

Review

The Completed Self: An Immunological View of the Human-Microbiome Superorganism and Risk of Chronic Diseases

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Abstract: In this review, we discuss an immunological-driven sign termed the *Completed Self*, which is related to a holistic determination of health vs. disease. This sign (human plus commensal microbiota) forms the human superorganism. The worldwide emergence of an epidemic of chronic diseases has caused increased healthcare costs, increased premature mortality and reduced quality of life for a majority of the world's population. In addition, it has raised questions concerning the interactions between humans and their environment and potential imbalances. Misregulated inflammation, a host defense-homeostasis disorder, appears to be a key biomarker connecting a majority of chronic diseases. We consider the apparent contributors to this disorder that promote a web of interlinked comorbid conditions. Three key events are suggested to play a role: (1) altered epigenetic programming (AEP) that may span multiple generations, (2) developmental immunotoxicity (DIT), and (3) failure to adequately incorporate commensal microbes as a newborn (*i.e.*, the incomplete self). We discuss how these three events can combine to determine whether the human superorganism is able to adequately and completely form during early childhood. We also discuss how corruption of this event can affect the risk of later-life diseases.

Keywords: chronic diseases; inflammation; patterns of comorbidities; developmental immunotoxicity; commensal bacteria; microbiome; superorganism; biosemiotics; sign; mucosal tissues

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1. Introduction

In this review of early-life development and its impact on health *vs.* disease, we present the tenet that the newborn human naturally engages in an immunologically-permitted merger with designated parts of the environment. This merger reflects where the infant has been both genetically and epigenetically and where the infant will be going in terms of a future health trajectory. The infant-environment merger also represents a significant biological sign. An effective merger provides for an optimized interaction between the environmentally-enhanced infant and the outside world. In contrast, corruption of this merger results in a life course of increased risk of disease. Much of this review will discuss the nature of this merger as a biological sign and how this key event affects the definition of immunologically-defined self, biological integrity and risk of later-life disorder and disease.

1.1. Signs, Biomarkers, and Health Outcomes

In the search for one or more signs that represent a crossroads of health *vs.* disorder and disease, we searched for a significant human health risk/benefit and a defining biomarker connected to this health outcome. This led us to focus on the health risk of chronic noncommunicable diseases (NCDs). We then identified the functional biomarker (*i.e.*, useful frame of reference) most closely affecting chronic diseases. In this case, the biomarker that most consistently connects the individual to chronic diseases is: misregulated inflammation [1–4]. The importance of misregulated inflammation as a frame of reference is further supported by the focus of Davidson and Seneff [5] in their review article appearing in this same special issue on biosemiotics. Effectively regulated inflammation in tissues is connected to effective host defense and good health, while misregulated inflammation leads to pathology and chronic disease. We then searched for one or more signs that connect regulated *vs.* misregulated inflammation to health *vs.* chronic disease employing immune system-based surveillance as a framework, since it has been previously employed for similar purposes [6].

Our initial focus was on signs connected to proper *vs.* misregulated inflammation focusing on developmental immunotoxicity and epigenetic programming. However, it became apparent that using a different frame of reference would produce an even more holistic sign that could connect inflammation to chronic diseases. That different frame of reference began with the most basic question: what constitutes a fully-formed human individual? The answer is that a fully-formed human is far more than what is encoded by the human genome [7]. The fully-formed human contains more microbial DNA than actual human DNA and is connected to the environment in a way that helps to both define and sustain the completed human [8]. Furthermore, alteration of the human microbiome appears to be just as likely to result in chronic disease as does alteration of key developing human eukaryotic cells (e.g., immune cells) [9]. The paradigm we present is one in which microbial-human symbiotes are the basic composite human that is needed for optimized, effective lifelong health. The fundamental sign

we seek is likely to be connected to this more complete individual that has also been termed the human superorganism [10].

This review: (1) Justifies the focus on chronic diseases and conditions as the principle out-picturing of human disorder. (2) Details the identification of misregulated inflammation as a signal for chronic diseases. (3) Introduces and discusses the concept of the *Completed Self* as a useful sign for health vs. chronic illness. (4) Details the process of human-microbial symbiotic formation in the neonate, and (5) Considers the impact of altered epigenetic programming (AEP) and developmental immunotoxicity (DIT) on formation of the human superorganism and/or expression of the full completed self phenotype.

1.2. Development of Self Identity from an Immunological Perspective

One of the first important questions is: who are we immunologically? Historically, there has been a perspective in immunology that the human genome encodes us and in order to have integrity and fidelity, our immune system must protect us from everything else (*i.e.*, the environment). Specialized immune cells such as alveolar macrophages, skin dendritic cells and gastrointestinal-associated lamina propria dendritic cells reside at the portals of exposure to the environment for the purpose of sampling the environment and helping to protect us from potential danger. But more recently, an expanded view of humans that includes a significant microbial super-genome has been proposed as a fundamental concept [11].

Studies suggest that when the immune system only sees and tries to defend what is encoded exclusively by the host mammalian genome, it is highly dysfunctional, less effective in maintaining homeostasis, and less well prepared to defend the host from the adverse outcomes of pathogenic challenge [12–14]. An updated view of self-identity is that a mammalian genome-encoded organism completely separate from the environment is disordered, dysfunctional in self-recognition, and more likely to have problems protecting the host from serious environmental challenge.

As pointed out by Oller [6], major histocompatibility complex (MHC) expression is a critical component in defining what is self from non-self. We tolerate self and attack, kill, expel or wall off what is non-self. Proteins expressed by MHC genes provide a translator system for identifying cells and proteins that belong to us from those that are intrusive and/or dangerous. At least for years that is what seemed like the essential paradigm for self-identity. But recent research has shown that the boundaries of what constitutes self have been dramatically blurred from traditional thinking. The reason an immune definition of self is important is that our bodies act to protect or defend the boundaries of self. Viruses, pathogenic bacteria, or significantly aberrant cells (*e.g.*, cancer cells) do not meet the criteria of self.

The traditional view indicates that host proteins and cells are the primary targets of self recognition such that anything else would be seen as foreign and subject to host defense responses. But this is actually not a holistic view of what is immunological self.

From childhood on, we are reliant on more than a trillion microbes that inhabit our gut, airways, skin, oral cavity, conjunctiva, and urogenital tract. These form what has been termed the microbiota with genetic components of these microorganisms known as the microbiome. In fact, if the human genome was underwhelming in terms of the number of genes identified vs. the number that had been expected, our commensal microbes have at least five times that number of genes. In other words, we

are carrying far more microbial genes than our own composed DNA. These microbial genes and organisms not only carry out their own metabolism, they are specifically tailored to our bodies based on our own individual characteristics. Each individual has both a unique fingerprint as well as a somewhat unique microbial signature.

A very minute portion of the human life span is reliant solely on personal, DNA-encoded protein products. This time period encompasses a few minutes surrounding birth, after which humans become reliant on a combination of personal DNA-encoded proteins as well as those of the microbiota that complete the human superorganism. Yet, as incomplete as a newborn infant is and as quickly as they must begin acquiring microbiota from their environment, impacts to this biologically-interconnected path can begin even before birth.

1.3. Prenatal Symbiosis

Prenatal development can be viewed as a symbiotic relationship between mother and fetus. One point made by researchers who embrace this view is that the placenta is developed by the mother and child in combination and possesses both maternal and fetal parts [15–17]. Additionally, the placenta has a certain plasticity, can sense the maternal fetal environment and responds dynamically to a changed environment [18]. Oller [6] discussed the fact that via the placenta, the “newly forming individual” is afforded with both immunological protection and nutrients as well as safety from potentially harmful effects of the mother’s own immune system.

As described by Martin *et al.* [19], the fetal immune system develops in a tight symbiotic and protected relationship with the mother in utero [20]. While the various cell types and components needed for immune function begin to emerge early in development, functional capacity is reduced particularly for those immune functions that would jeopardize the pregnancy and development of the embryo to full term [21]. This reduction occurs not only in the fetus but also in the mother as specific immune strategies protect against improper cell mediated and immune inflammatory responses. Carefully orchestrated control of regulated functional levels that are tailored to the stage of the pregnancy are needed to ensure fetal survival [22].

Several lines of evidence support this synchronized dual restriction of the mother’s and fetus’ immune capacities. The fetus develops successfully in what is largely a T helper 2 (Th2) preferred environment [23,24]. Th2 skewing of the immune function in the mother causes chronic diseases that are Th2 driven (e.g., systemic lupus erythematosus) to be exacerbated while Th1-associated disease symptoms (e.g., rheumatoid arthritis) are often lessened [25]. Additionally, women with recurrent miscarriages [26] or who experience preterm labor [21] generally fail to down-regulate their Th1 responses particularly at the maternal-fetal interface. They also have improper control of inflammatory cytokine levels at the placental interface [27].

1.4. Birth Delivery as the Transition

Historically, we have viewed birth as the critical transition from sheltered protection to a largely complete individual. If Th1 dampening and controlled inflammations are needed to immunologically maintain the symbiotic mother-fetus relationship, then parturition has different requirements. In effect, it is a dissociation of the symbiosis. In fact, there is evidence in animal models that macrophage

activation and an inflammation-like process is needed to initiate the events surrounding birth [28,29]. Shynlova *et al.* [30] described how proinflammatory cytokine-activated immune cells infiltrate the uterus and initiate labor.

Certainly, maturation must continue after birth and does for many physiological systems until at or near adulthood [31–33]. But having a fully-formed yet immature organism is completely different from having an organism that may be born incomplete and needs to add external components to be completed. It is this latter concept that is probably closer to reality given what we now know about microbial symbiosis. We will argue precisely the view that our microbiome is needed to complete us.

2. Results

2.1. The Completed Self Concept

Several investigators have suggested that it is more accurate and potentially useful to think of mammals as “superorganisms” composed of both mammalian and microbial cells, which are exquisitely interlinked to affect health [34,35]. No longer does our human-driven core constitute our *Completed Self*. Instead, as stated by Sleator [36], humans are more likely to be “a collective of human and microbial cells all working for the collective.” In actuality, we are multiple organisms when we exist as individuals free of our mother’s womb. Zhu *et al.* [37] termed the human gut microbiome as the “second human genome” and pointed to the fact that microbial genes outnumber human genes by 150 fold. Recently, Murdoch and Detsky [38] suggested healthcare needs to shift away from the traditional focus on just human physiology to a focus on the human superorganism. While the immune system is known to play the critical role of homeostasis in tissues, Eberl [39] argued that its principle role is not necessarily as a killer but as a homeostatic regulator of the human superorganism.

In our view of the *Completed Self*, we will argue that this is a paramount sign or signal determining health vs. disease. The focus of this paper is on chronic diseases as the most significant category of diseases. But, if self-completion is a key sign, there are many prenatal and perinatal factors that affect whether self-completion can occur successfully in the infant. These factors are illustrated in Figure 1 along with a developmental timeline.

2.2. Sources of Microbiota for Infant Self-Completion

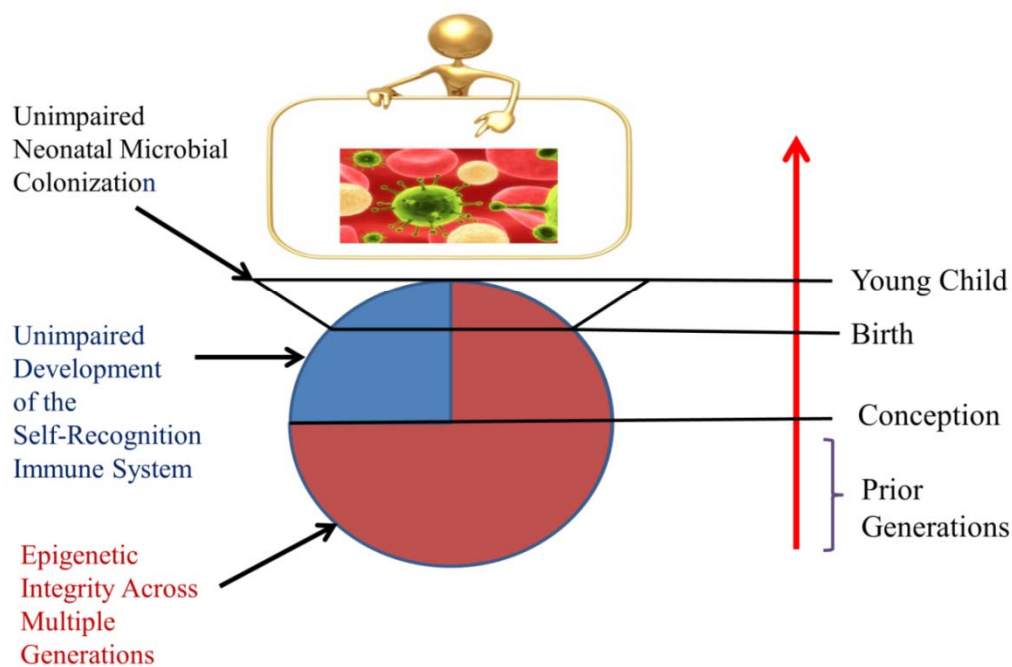
Introduction to a useful environment is among the most important considerations for the newborn, and the perinatal period is the most critical for acquisition of commensal microbes and completion of the self. While most of the attention is centered on birth and the neonatal period of microbial colonization, some investigators suggest that attention should be paid to maternal microbes including those at the maternal-fetal interface [40]. For example, differential prenatal fetal T cell priming and newborn levels of the cytokine interleukin-12 (IL-12) have been reported based on whether *Lactobacillus* had colonized the maternal vagina [41]. Therefore, the maternal microbiome is a consideration for the baby’s immune system before, during and after birth.

The newborn emerges from the womb essentially sterile. Microbial colonization of the infant’s gut, skin, lungs, conjunctiva and urogenital tract begins almost immediately upon birth. Factors that affect

the infant's microbiota colonization are: mode of delivery, feeding regime, maternal diet/weight, probiotic and prebiotic use and antibiotic exposure pre-, peri- and post-natally [42].

Figure 1. A timeline for formation of the *Completed Self* is depicted. Transgenerational epigenetics (via prior generations) and perinatal developmental immune processes combine with neonatal microbial colonization to establish the parameters of the human-microbiome superorganism. There are specific developmental windows for each contributing factor that determine whether the *Completed Self* is appropriately formed in the young child.

Critical Windows For Formation of The Completed Self



The baby's direct contact with the mother and the environment provides microbial exposure for colonization. Additionally, breast milk is an important source of gut microbiota for the infant. Urbaniak *et al.* [43] indicate that breast milk provides the infant with a significant amount and diversity of microbes that are lacking in formulas. Even probiotic supplemented formulas lack the diversity of bacteria that is provided to the infant via breast milk [43]. Differences in the microbial composition of breast milk have been reported. As an example, breast milk from obese mothers was found to be less diverse in bacteria than breast milk from non-obese women [44].

Colonization of the infant skin microbiota is also important in reducing the risk of later life diseases. Nagata *et al.* [45] found that the newborn's skin is populated with microbes transmitted directly from the mother's skin. Most of the transitions among commensal skin fungus appear to occur within 30 days of birth [45]. In contrast, Capone *et al.* [46] reported that most of the skin microbiota colonization occurs over a longer period during the infant's first year of life and the bacteria are distributed in a site specific manner.

Comparatively less research has gone into the colonization of conjunctiva, and collection methodologies to examine diversity can be challenging. Thus far, results suggest that the normal,

healthy conjunctiva also have a significant diversity of different microbes represented [47]. Information on critical developmental windows for establishment of the infant's microbiome is generally lacking to date. However, studies have been performed on potentially pathogenic microbes detected in premature neonates spending significant time in the neonatal intensive care unit [48].

As with conjunctiva, complete characterization of the normal vs. disrupted urogenital microbiota has lagged behind that of the gut, and critical windows for neonatal colonization have yet to be defined. Analysis of the healthy female genital tract has proved to be a challenge since present results suggest there is both significant microbe diversity and site specificity [49].

2.3. Critical Timing for Self-Completion

Ironically, the birth process itself may be useful for seeding commensal microbes and helping to drive immune maturation and effective balance. Several studies have shown that birth delivery mode affects neonatal immune balance. Shortly after birth, vaginally delivered newborns have enhanced colonization of certain gut bacteria (e.g., *Bifidobacteria* sp.) [50] and a more mature and effectively balanced (Th1 vs. Th2) immune system [51] than Caesarean-delivered babies.

Early-life introduction of commensal microbes appears to be crucial and difficult to correct later in life. Significantly, there appears to be a critical postnatal window during which bacterial colonization needs to occur to achieve effective mucosal immunity and avoid persistent problems in the adult. In a study in piglets, Mulder *et al.* [52] found that a hard-wiring of both adult gut microbiota and adult mucosal immunity occurred based on microbial exposures taking place during the first few days of life. They concluded that microbial exposure throughout early life is an important risk factor in the development of immune diseases in children.

2.4. Health vs. Disease: the Epidemic of Chronic Diseases and Conditions

In the present examination of signs that are linked to health vs. disease, our focus is on chronic diseases as the most significant category to represent human disease. One of the remarkable shifts in health during the latter portion of the 20th century has been the relative decline in mortality due to infectious diseases and its replacement with increased mortality due to non-communicable chronic diseases [53]. The Harvard School of Public Health and the World Economic Forum estimated that diseases such as diabetes, chronic respiratory diseases, and heart disease presently account for 63% of deaths world-wide and are projected to cost 48% of the global gross domestic product by the year 2030 [54]. The toll of chronic diseases is measured not only in premature death but also in seriously-challenged lives. Many adverse outcomes involve debilitating conditions that result in rising healthcare costs, lost wages, reduced quality of life and increased burdens for families and communities. In fact, chronic diseases have been suggested to pose “the single, greatest sustained threat to the stability of health care systems worldwide” [55].

Rising prevalence of chronic diseases is a priority concern in the United States [56], Europe [57], Asia [58], Australia [59], Africa [60], and South America [61]. The situation has become sufficiently serious that for only the second time in its history, the General Assembly of the United Nations brought a health topic to the floor for debate. The first instance concerned the topic of HIV/AIDS, which was discussed over a decade ago. In 2011, the topic was the chronic disease epidemic [62].

According to Mayes and Oliver [63], the transition from acute, communicable conditions among humans to chronic, noncommunicable conditions represents a massive, gradually developing, global crisis. There is concern that governments have been slow to address prevention of chronic diseases in keeping with the seriousness of the economic and societal impact. In fact, Mayes and Oliver [63] argue that several structural impediments limit much-needed responses. Among these is the fact that public health initiatives addressing chronic diseases have benefits that are dispersed and delayed. Additionally, when compared with medical treatments designed to manage symptoms of a disease, efforts to prevent something bad from happening may appear to be mundane, with both the prevention practitioners and their efforts remaining largely invisible [64]. Mayes and Oliver [63] suggested that a paradigm shift is needed in which “health in all policies” takes precedence.

In a recent article on chronic diseases, Freudenberg and Olden [65] posed the following challenge: “To lower the incidence of chronic diseases and thus the costs they impose on our society and health care system will require addressing the deeper causes of the increase in recent decades.” Table 1 shows some examples of health care cost estimates for pediatric chronic diseases.

Table 1. Healthcare and Other Costs Associated with Chronic Diseases and Conditions in Children.

Entryway Disease or Condition	Population studied	Period of study	Category of costs	Per annum amount per patient	Reference
Asthma	School age children in a 1996 Medical Expenditure Panel Survey	1996	Total economic impact, medical and lost parental wages	\$791	[146]
Asthma (difficult to control)	Children 6–12 years of age with difficult to control asthma from several US sites	2001–2004	Total asthma costs: medications, physician visits, hospital visits; lost work/school days	\$7,846	[147]
Autism spectrum disorders	US: Medicaid database from 42 states	2003	Total health care expenditures in Medicaid per child per annum	\$22,079	[148]
Childhood chronic kidney disease	Children from Canada (British Columbia and Yukon)	2009	Annual pharmaceutical cost	\$1,800	[149]
Pediatric Crohn’s disease	Pediatric patients in Canterbury, New Zealand	2010–2011	Total (direct and indirect) cost per person per annum	\$14,375 NZD	[150]
Pediatric food allergies	Children 0–18 years of age as one categories in the study	2007	Mean direct medical cost per child per annum	\$3,635	[151]

Table 1. Cont.

Entryway Disease or Condition	Population studied	Period of study	Category of costs	Per annum amount per patient	Reference
Kawasaki disease	Across US	1997– 1999	Median hospitalization cost	\$6,169	[152]
Pediatric arthritis	2 nd Children’s Hospital at Berlin-Buch cohort	1998– 2000	Mean cost per patient per annum	3,500 Euros	[153]
Type 1 diabetes	Texas	2004– 2005	Median direct costs per person per annum	\$4,730	[154]

Apart from the impact on quality of life, the per annum toll that begins in childhood and the increasing prevalence of these diseases and conditions provide the basis for more effective prevention. In the present review, we argue that three areas of priority could help to address the human burden of chronic diseases: (1) avoidance of adverse epigenetic alterations including those with stable transgenerational inheritance, (2) improved protection of the developing immune system from environmental insult, and (3) strategies to facilitate microbial-human symbiosis in childhood and formation of the *Completed Self*.

2.5. Chronic Diseases Are Connected as Interlinked Patterns

While some chronic diseases arise as multi-organ or systemic diseases (e.g., systemic lupus erythematosus (SLE)), the majority are directed toward a specific organ, tissue, or physiological system (e.g., asthma, inflammatory bowel disease). From a morphogenic viewpoint, cardiovascular diseases were seen as distinct from chronic kidney disease or hepatic steatosis, psoriasis had no bearing on rheumatoid arthritis, and gastrointestinal allergy or autoimmune thyroiditis had no impact on neurological problems. Medical coding of chronic diseases has had a similar effect in which conditions that may involve a common dysfunctional basis (e.g., autoimmunity) are viewed more by their organ or tissue specific site than by an actual biological categorization [66]. As a result, rheumatoid arthritis, psoriasis, inflammatory bowel disease and type 1 diabetes each may be treated by different specialists. But in fact, these chronic diseases may be more related than previously suspected. Recent findings indicate that these supposedly disparate chronic diseases that target different tissues are interlinked both in underlying biological dysfunction as well as in potential comorbid diseases risks [67].

The initial concept of interlinked patterns of diseases or conditions did not begin with a consideration of immune dysfunction based diseases. Instead, it was a comparatively narrow category of male reproductive conditions followed by a larger category of metabolic-dysfunctions that suggested the benefits of examining the landscape of chronic diseases and conditions from a more holistic perspective. One of the initial characterizations linking chronic diseases and conditions keyed to early life environmental conditions was in the area of testicular dysgenesis syndrome [68, 69]. With this syndrome, testicular germ cell cancer, cryptorchidism and some cases of hypospadias and male infertility have been linked with impaired development of the testis. This was followed by the conceptual framework of metabolic syndrome [70] where such interlinked conditions as insulin resistance, diabetes, and hypertension were seen as forming a matrix that represented an integrated

state of dysfunction. With metabolic syndrome, the interlinked conditions extended beyond a single tissue or organ affecting multiple symptoms as well as risk of multiple diseases.

In a series of papers, Dietert and collaborators applied the concepts of interlinked conditions to the identification of larger patterns of immune dysfunction-based, inflammation-driven, chronic diseases. The disease terrain that is interconnected via immune dysfunction and inflammatory misregulation is remarkably large encompassing many, if not most, chronic diseases and conditions [71–73]. This breadth of biological interconnectivity becomes evident with the realization that numerous chronic diseases have comorbidities that include one or more of the following: depression, sensory loss (including eyesight, hearing and/or sense of smell), frailty, and sleep disorders/problems [67]. Recently, specific risk of cancer was included among the immune dysfunction-inflammation based patterns [66]. In fact the causative and risk-based linkages among chronic diseases are so extensive that in many ways it can be useful to consider them as one or more units of conditions rather than myriad diseases.

2.6. Chronic Disease Patterns Begin Early in Life

The foundation for risk of chronic disease begins in early life [74–76]. Studies from the past two decades have demonstrated that the most critical windows for exposures to chemicals and drugs and toxicological risk of chronic diseases are the prenatal, neonatal and juvenile periods of development. Much of the original focus of developmental environment and adverse health outcomes was placed on prenatal conditions and risk of adult-onset diseases. For example, the developmental basis of adult health and disease became established through the “Barker Hypothesis” in which prenatal programming was linked with adult offspring cardiovascular disease [77,78]. Since the original observations, prenatal environmental programming, including low birth weight, have been associated with an elevated risk of such conditions as hypertension [79], insulin resistance [80], diabetes [81], atherosclerosis [82], and chronic kidney disease [83] again primarily focused on adult disease.

However, two key findings extend the prenatal programming-adult relationship to a much broader terrain. First, far more environmental factors are known to affect the risk of disease in the offspring than just maternal undernutrition. In fact myriad environmental factors ranging from specific dietary factors to drugs, chemicals, infections, and physical and psychological stressors are known to operate via early development to affect risk of later life disease. Second, it is clear that the impact of fetal programming occurs in children. Risk of prominent childhood-onset diseases is equally susceptible to fetal programming as is risk of more geriatric-onset conditions. Additionally, the fetal-derived bases of diseases like atherosclerosis are already present in children even if disease diagnosis may not occur until adulthood [84]. For these reasons, we will argue that the patterns of chronic diseases are already in place in children following early-life problematic exposures to chemicals and/or drugs.

A striking finding is that over half of US children have some form of chronic disease or condition and/or developmental delay. A 2011 study by Bethell *et al.* [85] based on 2007 data, found that 43% of US children had at least one of 20 designated chronic conditions. When obesity and developmental delays were included as additional inflammation-affected chronic conditions, that percentage was elevated to 54%. Almost one fifth of all children had conditions resulting in special health care needs.

Cost consideration for chronic diseases come in several forms including direct medical care costs, prescription drug costs, and lost income. The effect of adding comorbidities with increased aging is that more care and prescription drugs are likely to be required. Ironically, despite the shorter lifespan that can accompany chronic diseases, lifetime drug expenditures can exceed those of longer lived healthier populations. For example, Rappange *et al.* [86] found that lifetime drug costs among the obese were higher than those of a healthier-living cohort despite the former group having a shorter life expectancy. Asche *et al.* [87] compared the all-cause health care costs of newly diagnosed patients (1,411) with multiple sclerosis (MS) against a “healthy” comparison group (7,055) for a 12-month period. They found that the MS group costs were significantly elevated over those of the comparison group (\$18, 829 vs. \$4,028).

2.7. Misregulated Inflammation Is the Root of Most Chronic Diseases

Chronic inflammation as a result of unresolved acute inflammation has been suggested as a unifying basis for most, if not all, chronic diseases of today. It is the disorder that best predicts chronic diseases [2,88–90]. In fact, most chronic diseases are dependent upon chronic inflammation as a key factor in their development and/or maintenance [91]. Additionally, Prasad *et al.* [92] argue that all risk factors of chronic diseases up-regulate inflammation. The problem is so pervasive and extensive that Aller *et al.* [93] suggested that inflammation problems have the potential to exert an evolutionary impact. Gene-environment interactions are important in chronic inflammatory conditions [94], and this complements the idea that hypersusceptible subpopulations are likely to exist in which inflammatory dysfunction is more likely to occur under a set of early-life environmental conditions. Table 2 emphasizes the significance of immune dysfunction and misregulated inflammation to chronic diseases by illustrating suggested biomarkers associated with each of several different types of chronic diseases. The common occurrence of innate immune markers associated with inflammation is striking.

Chronic diseases linked with improper inflammation include: allergic and autoimmune conditions, various behavior disorders, sensory loss, sleep problems, frailty, depression [67], Parkinson's disease [95], as well as cardiovascular diseases, type 2 diabetes, chronic kidney disease, Alzheimer's disease and cancer [96]. In the latter case, cancer has emerged as one of the prime end-stage comorbidities of immune dysfunction and chronic inflammation. Immune problems resulting in chronic inflammation create an environment that elevates the risk of development and/or promotion of cancer [97,98]. This is consistent with the observed pattern that elevated cancer risk is associated with the tissue-specific targeting of chronic diseases involving inflamed tissues (e.g., lung cancer for asthma, skin cancer for psoriasis, and G.I. tract cancer for inflammatory bowel disease) [66].

It has been suggested that chronic low level inflammation is involved with most forms of heart disease [99]. Atherosclerosis represents a prime example of an immune-mediated, chronic inflammatory disorder [100]. With atherosclerosis there is a progression through a timeline during which the transition from acute to chronic (or unresolved) inflammation results in inflammation-driven hypertension [101].

Table 2. Suggested Immune and/or Inflammatory Biomarkers of Chronic Diseases and Conditions.

Disease/condition	Suggested biomarkers	Reference(s)
Alzheimer's disease	Microglia and astrocyte proinflammatory cytokines IL-1, IL-6, TNF-alpha with inflammasome activation; Low M-CSF production by macrophages containing amyloid-B deposits; Altered TLR regulation	[155–157]
Asthma and respiratory allergies	Altered signaling and/or levels of Toll-like receptors 2, 4, and 7; Increased IgE and/or IL-4 levels; Eosinophilic infiltration of tissues; Production of specific microRNAs	[158–160]
Atherosclerosis	TLR 4, MyD88, and the inflammasome activation; Elevation of IL-1 and IL-18, C-reactive protein; Lipoprotein-associated phospholipase A2	[161,162]
Autism	Increased proinflammatory cytokines and abnormal innate immune responses	[163]
Chronic obstructive pulmonary disease	Improper neutrophilic inflammation; Excessive ROS production; Excessive Th1 and Th17 activity; Impeded immune repair	[164,165]
Depression	Increased proinflammatory cytokines IL-1, IL-6, TNF-alpha; Elevated cortisol	[166,167]
Food allergies	Decline in TGF-beta producing T cells in the gut	[168,169]
Grave's disease	Dendritic cell polarization; impaired CD4+CD25+ regulatory T cell capacity	[170]
Hashimoto's thyroiditis	Decreased CD4+CD152+ T cells	[171]
Myalgic encephalomyelitis (Chronic Fatigue Syndrome)	Elevated proinflammatory cytokines; Elevated serum neopterin and PMN-elastase; blunted T cell memory	[172–174]
Multiple sclerosis	CD46 regulation; Activated microglial production of proinflammatory cytokines; Dysregulated Treg/Th17axis; Neuropilin-1 regulation	[156,175–177]
Osteoporosis	Urinary ratio of native (alpha) to isomerized (beta) CTX; Fragments of interalpha-trypsin-inhibitor heavy chain H4 precursor (ITIH4)	[178,179]
Parkinson's disease	Change in olfaction; Depression	[180]
Psoriasis	IL-1F6 as well as upregulation of TNF-alpha, IL-17A, and IL-23	[181]
Rheumatoid arthritis	Macrophage overproduction of IL-1, IL-6 and TNF-alpha; CD4+ Th1- and Th17-driven inflammation; inflammasome activation; Autoantibodies to Fc portion of host immunoglobulins	[182–184]
Sarcoidosis	A cytokine cascade of IL-1, IL-2, IL-6, IL-8, IL-12, IL-18, IFN-gamma, and TNF-alpha promotes the recruitment, activation, and proliferation of mononuclear cells and a Th1-driven granulomatous response; Overabundance of activated CD4+ T cells; Altered dendritic cell maturation	[164,185]

Table 2. Cont

Disease/condition	Suggested biomarkers	Reference(s)
Sjogren syndrome	Enhanced production of type 1 interferons by dendritic and other cells; Increased oxidative stress; Autoantibodies against the RNA-binding proteins SSA/SSB/RNP	[186,187]
Sleep disorders	IL-6 levels in relation to other inflammation-regulating cytokines	[188]
Systemic sclerosis	CD70 overexpression; Endothelial adhesion molecules; Soluble TNF-alpha receptor; Altered pulmonary surfactant production	[189–191]
Type 1 diabetes	Macrophage overproduction of inflammatory cytokines and CD4+ Th1 subpopulation driven inflammation	[192]

A similar relationship exists between inflammation and metabolic disorders. Osborn and Olefsky [102] argue that chronic tissue inflammation mediated by macrophages is a critical link between the immune system and metabolic-based chronic diseases. Obesity is integrally linked with inflammation and altered immune status [90]. Age-related adiposity has been linked with chronic inflammation and, in particular, shifts in T cell and inflammatory macrophage populations in adipose tissue [103]. Even later, end-stage types of diseases such as chronic kidney disease are also predicted by earlier markers of inflammation [104,105].

Not surprisingly, drugs designed to promote resolution of acute inflammation appear to show promise against multiple different chronic diseases. For example, resolvins are a category of bioactive autacoids of enzymatically converted omega-3 polyunsaturated fatty acids. Because of their capacity to resolve misregulated inflammation, they are a promising drug candidate to treat a variety of chronic diseases [106].

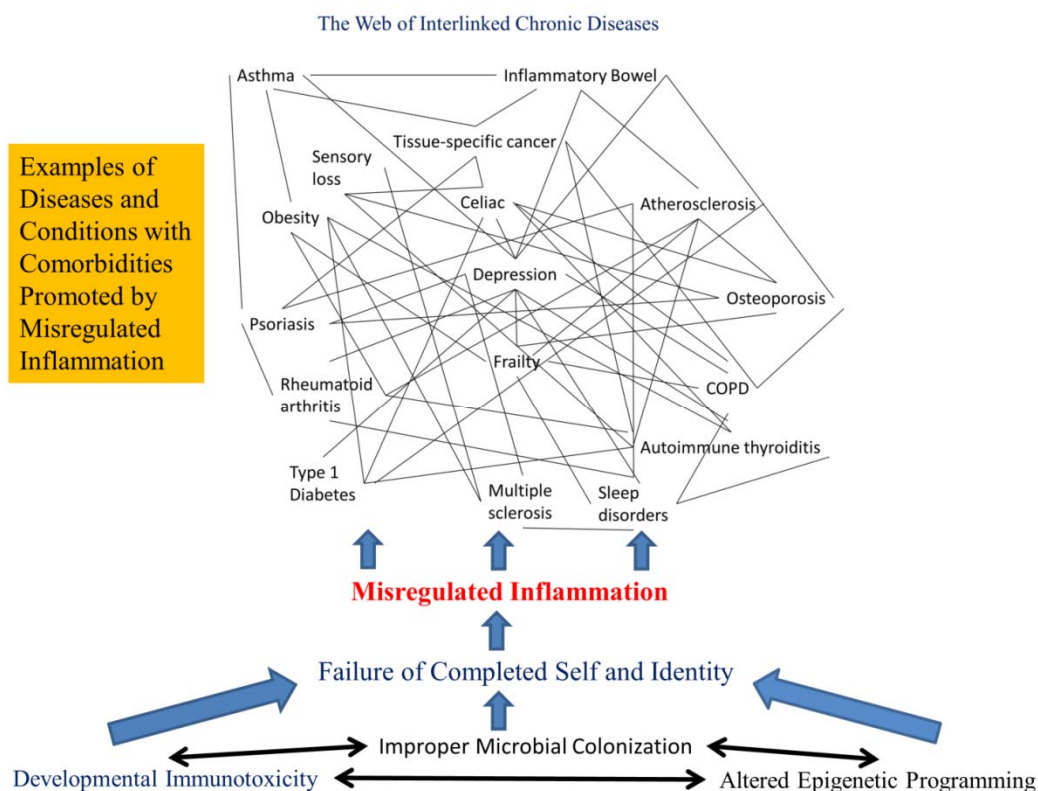
Improper inflammation in early life is a major factor in later life chronic diseases [107] and imbalances of innate immune cell populations have been suggested as a marker associated across many chronic diseases [108]. This is also telling since Netzer *et al.* [109] suggested that innate immune-promoted reactive oxygen species production may be key to a loss of translational fidelity. The researchers proposed that loss of this fidelity and capacity to produce a wider spectrum of modified proteins may be an adaptive response of mammalian cells to undue stress.

2.8. Human Avoidance of Misregulated Inflammation and Chronic Diseases

If chronic diseases are a primary adverse health outcome of dysfunction that should be avoided, then the question becomes what is the cardinal sign that could be used to distinguish health from a life course filled with chronic diseases? We present the tenet that fulfillment of the human superorganism (human genome + microbiome) is pivotal for health. The detailed summation will vary from individual to individual. But it is clear that the human superorganism needs to form efficiently, effectively, and completely in the infant. As follows, we discuss this concept under the rubric of what we term: the completed self. Additionally, we consider the three major components that determine whether the immunologically-defined *Completed Self* can form: (1) useful epigenetic programming, (2) effective developmental immune maturation, and (3) complete microbiota colonization. The relationships among these three factors, misregulated inflammation, the *Completed Self* and interlinked patterns of comorbid chronic diseases are depicted in Figure 2. Significantly, Figure 1 show that these processes

occur during specific critical windows of development, and failure of critical maturational steps during these windows can compromise formation of the *Completed Self* and increase health risks across a lifetime.

Figure 2. Early life interactions that disrupt formation of the *Completed Self* are suggested to be as a primary contributor to misregulated inflammation and risk of later-life chronic diseases. Reported comorbidities among selected chronic diseases and conditions are shown in this figure and are represented by the interconnecting lines among diseases. These comorbidities are extensive illustrating the extent to which much of human disease is interconnected and promoted by misregulated inflammation. For example, tissue-specific cancer is a later-life comorbidity of asthma (lung cancer), inflammatory bowel disease (gastrointestinal cancer) and psoriasis (skin cancer). Cardiovascular disease (e.g., atherosclerosis), depression, and frailty are common later-life comorbidities. It is suggested that environmental interference with human superorganism formation corrupts a biological sign for later-life health.



2.9. Three Key Factors That Affect Our Capacity for Self-Completion

Three major processes and, in turn developmentally-timed vulnerabilities, exist relative to formation of the *Completed Self*. Figure 2 illustrates the risk to formation of the *Completed Self* that is associated with AEP, DIT and/or altered neonatal microbial colonization.

2.9.1. Altered Epigenetic Programming (AEP) Across Generations

One key factor that can lead to misregulated inflammation and elevated risk of chronic diseases is AEP. Environmentally-induced epigenetic programming may reflect in utero or neonatal environmental insults similar to DIT (discussed in the following sections) or alternatively, it may be expressed across several generations and not reflect direct exposure and immune disruption. Regardless of the generations exposed and affected, an alteration in gene expression patterns that produces inappropriate responses to host challenge and misregulated inflammation appears likely to elevate the risk of one or more chronic diseases.

Several examples have been reported in the literature with a focus on inflammation-associated cancer. The gene, cytidine deaminase, and its activation through epigenetic alterations cause alterations in immunoglobulins via changes in somatic events. Epigenetic activation of this gene has been linked with chronic inflammation and cancer [110]. Chiba *et al.* [111] discussed potential gene targets of EP that have been associated with inflammation-associated development of digestive tract cancers. Likewise, Rau *et al.* [112] identified methylation of the gene caudal homeobox factor 1 as a pathway leading to inflammation and intestinal metaplasia in humans. In the liver, Nishida and Goel [113] have reported that consistent gene methylation patterns and histone modification can be associated with hepatocarcinoma.

Beyond cancer, Michael Skinner and colleagues [114] reported evidence that several classes of environmental toxicants produce F3 generation inherited DNA methylation patterns that were connected to a condition in rats modeling human polycystic ovary disease. This study provided a proof of concept for epigenetic transgenerational induction of chronic diseases. Diseases associated with several different tissues are connected to epigenetic changes. For example, a change in the cytokine gene producing interleukin-13 (IL-13) appears to be associated with allergic airway inflammation and remodeling [115]. Epigenetic reduction of histone deacetylase 2 and its activity has been connected to oxidative stress, lung inflammation and increased risk of chronic obstructive pulmonary disease (COPD) [116]. Ospelt *et al.* [117] proposed that epigenetically produced inflammatory memory may be the key to risk of rheumatoid arthritis (RA). These authors suggested that a stable activation of synovial fibroblasts may provide the key step leading to improper inflammation and RA. Taken together, these studies suggest that epigenetic alteration affecting regulation of inflammation is likely to contribute to multigenerational risk of chronic diseases.

2.9.2. Developmental Immunotoxicity (DIT)

Influence of the environment on the developing immune system, indirectly via the mother during gestation or directly on the child, represents the second process that can significantly affect formation of the *Completed Self* and risk of chronic diseases. The developing immune system is vulnerable to a variety of environmental modulating agents that collectively have been discussed under the rubric of developmental immunotoxicity (DIT) [118]. The agents can include environmental chemicals, drugs, diet, pathogens, medical devices, and physical and psychological conditions including maternal and fetal stress [118].

When toxicants have been compared across ages, the developing immune system has been shown to be more sensitive than that of the fully-matured adult [119,120]. Increased sensitivity of the immune system in early life can take several forms: (1) lower exposure doses are required to induce immunotoxicity, (2) more persistent adverse immune effects exist across a lifetime, (3) a broader spectrum of adverse effects are produced and (4) an increased vulnerability to later-life, environmentally-triggered immunotoxicity becomes established. Age-based, increased vulnerability for the immune system is not the only concern. Depending upon the environmental factors involved and the parameters measured, developmental immune effects can represent the most sensitive measures of adverse outcomes [121]. A recent example in which DIT helped in the determination of safe levels can be found in the US EPA's IRIS assessment of the widespread contaminant, trichloroethylene (TCE) [122].

Importantly, DIT has the capacity to interfere with later-life, positive environmental factors and their role in continued maturation of the infant's immune system [66]. This nullification effect of DIT for subsequent childhood environment-microbial enrichment has been shown in the case of risk of allergy. PCB exposure nullifies the otherwise beneficial effects of breastfeeding for risk of allergic sensitization [123] and pesticide exposure nullifies the benefits of growing up on a farm relative to risk of asthma [124]. As can occur with AEP, DIT can interfere with immune maturation and cause the blunting of otherwise beneficial effects of the microbiota. Theoretically, this can occur in two ways: (1) via direct interference with acceptance of commensal microbes as self or (2) via the limited capacity of the DIT-damaged neonatal immune system to respond to microbial pattern recognition signals for continued immune maturation. The end result is that DIT can block formation of the *Completed Self* or prevent us from fully benefitting from the presence of our microbial partners.

The risk factors for DIT include environmental chemicals and drugs (e.g., environmental tobacco smoke, lead, mercury, polychlorinated biphenyls, paracetamol), maternal and neonatal diet, maternal and childhood infections, neonatal microbial exposures, birth delivery mode, and maternal and neonatal stress [118,125]. The determination of whether a specific environmental risk factor produces biologically-significant DIT is based on the genetics of the individual, prior exposure history, the exposure dose, the duration of exposure, the critical developmental windows of exposure, and gender [126,127]. A key point is that qualitatively different immunotoxic outcomes can occur depending only on the developmental timing of exposure. The implications are that environmental health risks for the immune system are both age- and gender specific and need to be treated as such in terms of safety evaluation and prevention.

2.9.2.1. DIT and Misregulated Inflammation

Recently, the role of DIT, innate immune cell development and risk of inappropriate inflammation were reviewed by Leifer and Dietert [128]. Major developmental immunotoxicants such as the heavy metals, lead, mercury, and cadmium and dioxin are known to impact innate immune cell responses to challenge and to promote inappropriate inflammatory responses leading to tissue damage. For example, Kasten-Jolly *et al.* [129] found that developmental exposure of mice to lead targeted changes in innate immune cell gene expression as a major outcome. They further argued that the multi-system adverse effects following developmental lead exposure could be related to systemic inflammation.

Hogaboam *et al.* [130] reported that developmental exposure of mice to 2,3,7,8-tetrachloro-dibenzo-p-dioxin causes the offspring to mount an excessive neutrophil-driven inflammatory response in the lung in response to influenza challenge. These types of toxicant-induced misregulation of inflammation are likely contributors to chronic diseases. Finally, Dietert [131] reviewed the widespread capacity of endocrine disrupting chemicals to disrupt immune maturation and produce misregulated inflammation following early life exposures.

2.9.2.2. DIT and Infectious Agents Can Combined to Initiate Chronic Diseases

Among the early-life environmental risk factors for immune-based disease, some of these factors such as environmental toxicants appear to cause immune dysfunction and disease. In contrast, other environmental risk factors such as infectious agents (e.g., respiratory viruses) may act as triggers of disease rather than necessarily serving as causes. For example, certain infections in children can produce tissue damaging immune responses from an already maturationally-dysfunctional childhood immune system [132].

In addition to allergic and autoimmune diseases, neurodegenerative diseases appear to have a similar association to infections. Deleidi and Isacson [133] suggested that triggers of inflammation such as viral infections are critical in the initiation of many neurodegenerative chronic diseases. These authors stress the importance of activation of microglia and production of proinflammatory cytokines prior to the development of Huntington's disease, Alzheimer's disease, and Parkinson's disease.

2.9.3. Altered Neonatal Microbial Colonization

At birth most mammals, including humans, have yet to encounter microorganisms. That will change rapidly and the subsequent interactions define the playing field for what is self and then tolerated *vs.* what is a danger and needing to be attacked. As described by Vassallo and Walker [134], colonization of the infant's gut with microbes is a critical step in microbe-host programming that results in a balanced mutualism, which can greatly impact the later-life health and risk of disease in the individual. Comparison of the number of microbial cells to mammalian cells in humans is staggering with microbes outnumbering the latter by at least a magnitude [135]. Our commensal microbes are not an after-thought. Once we are separated from our mother's body, we become significantly microbial. These microbes also play a critical role in necessary further maturation and programming of the developing immune system [136]. Martin *et al.* [19] stressed that while environmental microbes had been viewed as significant in postnatal immune maturation, it is more likely that commensal microorganisms (the microbiota) are the primary drivers of immune maturation. In his review, Oller [6] discussed the importance of the gut microbiota and, in particular, how an individual's own genetic background can shape the composition of the microbiota. This is a very significant point in that different individuals are likely to differ in the exact microbial partners that help form the *Completed Self*.

3. Discussion

3.1. DIT, Missing Microbes, and Future Health

Beyond this early-life co-dependency, perinatal immune status and microbiota status fit together to ultimately affect the risk of chronic inflammation and later-life disease [137]. De Palma *et al.* [138] described studies in which the specific microbiota composition of the gut affected dendritic cell maturation and were shown to either lead to normal and effective functional outcomes or alternatively, to immune dysfunction. Substitution of probiotic *Bifidobacterium* with enterobacteria was shown to drive dendritic cell maturation toward a celiac disease-like inflammatory phenotype.

There are similarities in outcomes between DIT and impaired microbiota formation. These can be seen in the lack of effective immune homeostasis and in an elevated risk of specific immune-inflammation-driven chronic diseases. For example, a reduced diversity of gut microbiota in an infant has been reported to elevate the risk of allergic disease [139]. Remarkably, similar outcomes have been reported for DIT-associated perinatal exposures to marine pollutants [123], paracetamol [140], and not surprisingly, antibiotics [141]. However, in the case of perinatal exposure to antibiotics it is unclear whether the developmental target for later-life disorder and disease is the microbiome, the developing immune system, or both.

Abt *et al.* [142] examined the effects of antibiotic depletion of commensal bacteria in mice on immune cell development. They found that both innate and adaptive immunity were impaired with the absence of commensals and that innate immune cells such as macrophages were unable to support antiviral host defense. They argue that the microbiota help to establish an activation threshold of the innate immune system and that is needed for antiviral immunity [142]. Additionally, commensal bacteria are reported to be able to shift the course of hematopoietic development and, thereby, affect the sensitivity toward allergic inflammation [143].

3.2. Reducing the Risk of Chronic Diseases and Conditions: Prevention and Proactive Strategies

Not surprisingly, prevention of chronic diseases by keeping people out of harm's way of environmental hazards has been emphasized as the most effective solution to the ongoing crisis [144]. In a recent review, Sears and Genius [145] describe the public health process for addressing chronic diseases that can include risk recognition and chemical assessment then exposure reduction, remediation, monitoring, and finally, avoidance. One of the reasons to focus on avoiding problems early in life is the previously discussed interlinked patterns of chronic diseases. Once an individual receives an initial diagnosis of a chronic disease or condition (often during childhood), the probability is that additional chronic diseases will emerge later in that individual's life [73]. Therefore, prevention can be viewed as not simply reducing the risk of one chronic disease in an individual but rather of multiple debilitating conditions over the course of a lifetime.

However, where the current paradigm leads is not simply toward prevention of environmental insult. Instead, there is a broader focus on the *Completed Self* as the best indicator for a lifetime of optimized health. This broader focus would include both: (1) protection of host self-recognition and defenses (*i.e.*, the immune system) across generations and (2) proactive strategies to ensure that newborns are able to incorporate their microbiome in a complete, efficient and timely manner.

Individuals and their specific tailored-microbiological components will vary. However, it seems likely that measures reflecting the status of human superorganism formation will be on the horizon and can be used to guide a holistic approach to children's health

4. Conclusions

We discussed the utility of an immunologically-defined sign, formation of the *Completed Self* or human superorganism, whose integrity is essential for a healthful life. Three major components affect the formation and integrity of this sign: useful epigenetic programming, effective immune development, and complete microbiota acquisition. Because the *Completed Self* needs to form in the neonate, prenatal and perinatal protection of this process is paramount to reduce the risk of chronic diseases, lower healthcare costs and improve quality of life.

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