Holt; New York: 1892.

Kaiser D, Sandman CA. Physiological patterns during complex problem solving during warning and non-warning conditions. Journal of Comparative and Physiological Psychology. 1975; 89:357–363. [PubMed: 1176660]

Kaplan J, Land S. Influence of maternal-fetal histocompatibility and MHC zygosity on maternal microchimerism. Journal of Immunology. 2005; 174:7123–7128. doi: 10.4049/jimmunol.174.11.7123.

Kostovic I, Judas M, Rados M, Hrabac P. Laminar organization of the human fetal cerebrum revealed by histochemical markers and magnetic resonance imaging. Cerebral Cortex. 2002; 12:536–44. [PubMed: 11950771]

Lacey JI7, Lacey BC. The law of initial value in the longitudinal study of autonomic constitution: Reproducibility of autonomic responses and response patterns over a four-year interval. Annals of the New York Academy of Sciences. 1962; 98:1257–1290. 1322–1326. [PubMed: 13927897]

Lacey JI, Lacey BC. Verification and extension of the principle of autonomic response-stereotypy. American Journal of Psychology. 1958; 71:50–73. [PubMed: 13521020]

Lacey JI, Bateman DE, Van Lehn R. Autonomic response specificity: An experimental study. Psychosomatic Medicine. 1953; 15:71–82.

Lacey JI, Lacey BC. Two-way communication between the heart and the brain: Significance of time within the cardiac cycle. American Psychologist. 1978; 33:99–113. [PubMed: 637402]

Lecanuet, J-P.; Granier-Deferre, C.; Busnel, M-C. Human fetal auditory perception.. In: Lecanuet, j-p; Fifer, WP.; Krasnegor, NA.; Smotherman, WP., editors. Fetal Development: A Psychobiological Perspective. Lawrence Erlbaum Associates; Hillsdale, NJ: 1995. p. 239-262.

Levitt P. Structural and functional maturation of the developing primate brain. Journal of Pediatrics. 2003; 143:S35–S45. [PubMed: 14597912]

Lowery CL, Govindan RB, Preissl H, Murphy P, Eswaran H. Fetal neurological assessment using noninvasive magnetoencephalogaphy. Clinical Perinataology. 2009; 36:701–709.

McCanne T, Sandman CA. Instrumental heart rate responses and visual perception: A preliminary study. Psychophysiology. 1974; 11:283–287. [PubMed: 4424062]

McCanne TR, Sandman CA. Operant autonomic conditioning and Rod-and-Frame performance. Journal of Personality and Social Psychology. 1976; 34:821–829. [PubMed: 993982]

Parer JT. Fetal circulation. The Global Llibrary of Women's Medicine and Healthcare. 2014 (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10194.

Porcaro C, Zappasodi F, Barbati G, Salustri C, Pizzella V, Rossini PM, Tecchio F. Fetal auditory responses to external sounds and mother's heart beat: Detection improved by Independent Component Analysis. Brain Research. 2006; 1101:51–58. [PubMed: 16784726]

Sandman, CA. Afferent influences on the cortical evoked response.. In: Coles, M.; Jennings, JR.; Sterns, JA., editors. Psychophysiological Perspectives: Festschrift for Beatrice and John Lacey. Van Nostrand Reinhold Co., Inc.; New York: 1984. p. 242-259.

Sandman C,A, Buss C, Head K, Davis EP. Fetal exposure to maternal depressive symptoms is associated with cortical thickness in late childhood. Biological Psychiatry. Advance online publication. 2014 doi: 10.1016/j.biopsych.2014.06.025.

Sandman, CA.; Class, QA.; Glynn, LM.; Davis, EP. Neurobehavioral disorders and DOHaD.. In: Rosenfeld, C., editor. The Epigeonome and Developmental Origins of Health and Disease. Academic Press; Waltham, Mass.: in press

Sandman CA, Davis EP. Neurobehavioral risk is associated with gestational exposure to stress hormones. Expert Reviews in Endocrinology and Metabolism. 2012; 7:445–459. doi: 10.1586/eem.12.33.

Sandman CA, Davis EP, Buss C, Glynn LM. Exposure to prenatal psychobiological stress exerts programming influences on the mother and her fetus. Neuroendocrinology. 2011a; 95:7–21. doi: 10.1159/000327017. [PubMed: 21494029]

Sandman CA, Davis EP, Buss C, Glynn LM. Prenatal programming of human neurological function. International Journal of Peptides. 2011b; 2011:1–9. doi: 10.1155/2011/837596.

Sandman C,A, Davis EP, Glynn LM. Morrison J. Psychobiological stress and preterm birth. Preterm Birth: Mother and Child. 2012:95–124. doi: 10.5772/27539.

Sandman, CA.; Glynn, LM.; Davis, EP. Neurobehavioral consequences of fetal exposure to gestational stress.. In: Kisilevsky, BS.; Reissland, N., editors. Advancing Research on Fetal Development. Springer; New York, NY: in press

Sandman CA, Glynn L, Wadhwa PD, Chicz-DeMet A, Porto M, Garite T. Maternal HPA disregulation during the third trimester influences human fetal responses. Developmental Neuroscience. 2003; 25:41–49. [PubMed: 12876430]

Sandman CA, McCanne TR, Kaiser DN, Diamond B. Heart rate and cardiac phase influences on visual perception. Journal of Comparative and Physiological Physiology. 1977; 91:189–202.

Sandman C, Wadhwa P, Chicz-DeMet A, Porto M, Garite T. Maternal corticotropin-releasing hormone and habituation in the human fetus. Developmental Psychobiology. 1999; 34:163–173. [PubMed: 10204092]

Sandman CA, Wadhwa PD, Hetrick W, Porto M, Peeke HV. Human fetal heart rate dishabituation between thirty and thirty-two weeks gestation. Child Development. 1997; 68:1031–1040. doi: 10.2307/1132289. [PubMed: 9418223]

Sandman, CA.; Walker, BB.; Berka, C. Influence of afferent cardiovascular feedback on behavior and the cortical evoked potential.. In: Cacioppo, J.; Petty, R., editors. Perspectives on Cardiovascular Psychophysiology. Guilford Press; New York: 1982. p. 189-222.

Schneider U, Schleussner E, Fiedler A, Jaekel S, Liehr M, Haueisen J, Hoyer D. Fetal heart rate variability reveals differential dynamics in the intrauterine development ofthe sympathetic and parasympathetic branches of the autonomic nervous system. Physiological Measurement. 2009; 30:215. doi:10.1088/0967-3334/30/2/008. [PubMed: 19179746]

Takahashi E, Folkerth RD, Galaburda AM, Grant PE. Emerging Cerebral Connectivity in the Human Fetal Brain: An MR Tractography Study. Cerebral Cortex. 2012; 22:455–64. [PubMed: 21670100]

Walker BB, Sandman CA. Human visual evoked responses are related to heart rate. Journal of Comparative and Physiological Psychology. 1979; 93:717–729.

Zhan J, Dinov ID, Li J, Zhang Z, Hobel S, Shi Y, Lin X, Zamanyan A, Feng L, Teng G, Fang F, Tang Y, Zang F, Toga AW, Liu S. Spatial-temporal atlas of human fetal brain development during the early second trimester. Neuroimage. 2013; 15:115–126. [PubMed: 23727529]