

**A Pre-Birth Guide to Personhood: How Genetic, Epigenetic and Developmental  
Milieu Factors Influence Pre-Fertilization, Embryonic, Fetal and Neonatal  
Attributes of Future Individual Humans**

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## **Abstract**

Discrete events and processes influence development of individual future humans. While we do not wish to redefine personhood, we relate a newly discovered epigenetic event to sources of individuality of future humans. Genetic and epigenetic events and developmental milieu processes diversify developmental trajectories of future individual humans prior to societal entry via parturition. First, fertilization and epigenetic resetting of each individual's organismic clock to time zero ( $t=0$ ) at day 15 of embryogenesis, are two discrete discrete biological events that impact a future individual human's attributes. Second, those two discrete discrete biological events are immersed in the continuous developmental process spanning pre-fertilization and gestation, further driving individualization of diverse attributes of each future human before the discrete blatant biological event of parturition (birth) and societal entry. Exposures of the gravida to multiple diverse exogenous exposures means that morphogenesis and physiogenesis of every embryo/fetus has individualized attributes for its future human lifespan.

Keywords: personhood, epigenetics, biological organismic clock, physiogenesis, potential human, future human

## Background

Across human history, by introducing an individual human into society, the discrete, blatant biological event of parturition marked the attribution of and beginning of personhood for that individual human. In recent decades, the concept of personhood has been elaborated and debated in multiple contexts including legal, theological, scientific and philosophical. Notably, discourses relating to the time at which personhood can be attributed to a developing potential or future human have oftentimes reached divergent conclusions (Kerckhove and Waller 1998; White 2013). It is our current contention that both new and well-established scientific insights can provide a framework by which such considerations regarding future human individuality can be better made. In the scientific realm, advances in reproductive technologies across recent decades necessitated carefully considered ethical and scientific assessments and implementation of guidelines for medical and scientific practices (Ethics Advisory Board 1979; Warnock 1984). As scientific knowledge has accumulated about human birth, gestation, implantation, fertilization, gametes, and genetics, the beginning of human personhood has been defined by various endpoints related to each of these biological processes (Warnock 1984). Associated with each such biological endpoint, ethical, legal, theological and social interpretations have been superimposed. Herein we propose that recent epigenetic discoveries disclose a new basis for both a) unique non-genetic individual pre-fertilization attributes to gametes (oocytes and spermatozoa) by heritability of parental epigenetics and more importantly, b) demonstration of a resetting of organismic epigenetic time by a molecular embryonic event at the time of gastrulation/formation of the primitive streak (Kerepesi et al. 2021). It is important to

note that we do not wish to redefine personhood or argue for a specific definition of the term. We are simply presenting our scientific and ethical framework of prepartum human development to highlight how this newly identified biological event should be integrated into future discussions regarding personhood and prenatal acquisition of many attributes of future individual humans.

### **Pre-Societal Determinative Transformational Events for Future Individual Humans**

Many genetic, epigenetic, and developmental milieu effects from pre-conception through birth determine that individual's unique combination of attributes upon societal entry. For our purposes in this paper, we define three terms as follows:

1. Potential human: The stages of human development spanning initial interactions of one female and one male gamete such as the spermatozoa binding to the zona pelucida up to formation of the primitive streak.
2. Future human: The stages of human development spanning the embryo at the primitive streak stage that has undergone resetting of the epigenetic clock through parturition and birth.
3. Physiogenesis: The partner concept to morphogenesis; meaning the acquisition of molecular, cellular, tissue, organ, system and organismic level functions to allow future individual life.

We present our framework that a future human becomes an individual by the overlaying of a complex individualization process onto the three known discrete determinative events, namely fertilization, the novel epigenetic time reset and birth.

A) Although we are arguing that a novel biological parameter that should be considered in assessing personhood for future individual humans is the resetting of the epigenetic clock at approximately Day 15 of embryonic life as recently demonstrated by Kerepesi et al (2021),

B) we also argue that it is insufficient to reflect on determination of personhood by any parameter without also considering the process of pre-societal developmental individualization of future humans. A spectrum of factors influences acquisition of individuality prior to entry into society (birth).

Individualization of attributes occurs both before and after the epigenetic reset of time zero and the acquisition of such attributes may be genetic or non-genetic. There are three discrete events and multiple continual/continuous processes that determine the individual attributes of a future individual human. Across the course of development, becoming an individual is a process, and individualization is, in fact, a summation of all of the developmental determinants that cause or modify the acquisition of biologically definable metabolic, morphologic, behavioral, and reproductive attributes.

### *The Two Discrete Discreet Events of Fertilization and Epigenetic Time Reset*

1. Fertilization and Parental Genetics. It is widely understood that the genetic attributes of each individual are robustly dependent upon parental genomes and that individual diversity within a population is profoundly dependent upon random assortment of alleles and meiotic recombination that had occurred in parental gametogenesis. In the process of recombination, crossing over appears to be essential for correct segregation of homologous chromosomes. In the first meiotic division, there are two major meiotic

recombination pathways that are initiated by DNA double-stranded breaks. The two major recombination pathways are the crossover pathway via formation of chiasmata at metaphase I, and the non-crossover pathway which does not involve formation of chiasmata but can produce “gene conversion” which is effectively a double crossover of a short DNA segment. (Handel and Schimenti 2010)

The key biological consequence of these processes in gametogenesis is diversification of the genomes of progeny. Each array of inherited genes provides combinations that may mimic or diverge from the phenotypic traits of the parents, because most human traits are a product of a non-Mendelian complex interaction of multiple genes. (de Magalhães and Wang 2019)

2. Epigenetics and the Epigenetic Organismic Clock Reset to Time Zero (t=0) on Embryonic day 15. The broad context of epigenetics in human embryonic development is that there is a general “wiping the slate clean” but also a rather modest degree of retention of some parental epigenetic marks (Figure 1). This predominant but incomplete erasure of epigenetic marks has attracted great research interest as well as debate about how important or unimportant epigenetic inheritance may be for any individual (Boskovic and Rando 2018; Heard and Martienssen 2014; Osumi & Tatehana 2021; Soubry et al. 2021; Thompson and Einstein 2010; Tuscher and Day 2019).

As an outgrowth of epigenetics research in the embryo, Kerepesi et al. (2021) have focused on the opportunity to assess temporality of epigenetic events. Their recent publication makes the case that they have characterized the time and event that is THE beginning of aging for each individual mammal. From Kerepesi et al. (2021):

“...we developed a new multi-tissue epigenetic clock using machine learning and applied it, together with other existing aging clocks, to assess prenatal development in mammals from the perspective of aging. This approach uncovered a rejuvenation period during early embryogenesis and the timing of the beginning of aging in mammals. [In the mouse] ...the epigenetic age dynamics showed a clear U-shaped pattern in every case... Organismal aging begins after this rejuvenation event...The observed epigenetic age minimum at E6.5/E7.5 corresponds to gastrulation, the period where the three germ layers are formed...

Our study suggests that the germ line ages but is rejuvenated in the offspring at some point during early embryogenesis. This rejuvenation occurs during early post-implantation stages corresponding to gastrulation when the offspring reaches its minimal biological age. We propose that this minimum, the ground zero, marks the beginning of aging of an organism... The data indicate that ground zero lies between E4.5 and E10.5 in mice, most probably at E6.5/E7.5. This period corresponds to the germ-layer specification (gastrulation) accompanied by the exit from pluripotency...

The beginning of aging is subject to debate. It is often discussed that aging begins after completion of development, at the onset of reproduction, and at the time when strength of natural selection begins to decrease. However, our recent analysis of deleterious age-related changes revealed that aging begins early in life, even before birth (61).

Our current work now pinpoints the beginning of aging to ground zero... Overall, this work identifies a natural rejuvenation event during early life and suggests that

organismal aging begins during embryogenesis, approximately at the time of gastrulation."

*Diverse Developmental Milieu Factors Influence Pre-Fertilization, Embryonic and Fetal Attributes of Future Individual Humans*

The range of potential cell types during human *in utero* development that might be affected by exogenous factors are not yet fully elucidated, but there is a global effort underway to do precisely that; namely, to create a comprehensive reference map of cells during development (Haniffa et al 2021). Even though the precise identity of cellular targets during development are not fully known, stochastic environmental and intrauterine milieu factors are known to impact the developmental trajectory of future humans (Thompson and Einstein 2010; Skogen and Overland 2012). Considerations of such effects in individual humans fall within a number of scientific and medical disciplines, but no matter the exposure-outcome scenario or any assessed need for therapeutic interventions (Hughes et al 2016), the core concepts such as growth and differentiation are basic biology. The conceptual challenge in development with or without exogenous perturbations is to formalize how emergent properties arise via dynamic interactions at both higher and lower levels of biological organization. Such theoretical and analytical network modeling research is occurring (Cavigelli et al 2021), with, for example, more than 100 studies currently underway under the auspices of the National Institutes of Health MultiScale Modeling Consortium (<https://www.nibib.nih.gov/research-funding/interagency-modeling-and-analysis-group-imag>).



Structure and function are inextricably intertwined in all of biology, and development is the sequential process by which the integration of morphology and physiology in a future organism advance and may permit that individual organism to attain life.

Disruptions of development occur and there is a long history of scientific study of such variations from the normative patterns. Specifically, the scientific discipline of teratology was historically rooted in morphogenesis and disorders thereof, and we assert that the later broader term of developmental toxicology had helped add dynamic integrated elements that we herein call “physiogenesis” as its *sine qua nom*, as it focuses on how exposures to various physical, chemical, biological and social factors may adversely affect the health and functional well-being of an individual human.

While teratology/developmental toxicology research primarily seeks to understand adverse effects of the many exposures that inevitably occur during development of an individual human, it is widely acknowledged that many exposures will either have healthful effects or have no plausible impact on the future well-being of that individual human. Thus, we offer an inverse view that taken *in toto*, whether adverse, salutary or neutral, the effects of diverse developmental exposures alter the developmental trajectories of each future individual human and consequently provide countless patterns of individualization of all future humans (Figure 2).

After implantation, the fetal environment and the fetal developmental trajectory is obviously dependent upon maternal metabolism (nutritional adequacy, excesses or inadequacies), intentional exposures (dietary choices, personal habits, substance use or abuse, etc.), environmental/unintentional exposures (physical, chemical or infectious agents and familial and socioeconomic stressors), as well as maternal pre-pregnancy

comorbid diseases and obstetrical disorders such as gestational diabetes, preterm labor, and early or late onset preeclampsia. All of these factors (see Hughes & Waters 2016, multi-authored chapters 3-10) may influence fetal development and thereby nudge the fetus along a different developmental path than is followed by others. Once again, each of these types of exposure during development modify that future human and diversifies the spectrum of persons who later enter society at parturition.

There are a number of classes of exposures that are well-known to affect human development prior to birth. Some of these prenatal exposures are quite specific such as drugs prescribed to pregnant women to treat an underlying disease (Bastow et al 2017; Dutta 2015); while others are generalized such as inhaled fine to ultrafine particulates that appear to adversely affect infants' respiratory and immune systems, brain development, and cardiometabolic health (Johnson et al 2021). Additionally, there are many exposures that are not proven with certainty to affect human prenatal development but are widely thought to be probable or possible human teratogens/developmental toxicants. The following are brief profiles of the key classes of such developmentally influential agents.

Mutagens. All humans are exposed to mutagens (American Cancer Society 2021) including oxidative stress, ionizing radiation, naturally occurring compounds such as mycotoxins as well as environmental contaminants and pharmaceutical agents. Exposures to mutagens and consequent stochastic mutagenic effects (Verheyen, van Deun, and van Miert 2017) during the stages of parental gametes, zygote, embryo and fetal intervals are a source of *de novo* mutations that are acquired differences in an individual's genome. These individualization effects are dependent upon the several

characteristics of the exposure such as the compound or compounds, the dose, the duration, the timing during developmentally sensitive windows, and the individual's or maternal genetics that may modify resistance to or susceptibility to the effects of mutagens in various tissues and organ systems.

Prior to fertilization, the individuality of a potential human derives from the genetic diversity among the oocytes and spermatozoa that were produced by the potential parents. Obviously, the genetics of the potential mother and father are profoundly important in determining spectrum of individual possibilities for that potential human. Another source of individuality can derive from the age of the parents, particularly the father. The reasoning is that the prolonged decades of sperm production offer more opportunities for de novo mutations to occur and be present in spermatozoa that may participate in fertilization of an oocyte (As reviewed by Osumi & Tatehana 2021). From Coorens et al (2021):

“From fertilization onwards, cells of the human body continuously experience genomic damage, either from intrinsic causes or exogenous exposure to mutagens. Although almost all DNA damage is repaired and the genome is replicated with extremely high fidelity, cells steadily acquire somatic mutations throughout life. Some mutations that are present in a cell are shared with other cells. Because identical mutations rarely happen by chance, shared mutations often indicate a shared developmental history. Once gained, mutations are rarely lost. Thus, past developmental relationships from embryonic, fetal, childhood and adult phases of life can be identified from mutations in adult cells...This research exemplifies somatic mutations as lineage tracing markers of human development. By

constructing phylogenies from many normal tissue samples, it is possible to deduce the life history of a cell from its inception as a zygote, through embryogenesis and early development to its final destination as a differentiated adult cell... This research demonstrates the variability of human embryogenesis in the shaping of different lineages and tissues through developmental bottlenecks. Understanding patterns of normal human development can contextualize disorders of development, especially when caused by post-zygotic genomic aberrations, such as early drivers of childhood cancers or mosaic overgrowth syndromes. Further studies using somatic mutations as natural lineage markers may help to address fundamental questions of human ontogeny.”

Non-Mutagens. Some chemical exposures are intentional such as use of medicinal drugs or substances that are recreational or addictive that may be legal or illicit. Maternal exposures to these classes of compounds, particularly during pregnancy, are known in many instances to produce adverse effects on the embryo or fetus. Less clear-cut but potentially quite important are exposures to these classes of bioactive chemicals of either parent prior to or during gametogenesis, fertilization, implantation and embryonic stages of development.

Since it is widely reported that only about one half of all pregnancies are planned, a vast majority of women take at least one prescription drug during pregnancy, and approximately two thirds take a medicinal drug of some sort during the first trimester, there are numerous pharmaceutical drugs that have been reported to cause birth defects when exposures occurred *in utero* (Bastow et al 2017; Capra et al 2013; Dutta 2015). Even for common over-the-counter medications such as those containing

acetaminophen (paracetamol), there is justification for considering that fetal developmental effects on neurological, reproductive and urogenital systems may occur (Bauer et al 2021). It is worth noting that the terminology used to describe associations of developmental effects in the setting of maternal use of medicinal drugs may seem somewhat tentative and focused primarily on more prominent effects typically called birth defects. Some uncertainty about associating prescription or over-the-counter medication use with developmental effects is valid because the mother typically has an active disease or undiagnosed signs and symptoms, any of which may present certain risks *per se* to the fetus; then the usage of a drug is superimposed in that setting. Nonetheless, regulatory authorities require manufacturers to report such adverse events through safety reporting systems and such data demonstrate to some extent the potentialities for effects in the offspring.

The other prominent class of voluntary chemical exposures that could impact development *in utero* or during lactation are recreational or addictive substances. As noted currently by the U.S. National Institute on Drug Abuse (2021), these include marijuana (cannabis), stimulants (cocaine and methamphetamine), MDMA (3,4-Methylenedioxymethamphetamine, Ecstasy, Molly), opioids (heroin, diverted prescription opiates), alcohol (ethanol) and nicotine (tobacco products and e-cigarettes). The scientific literature demonstrating the impact of these classes of exposures and the broad range of developmental effects is truly massive (NIDA 2021) and unequivocal. Less certain but of potential significance is the suggestive evidence from a number of research reports showing that exposures that precede the fetal interval may pose an

explicit morphogenic developmental risk or have a physiogenic effect that only manifests in the offspring long after birth. We shall cite one of each for illustration.

First, in a recent meta-analysis, Zhang et al (2019) studied the relationship between parental alcohol exposure and risk of congenital heart disease (CHD) in their offspring. In the pooling of data from more than 50 studies with >40,000 CHD cases and >290,000 controls, there was the expected finding of an increased risk with maternal alcohol exposures (odds ratio (OR) = 1.16; 95% confidence interval (CI): 1.05–1.27) but also with paternal (OR = 1.44; 95% CI: 1.19–1.74) alcohol exposures. To the best of our knowledge, the molecular or cellular mechanisms underlying this reported risk are unknown.

Second, Northstone et al (2014) used the Avon Longitudinal Study of Parents and Children's questionnaire data on smoking and smoking onset from >9800 fathers and the data regarding growth of their children from 7–17 years. In brief, after adjusting for potential confounders, the investigators found that for the men who reported regular smoking at <11 years of age, the adjusted mean differences in BMI, waist circumference and total fat mass in their sons were significantly greater from age 13 years onwards. From the concept that "Smoking by boys in mid childhood may contribute to obesity in adolescent boys of the next generation." Northstone et al 2014), Hammer et al (2021) recently reported data from their work in an animal (mouse) model offering a degree of mechanistic explanation for non-genomic transmission of such observations about paternal physiogenic effects on their offspring as follows: "miRNAs in the plasma microenvironment of spermatozoa may represent a mechanism for transmittable epigenetic changes to offspring and development of metabolic or

respiratory diseases, further highlighting paternal smoking as potential risk factor for offspring's health." These data strengthen the idea that tobacco smoking by human male teenagers increases the risk of overweight and obesity in their male offspring.

Another group of embryonic/fetal exposures is parental diseases. Numerous chronic or recurrent diseases occur in women who become pregnant, sustain the pregnancy, and undergo labor and delivery. The range of such concurrent illnesses that could potentially impact growth and development of each future human was demonstrated by Jolving et al (2016) in their nationwide (Denmark) registry-based cohort study that included all women who gave birth (> 1.3 million) between 1989 and 2013. These investigators specified 23 maternal chronic diseases within the decade preceding childbirth. While noting that the overall prevalence of maternal chronic disease increased from 3.71% in 1989 to 15.76% in 2013, the ten most prevalent diseases during pregnancy were chronic lung disease/asthma (1.73%), thyroid disorders (1.50%), anxiety and personality disorders (1.33%), mood disorders (0.74%), epilepsy (0.69%), inflammatory bowel diseases (0.67%), polycystic ovarian syndrome (0.52%), diabetes mellitus (0.48%), hypertension (0.43%) and rheumatoid arthritis (0.38%).

While much remains unknown about the potential impacts of many such comorbid conditions on a fetus during gestation, several maternal diseases that frequently occur during pregnancy are known to impact fetal development, oftentimes posing risks to normal *in utero* growth and development. To the extent that potential fetal developmental effects of medications used to treat such diseases can be assessed and set aside, there are still clear attributable risks to the fetus if the gravida has one or more comorbid diseases. Such demonstrated risks include fetal growth (small for

gestational age/low birth weights or high birth weights) but also metabolic and neurocognitive effects in the neonate and the child. For example, associations of maternal comorbidities during pregnancy and perinatal and childhood outcomes include (Capra et al 2013; Lahti-Pulkkinen et al 2020) the following:

- Maternal depression with low birth weight infant and later central adiposity in the child;
- Maternal diabetes (type 1, type 2 or gestational), hyperglycemia or obesity with high birth weight infant and later metabolic syndrome and obesity in the child;
- Maternal overweight/obesity with higher likelihood of autism spectrum disorders or neurodevelopmental delays;
- Maternal asthma (with exacerbations) with increased risk of preterm delivery and low birth weight infant (particularly in males);
- Maternal sleep deprivation and sleep-related breathing disorders with low birth weight infant (small for gestational age) and a higher risk of mortality;
- Maternal anemia with low birth weight infant (intrauterine growth retardation) and increased risk of preterm delivery; and
- Maternal hypertensive disorders of pregnancy (gestational and chronic hypertension, preeclampsia) with higher likelihood of childhood mental disorders.

While it may seem intuitive that maternal diseases during pregnancy could logically impact outcomes of her infant, some data show that paternal health also influences the health of his infant. It is reasonable to suppose that the father's health could be a genetic precursor of sorts for his infant or that cohabitation of the two parents might lead to predisposing environmental effects on their offspring. However, at least some



interesting correlations that may be causations were suggested by Kasman et al (2020) in their inquiry about whether prepartum and neonatal outcomes are associated with pre-existing paternal health factors. In this retrospective cohort study in the United States of children born between 2009-2016, paternal health status as reflected in diagnoses of various chronic diseases was compared to the primary outcome of preterm birth (meaning live birth before 37 weeks), as well as several secondary outcomes including low birth weight, neonatal intensive care unit (NICU) stay, gestational diabetes, preeclampsia, eclampsia, and length of maternal stay. By use of a research database covering reimbursed health care claims data on inpatient and outpatient encounters through employment-sponsored health insurance, the investigators assessed 785,809 singleton live births, with 6.6% born preterm. Kasman et al (2020) reported “The presence of paternal comorbidities was associated with higher odds of preterm birth, low birth weight (LBW), and NICU stay. After adjusting for maternal factors, fathers with most or all components of the metabolic syndrome had 19% higher odds of having a child born preterm (95% CI 1.11–1.28), 23% higher odds of LBW (95% CI 1.01–1.51), and 28% higher odds of NICU stay (95% CI 1.08–1.52). Maternal morbidity (e.g., gestational diabetes or preeclampsia) was also positively associated with preconception paternal health.” These findings suggest but do not causally establish that preconception paternal comorbidities may modestly influence obstetrical and neonatal outcomes.

In addition to those parental disease and drugs exposures, the future human is subject to numerous other chemical, social, stochastic obstetrical and microbiological exposures that are known or suspected to impact human embryonic/fetal development.

It is not possible to fully review all of these embryonic/fetal exposures compounds in this document, but we will describe a few notable classes.

There are hundreds of naturally-occurring and man-made compounds that have been demonstrated to be present in either amniotic fluid (Foster et al 2000; Foster et al 2002; Hughes et al 2001) or umbilical cord blood (Wang et al 2021), raising the reasonable prospect that at least some of them may influence development.

One prominent group of compounds has been named “endocrine-disrupting chemicals” (EDCs) which means “an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action” (Endocrine Society 2018). There is now broad agreement but not consensus that “Individuals and populations are exposed to EDCs, and common non-communicable diseases have been associated with environmentally-relevant doses of EDCs in human epidemiological studies...It is now well established that developmental exposure to EDCs can alter the epigenome of offspring, affecting gene expression and organogenesis, thereby altering an organism’s sensitivity to disease later in life.(Endocrine Society 2018).” More recent research into the potential neurodevelopmental effects of EDCs (Lopez-Rodriguez et al 2021), suggest that some effects may include alterations in brain development that advance or delay puberty or alter neuroendocrine control of reproduction thus impairing fertility. Various data suggest that neurodevelopmental effects of EDCs may occur via action on steroidal and non-steroidal receptors but also via alterations in enzymatic, metabolic and epigenetic and other cellular pathways during development (Lopez-Rodriguez et al 2021). It may be possible to link such mechanistic complexity of EDC actions to various individual neuropsychiatric outcomes by use of network analysis tools. In an upcoming

paper, Raja et al (2022) report that such an analysis seems to show that genes, receptors and signaling pathways interact as a consequence of exposures to EDCs and in turn are associated with disorders such as major depression, alcoholism, psychotic disorders, autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), cerebral palsy, and sex-specific aggressive and emotional behavior.

In addition to those parental disease and drugs and environmental chemical exposures, maternal environmental stressors (natural disasters; famine, social stressors) also influence development of her offspring.

Tragic large-scale disasters have served as natural (or man-made) experiments wherein many pregnant women were exposed to various forms of deprivation or other stressors, and subsequent assessments of their offspring have shown a number of important health effects.

One such well-recognized event was the Dutch famine of 1944-1945. Even now, decades later, additional reports are being published that demonstrate the life-long persistence of the *in utero* developmental effect(s) that occurred. Lumey et al (2021) analyzed the heights and weights of 371,100 men in the Netherlands when they were examined for military service at age 19 years. The men born between 1943 and 1947 either did or did not experience prenatal exposure to the Dutch famine. These investigators found that there was an overall 1.3-fold increase in the risk of being overweight or obese at age 19 after prenatal famine exposure in early gestation, and the attendant 30% increase in overall mortality through age 63 relative to those with a normal BMI.

A second such large-scale disaster was the 1998 Quebec Ice Storm. Within the last few years, Paxman et al (2018) sought to gain some mechanistic insights into the physiological phenotypes seen in the population exposed *in utero* by use of proton nuclear magnetic resonance spectroscopy to analyze urinary metabolomes of male and female adolescents. Overall these investigators found that higher prenatal stress exposure led to alterations in metabolic pathways involved in energy metabolism and protein biosynthesis; findings that are consistent with dysregulation of energy and protein metabolism as would be expected in insulin resistance, diabetes, and obesity. Finally, a third such event was the Great Tangshan Earthquake (China) in 1976. In this instance, another recent study by Guo et al (2019) assessed data from >94,000 Chinese individuals born between 1975 and 1979. The investigators studied the relationship between the occurrence of schizophrenia (diagnosed by psychiatrists) and earthquake severity by seismic intensity. In brief, in comparison to an unexposed cohort, the cohort exposed to the earthquake *in utero* had higher risk of schizophrenia (odds ratio, 3.38; 95% CI 1.43–8.00). Notably, when assessed by the trimester of pregnancy in which exposure occurred, earthquake exposure during the first trimester of pregnancy showed a further increased risk of adulthood schizophrenia (odds ratio, 7.45; 95% CI 2.83–19.59).

Though such disasters illustrate the impact that external factors may have on development, societal elements that broadly affect many more individual future humans are embedded in the concept of socio-economic status (SES) as a summary of the availability of material and social resources to any individual. Childhood SES is one of

the strongest predictors of lifelong well-being and appears to be associated with the duration and functional complexity of individual brain development (Tooley et al 2021). The cellular and molecular mechanisms that mediate such effects of SES or other social factors such as familial adversity are not fully understood, but epigenetics appear to play an important role (Tremblay et al 2016; Tremblay et al 2018). As noted by Tremblay et al (2016);

“...there is now emerging evidence that early social-familial adversity leads to long lasting epigenetic alterations. These alterations may influence brain development, and, consequently, the ability to learn to regulate and control aggressive behaviour...In addition, the finding that many of these biological factors involved in chronic physical aggression develop very early (i.e., before birth), highlights the need to not only study the impact of the early postnatal environment on physical aggression, but also to take into account what is happening between conception and birth.”

“Indeed, a number of studies have now identified perinatal risk factors for a wide variety of behavioral problems (e.g., hyperactivity, opposition, rule breaking) that are highly related to maternal characteristics and maternal behavior during pregnancy. The effects of the perinatal environment on gene expression is presently the most interesting hypothesis. However, the reader needs to realize that we are only starting to explore this avenue.”

“The benefits of prevention starting as close as possible to conception seems obvious. If the earlier the risks the more widespread the negative effects, then the corollary is the earlier the preventive intervention the more widespread the benefits.

The later we intervene, the less chance we have to impact the basic weaknesses of the organism...Preventive interventions should help at risk pregnant women live a life style that will facilitate 'normal' gene expression.”

Yet another variable that impacts development of some individual future humans is what we have called stochastic obstetrical factors. The uterine microenvironment may be modified by any of the exposures described above, but there are occasional other presumably random events related to location and qualitative aspects of implantation and thus placentation *per se*. For example, if random implantation occurs over an underlying uterine leiomyoma (fibroid), then as the pregnancy progresses, that fetus may be subject to reduced placental perfusion or placental abruption events that could impact growth in utero, lead to premature delivery or pose a risk of hemorrhagic compromise or even stillbirth. Another variable that may be random or iatrogenic as part of infertility therapies is twinning, or higher multiple birth.

#### Fetal and Maternal Microbiomes.

New scientific discoveries demonstrate the impact of fetal and maternal microbiomes on prenatal development and perinatal outcomes.

- 1) There is a fetal microbiome. New data show that *in utero*, as early as the second trimester, there are live microbes in healthy human fetal tissues (Mishra et al 2021); and
- 2) The maternal vaginal microbiome influences the risk of preterm birth (Flaviani et al 2021).

The long-held “sterile womb” dogma has been fading as evidence for an *in utero* colonization hypothesis had become more substantiated (Perez-Muñoz, et al 2017).

New data show that fetal immunological development *in utero* at least in part depends upon prepartum exposure of each fetus to microbes; from (Mishra et al (2021):

"The events occurring during fetal gestation are essential for the overall development and growth of the individual. Key factors transferred from the mother to the fetus during this process establish the cornerstones of early life immunity and life-long tolerance. Various studies have recently suggested that certain antigens as well as bacterial entities may cross the placental barrier and make their way to fetal organs... All these observations open a new avenue in developmental immune-priming wherein maternal-derived microbial entities may condition the progeny toward future antigenic exposures in life.

Our findings demonstrate that healthy human fetal tissues (in the 2nd trimester of gestation) contain effector T cells, a sparse biomass of bacteria, and an active memory T cell response toward fetal bacteria. We also demonstrate direct spatial localization of bacterial entities, localized within the lumen of developing fetal gut, during the 2nd trimester of gestation. These data are in line with recent studies that indicated antigenic priming of the fetal immune system begins during gestation...However, our study demonstrates for the first time that such microbial presence primes the fetal immune system, thereby putting early microbial memory in the context of fetal immune priming, a concept not explored before in fetal immunity...Taken together, these findings have wider implications in understanding the key factors involved in fetal immune system development and priming in utero, which may set the basis for life-long health and immunity of the organism...the existence of a spatially diverse microbial signal in fetal tissues, their ability to

culture-expand anaerobically, and the presence of microbial antigen-specific memory T cell activation, are difficult to reconcile with either systematic biases or random noise. Collectively, our data suggest a low but consistent presence of microbes in at least some of the healthy human fetuses in the 2nd trimester of gestation."

While there is wide acceptance in obstetrics that vaginal organisms may contribute to ascending infections that produce chorioamnionitis and preterm labor and deliveries, new data show that even in the absence of intrauterine infections, the maternal vaginal microbiome influences the risk of preterm birth (Flaviani et al 2021). In their study of spontaneous preterm birth, Flaviani et al (2021) studied the interactions between the cervicovaginal metabolic environment and microbiota in tandem with the host innate immune response in a prospective United Kingdom (UK) longitudinal cohort of pregnant women. Analysis of cervicovaginal samples (10–15+6 weeks) identified potentially novel interactions between risk of spontaneous preterm birth (sPTB) and microbiota, metabolite, and maternal host defense molecules in an ethnically heterogeneous pregnant population (n = 346 women; n = 60 sPTB < 37 weeks' gestation, including n = 27 sPTB < 34 weeks).

These findings indicate that the maternal microbiome may poise a pregnancy to either be more likely to go to term, or to deliver prematurely and thereby impact an individual neonate and modify its post-natal developmental trajectory and oftentimes compromise one or more of its life-long functional outcomes.

All of these sources of developmental diversification of individual future persons that spans the time and events from maternal and paternal gametogenesis across pre-



fertilization, fertilization, implantation and embryonic and fetal development up to the time of parturition provide the background continual process that defines the characteristics of each future human prior to the discrete event of birth.

### *The One Discrete Blatant Event of Parturition*

#### 3. Birth and Societal Entry.

The event that introduces a human into society is parturition, and this process presents its own set of challenges that may make a penultimate impact on the developmental outcome of the neonate. For the fetus, several maternal medical and obstetrical risk factors pose risks that may influence the infant's lifelong health and functional status in diverse ways.

In High Income Countries (HIC), some of the common maternal factors at the time of parturition that impact the neonate are hypertensive disorders of pregnancy (including preeclampsia), age, weight status, diabetes (pre-existing or gestational), substance use, depression, breech presentation and previous Cesarean birth(s) (Scrimshaw and Backes 2020). Additionally, among the most dangerous obstetrical complications during labor and delivery for the fetus are uterine rupture, shoulder dystocia, umbilical cord prolapse, chorioamnionitis and fetal macrosomia.

In Low and Middle Income Countries (LMIC), the recent study by Baguiya et al (2021) show the devastating impact of maternal pre-existing conditions and suspected or confirmed infections on neonatal outcomes. This multinational team of investigators conducted a study in 2017 in 408 hospitals in 43 LMIC in all WHO regions. Women (n=1219) with suspected or confirmed infection during pregnancy at 28 weeks or more

of gestational age were followed, along with their infants, up to day 7 postpartum. Neonatal Near Miss (NNM) cases were defined by the criteria of birthweight <1750 grams, gestational age at birth between 28 and 33 weeks, 5 min APGAR score <7, or use of any of several acute interventions (e.g., parenteral antibiotics, ventilation support, Intubation at birth or other medical or surgical interventions). These investigators reported neonatal outcomes to be

- 1) 64% (n=780) babies alive without severe complications,
- 2) 25.9% (n=316) were NNM cases and
- 3) 10.1% (n=123) perinatal death (stillbirth and early neonatal death);

and commented "Overall, one-third of births were adverse perinatal outcomes. Pre-existing maternal medical conditions and severe infection-related maternal outcomes were the main risk factors of adverse perinatal outcomes."

In multiple ways, whether births occur in HIC or LMIC, any of these peripartum risks may impact the fetus/neonate by causing cerebral palsy, Erb's palsy, hypoxic ischemic encephalopathy ("HIE") (perinatal asphyxia), cerebral hemorrhages, hematomas or periventricular leukomalacia ("PVL") as seen in premature infants. If PVL (which can lead to cerebral palsy or epilepsy) is seen as an overt consequence of premature birth, there is strong evidence of more subtle central nervous system developmental effects as well, since a recent study in a cohort of >4 million persons found that preterm and early term birth were associated with significantly increased risks of autism in boys and girls (Crump, Sundquist and Sundquist 2021).

All of these diverse, mostly adverse, effects change the life-long trajectories of countless humans in multiple individualized ways.

## **How Do Medical and Scientific Research Guidances Relate to Our Scientific and Ethical Framework of Prepartum Human Development?**

In historical terms, as human *in vitro* fertilization procedures were developed and procedures were regularized in this area of medicine, reviews were conducted by multi-disciplinary committees that provided insightful considerations from many diverse perspectives. Two leading examples were those published in the United States (Ethics Advisory Board 1979) and the United Kingdom (Warnock 1984). While the US panel's report provided careful evaluative remarks on "The Status of the Early Human Embryo" (pages 27-33 and 48-51 in Ethics Advisory Board 1979), the UK panel's report, widely called "The Warnock Report" also made careful evaluative remarks (pages 60-72 in Warnock for the Committee 1984) and proposed that human embryos should not be sustained *in vitro* for more than fourteen days for any purpose. In some jurisdictions (such as the UK), this proposal became law, and in virtually all portions of the globe, this interval became the explicit or *de facto* guidance for all clinics and laboratories that participated in human *in vitro* fertilization clinical practice and/or research.

Over the subsequent decades, there have been countless discussions about the "14-day rule;" however, only recently has a pertinent professional scientific society taken the step of formally changing their position. Specifically, in May 2021 the International Society for Stem Cell Research (International Society for Stem Cell Research 2021), issued their "Guidelines for Stem Cell Research and Clinical Translation" and included on page 12 their argument for changing and support for ending the 14 days post-fertilization restriction. As expected, this new position has evoked great interest and

commentary among many medical and scientific professionals (Powell 2021; Sawai et al 2021). We hope that no matter the perspective of any person or the position of any organization engaged in this renewed discourse about the “14 day rule,” each will duly consider the framework we are presenting herein as they formulate their new or renewed points-of-view.

## **Summary and Conclusions**

As modern scientific discoveries have revealed demonstrable facts about additional biological processes and events prior to birth, scientific and ethical considerations are pertinent to assess any other discrete or continuing components that contribute to individualization before the societal entry of an individual human by birth. While we do not attempt to redefine personhood or argue for a specific definition of the term, we highlight a newly discovered novel biological event, its role in the developmental trajectory of future individual humans and its relevance to discussions regarding the diverse sources of individuality of future humans. We present the genetic, epigenetic and developmental milieu events and processes that, when combined, produce the distinguishing features of a human prior to its entry into society via birth. Accordingly, we present the novel argument that A) there are now two known discrete discreet biological events that are pertinent to determining a future individual’s identity; namely, fertilization and the additional discrete biological event of epigenetic resetting of that individual’s biological organismic clock to time zero ( $t=0$ ) around day 15 of embryogenesis and B) those two discrete discreet biological events are immersed in a continual complex developmental process that spans pre-fertilization and gestational intervals that drives individualization of diverse attributes of each future individual

human preceding the discrete blatant biological event of birth and societal entry of that human. During prenatal development, each future human is subject to various and variable exposures of the gravida to multiple physical, chemical, biological and social factors as well as to its own unique maternal *in utero* environment. These diverse exogenous exposures of every embryo/fetus influence its morphogenesis and physiogenesis thereby individualizing its future attributes, health and functional well-being across its individual human lifespan within society.

### **Author Contributions**

C.L.H. and G.C.H. jointly conceived the key concepts. C.L.H. researched the literature and wrote and edited the manuscript. G.C.H. reviewed the literature and wrote and edited the manuscript. C.L.H. is the guarantor of this work and, as such, had full access to all the cited literature including the published data, and takes responsibility for the integrity of the information presented. Both authors read and approved the final manuscript. Both authors declare that they have no competing interests.

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**Figure 1**

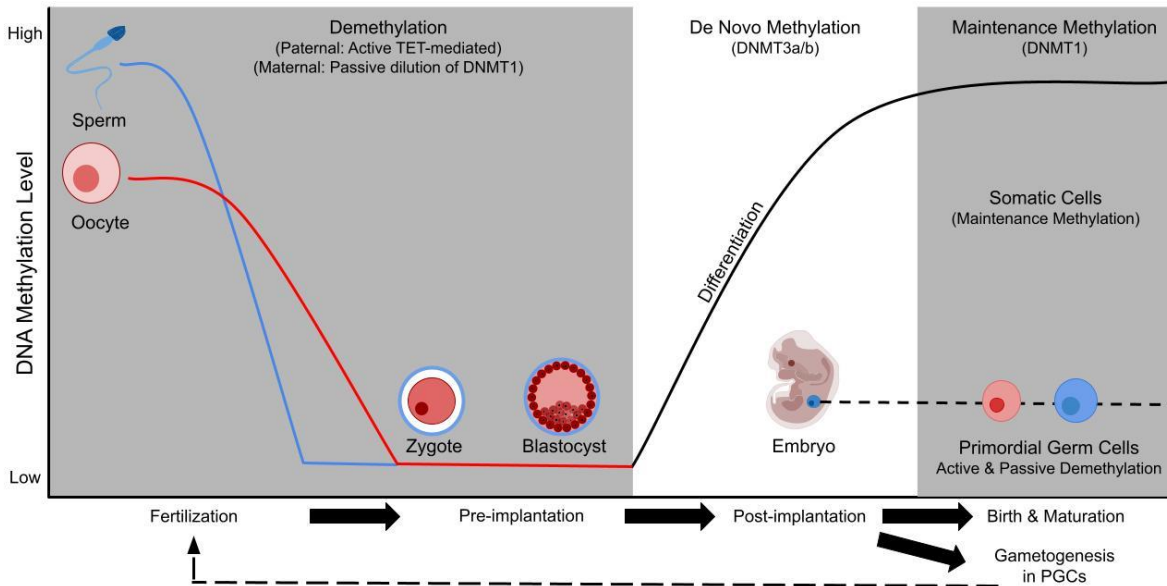


Fig. 1 Changes in the Important Epigenetic Mechanism known as DNA Methylation. The DNA in parental gametes has many attached methyl groups. Soon after fertilization, the vast majority but not all of those pre-existing methylation "marks" on the DNA are removed. In the zygote, there are specific demethylation mechanisms that produce the major first wave of reprogramming of the epigenome. Soon after implantation, the newly reported event of resetting of the epigenetic organismic clock to "time zero" (Kerepesi et

al. 2021) occurs at about embryonic day 15, and then DNA re-methylation accelerates in association with rapid differentiation of the embryo. Thereafter, differentiated somatic cells in the embryo, fetus and infant have particular DNA methylation patterns that seem to mostly be sustained across the rest of the individual's lifespan. (Redrawn from Tuscher and Day 2019).

**Figure 2**

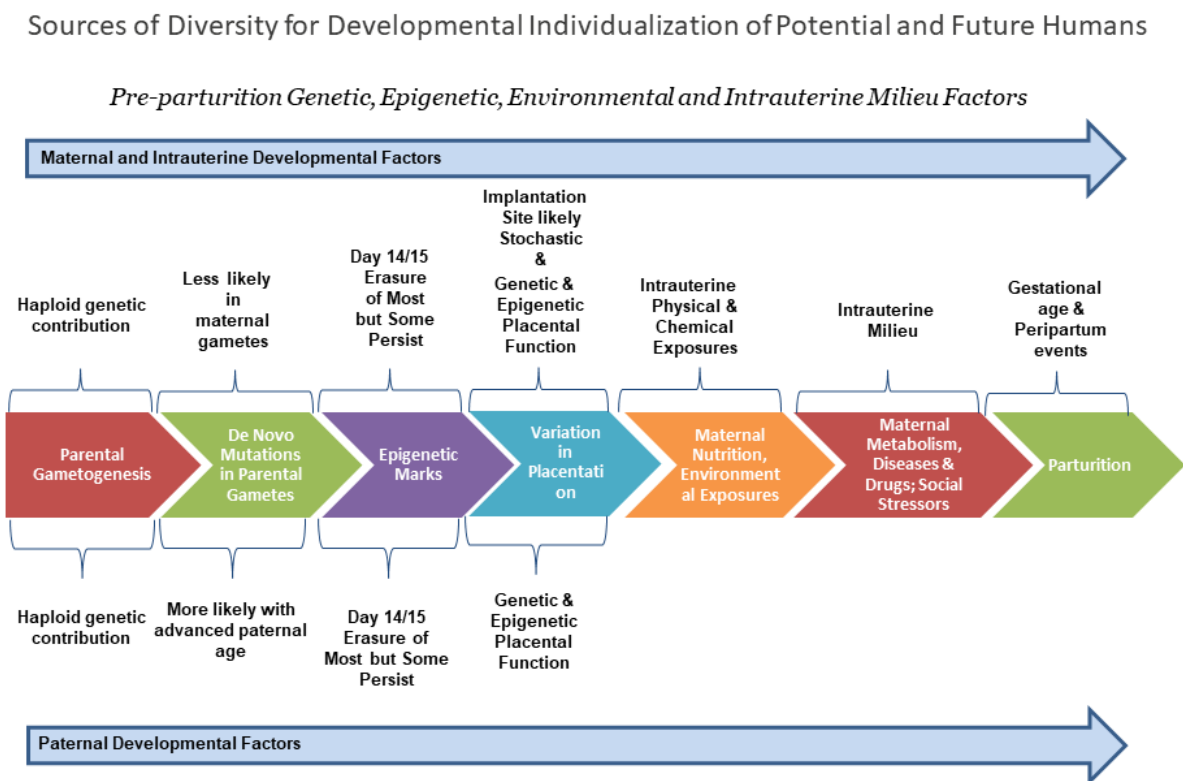


Fig. 2 Sources of Diversity for Developmental Individualization of Potential and Future Humans. Pre-societal continuous individualization for a future individual human spans the other discrete events and encompasses multiple exogenous factors. Along the timeline of individual prenatal development, known paternal developmental influences

are more clustered in earlier stages, while maternal and intrauterine developmental influences rather obviously continue up through completion of parturition.