Twentieth Century Dogmas Prevent Sustainable Healthcare

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Abstract

One of the major impediments to sustainable healthcare is a rigid adherence to several outdated twentieth century scientific dogmas. At the center of these pre-microbiome dogmas is the mischaracterization of humans by much of the healthcare industry. We have been and, in many cases continue to be, viewed as a single species rather than a microbiome-driven, multi-species superorganism containing trillions of microbial co-partners. This prior and ongoing misunderstanding of the basic biology of humans across broad sectors of medicine, the healthcare industry, public health and governmental officials and some patients resulted in errors. These errors were not only in delivered healthcare but also in safety evaluations to protect human health (i.e., food, drug, and environmental chemical safety assessment which did not take inconsideration the microbiome). The continued pursuit of preventative and therapeutic medicine using the single-species fallacy (and ignoring the fact that we are a majority microbial by both genes and cells) has ramifications. It spurs on the epidemic of noncommunicable diseases and conditions (NCDs) as well as the loss of human microbiota needed for colonization resistance against pathobionts. This opinion paper:

a) Describes the scientific evidence that repudiates seven outdated scientific dogmas.

b) Explains why these archaic dogmas should no longer drive healthcare and

c) Indicates why they must be discarded for real gains to be made in the sustainability of healthcare. Additionally, two last-century erroneous assumptions are discussed.

These old-school scientific assumptions about the relationship between immune dysfunction and human disease affect when and how regulated safety assessment for the immune system (Immunotoxicity Testing) would be performed. These two assumptions need to be reversed and more relevant and timely immunotoxicity assessment needs to be required by regulatory agencies to protect the human superorganism.

Keywords: Scientific dogmas, Human superorganism, Holobiont, Pathobiont, Microbiome, Safety assessment, Inflammation-mediated damage, Microbiota-immune co-maturation, Sustainable healthcare, Human disease convergence

Abbreviations: NCDs: Noncommunicable diseases and conditions; WHO: World Health Organization; FDA: Food and Drug Administration, NHS: National Health Service; CDC: Centers for Disease Control and Prevention; NIH: National Institutes of Health; USDA: United States Department of Agriculture

Introduction

Sustainable healthcare may be defined in several different ways depending upon one’s experiences, expertise, priorities, and perspective. In 2015, we [1] proposed that a path to sustainable healthcare must first and foremost deal with the 21st century reality that humans are majority microbial by several measures. We do not exist merely as human mammals, but rather are superorganisms (or holobionts) composed of thousands of different microbial species. Human superorganism health is only possible when those thousands of different species are nurtured and given preventative and therapeutic healthcare designed for the superorganism patient. Until and unless healthcare fully embraces the 21st-century reality of the human superorganism, no amount of “greening” of medical facilities (e.g., reduction in plastics) and practices or envisioned transhuman manipulations (the transplantation of nanomaterials,
metals, and electronics into the body) will matter; healthcare will never become “sustainable.” Microbiome degradation is the surest path to

1. Ever-increasing levels of human disease, and
2. Plummetting resiliency in humans. Humans as superorganisms are interconnected to non-human microbiomes in soil, air, water, plants, and animals [2]. As these are equally degraded, it will lead to the destruction of life on earth.

This opinion article details the scientific dogmas that emerged during the mid-latter part of the twentieth century that are no longer scientifically correct but, nevertheless, continue to drive most of prevailing medicine and healthcare. Archaic twentieth century dogmas need to disappear completely and be replaced by new dogmas spawning healthcare approaches that focus on the actual patient, the human superorganism. An early, partial version of the now archaic 20th century dogmas was orally described during a January 2019 invited lecture in the Emerging Sciences Series of the National Academy of Sciences (NAS) in Washington, DC [3]. Table 1 contains the first complete, published version of the disappearing dogmas. When considered in combination, these outdated dogmas ushered in the failed healthcare approaches that generated both our current epidemic of non-communicable diseases and conditions (NCDs) as well as our loss of colonization resistance and increased vulnerability to infectious diseases/pandemics.

In addition, the current paper includes a discussion of two erroneous regulatory assumptions based on 20th century science that concerned safety testing for the immune system for exposure to food, food additives, drugs, and environmental chemicals. In hindsight, these safety assessment assumptions resulted in two problems:

1. Under testing for immune safety, and
2. Measurement of biomarkers that were largely irrelevant as indicators of immune-inflammation-driven human disease. The lack of required screening for disease-relevant immunotoxicity hampered the overall risk-benefit analysis of xenobiotics [4].

Disappearing Dogmas

Seven, twentieth century dogmas are shown in Table 1. These now-archaic dogmas are significant in that they describe various aspects of fundamental biology, safety, and human disease that impact how we pursue healthcare and protect humans from hazards. These include:

A. human immune development,
B. germ theory and how we interact with microbes,
C. the control of speciation,
D. the prime directive for safety testing of drugs, food, food additives, and environmental chemicals,
E. the partitioning of human diseases into different categories,
F. the vulnerability of humans in nature, and
G. standards to ensure that food is safe for human consumption. Importantly, these seven scientific dogmas were widely accepted and taught during the latter part of the twentieth century and continue to be a driving force in human medicine and healthcare. However, the last-century science behind these seven dogmas has been proven to be incorrect as detailed in Table 1.

| 20\textsuperscript{th} Century Dogma | New 21\textsuperscript{st} Century Understanding | Adverse Outcome(s) of Dogma Adherence | Key References |
|-----------------------------------|-----------------------------------------------|--------------------------------------|----------------|
| 1. The newborn is fully prepared immunologically to fight all diseases. | The newborn immune system must postnatally co-mature with the microbiome to be immunologically balanced and fully prepared to fight diseases. When this fails to happen, infectious, autoimmune, inflammatory, and allergic diseases are more likely to occur in childhood and extending throughout the lifespan. | By failing to recognize the inherent immune functional incompleteness of the newborn and to facilitate co-maturation of human microbiome and the infant immune system, immune imbalances and immune dysfunctions were allowed to become established in the child and to persist across the lifespan. | [23-30] |
| 2. Barriers defining species are driven by host chromosomal genes (hybrids lethal or sterile). | Immune-microbiome incompatibility can also determine species barriers (antibiotic destruction of the microbiome can remove some species barriers). This highlights the almost sacred biological bond that has existed for millennia between the immune system and friendly microbiota. They are inseparable from both an evolutionary and a systems biology perspective. | By failing to recognize the integral connection between microbiota and the immune system at the level of organismal integrity, we failed to realize that immune protection of self requires a high level of microbiota-immune compatibility, and that immune inflammation-driven self-damage of tissues and organs is a default outcome of microbiome-immune problems. | [34-39] |
Much of the new data and scientific evidence resulting in new dogmas stems from the explosion of research into the microbiome [5], and the recognition that the microbiome plays a huge role in determining human [6-9], as well as animal [10-14] and plant health [15-17]. Earth is fundamentally a microbial planet [18,19], and most complex organisms on earth have microbiome co-partners that contribute to a spaceship earth concept in which the interlinked microbiome contributes to health vs. disease [20,21]. Ironically, some sectors of agriculture and earth’s ecological management have been completely ready to discard archaic dogmas and fully embrace the chicken superorganism [12] and soil-plant [13] microbiomes as being the most critical features of health management. One Health refers to the combination of knowledge that flows between and supports human medicine and veterinary medicine. The veterinary medicine component of One Health seems to be willing to discard the archaic and false dogma that their patients are single species medicine components, while human medicine and veterinary medicine. The veterinary medicine component of One Health seems to be willing to discard the archaic and false dogma that their patients are single species medicine components, while human medicine and veterinary medicine components are completely noncommunicable.
wildlife, and food-producing animals in receiving the latest science-driven health benefits.

**Dogma #1**

The first archaic dogma that still affects human healthcare is the idea that babies are born with immune systems that are peripherally distributed and balanced across the newborn's tissues, that mucosal immunity is fully in place, and that the baby's immune system is fully ready to withstand all pathobiont challenges and to greet all vaccinations with ringing success. As shown in Table 1 Dogma 1, this assumption could not be further from the truth [23-30]. The baby's immune system has been selectively suppressed during in utero development, and the baby emerges from the womb with an immune system that is incomplete, unbalanced, misregulated as per inflammation and programmed more for future disease than future health. The infant immune system must co-mature with the newly installed and fed microbiota [31]. Only when and after this happens is the baby's immune system truly ready to go. Disruption of the seeding, colonization, and feeding of the newborn's microbiota (e.g., mode of delivery, antibiotic treatments, formula feeding) without appropriate microbiota remediation is a major problem for future health [32].

**Dogma #2**

Recent research into the immune-microbiome connection (Table 1, Dogma 2) has two major implications. It not only establishes that the bond between the immune system and the microbiome is biologically sacred, it also changes much of how we view the origins of species. During the 20th century the concepts of species evolution, including natural selection for chromosomally-inherited species separation as advocated by Charles Darwin, were increasingly accepted and touted. In contrast, the different theories of Jean-Baptiste Lamarck who advocated for environmental adaptation were gradually discredited [33]. The restoration of Lamarck's ideas began once the importance of transgenerational epigenetics and inherited environmental adaptation was recognized. According to strict Darwinian theory, rigidly fixed chromosomal gene incompatibilities that separate species result in hybrid lethality and/or sterility. But a major exception has been found through the work of Seth Bordenstein (Vanderbilt University) and others that shatters the strict Darwinian view of how species are separated and how that separation is maintained.

In some species, when an immune system is presented with a microbiome that was never encountered by prior generations, the immune system can react against the "foreign" microbiome and attack it. This can result in hybrid lethality in the offspring caused by a massive inflammatory response. In effect, the immune-microbiome dysbiosis inhibits successful reproduction and as a result, produces a new species. But this is not a rigid species separation as Darwin might have envisioned. Instead, it is "flexible" and environmentally adaptable in line with Lamarck's theories. For example, when species that are separated by immune-microbiome incompatibilities are treated with antibiotics (essentially eliminating the immune-offending microbiome), the species barrier goes away. The formerly different species are at least temporarily members of the "same tribe." Any lingering doubt concerning the importance of immune-microbiome interactions should be eliminated by these new scientific findings. The new scientific 21st century scientific dogma is:

1. That the superorganism (also called the holobiont) may well be the significant evolutionary unit and,
2. That immune-microbiome status can determine whether a new species exists or not [34-39].

It is worth considering that immune-microbiome dysbiosis resulting in immune-inflammation-inflicted NCDs may simply be a milder version of self-rejection (immune-microbiome incompatibility) than occurs via hybrid lethality across a species barrier. The key take-home lesson for healthcare from this new science is for good health and appropriately regulated inflammation, it is necessary to keep the immune system and the microbiome operating in sync.

**Dogma #3**

One of the dogmas of the 20th century that has been a challenge to overcome is the idea that the only good microbe is a dead microbe. The long history of incarnations of the germ theory of disease became paired with new tools: an arsenal of antibiotics. The result was what became an indiscriminate killing spree against bacteria. The ability to cure previously untreatable bacterial infections quickly turned into antibiotic overuse and an epidemic of NCDs [40,41].

The 20th century mantra of kill all microbes that still shows up in overuse of antibiotics as well as sanitizers/cleaning agents ignores three facts.

1. Elie Metchnikoff was an early 20th century Nobel Prize-winning immunologist. His contribution to science and medicine was in discovering macrophages and their functional capacity to phagocytize (engulf) and then kill bacteria. What is less well known is that Metchnikoff did not believe that all bacteria should be engulfed and killed. Quite the contrary. He was an early proponent of probiotics. Metchnikoff believed that consumption of probiotics led to a longer, healthier life [42].
2. Alexander Fleming was the discoverer of penicillin. His discovery led to the antibiotic revolution of the 20th century. Given the era in which Fleming worked and the importance of his discovery in saving lives, one might assume that Fleming was
a proponent of the mantra that “the only good microbe is a dead microbe.” But this was not the case. Alexander Fleming loved microbes and was a pioneer in creating art using pigmented bacteria and fungi [43,44].

3. The reality is that we as human superorganisms are by several measures mainly microbial [45]. The killing of bacteria by antibiotics beyond the specific target pathobiont is, in reality, the destruction of a necessary part of our body. It has been a challenge for healthcare to place the human microbiomes in the category of vital organs [46]. But 21st century science indicates that is precisely the role played by our various microbiomes (gut, skin, airways, urogenital tract, breast tissue and breast milk). Table 1, Dogma 3 illustrates the vital role played by our friendly microbes, which includes not only regulation of the immune system and control of neurochemical, hormonal, and metabolic functions, but also the front-line defense of colonization resistance against pathogens [47-53]. Ironically when our friendly microbes are killed, we are at greater risk of infections [54] as well as NCDs.

Dogma #4

In an era in which the medical priority was to sanitize humans of any and all microbes, protection of human microbiota was viewed as not only illogical but also potentially harmful for human health. As the result and as described in Dietert and Silbergeld [55] one of the driving forces in standardizing 20th century human health protection (the U.S. National Research Council’s 1987 model for environmental expos health risk assessment) completely excluded the microbiome.

In the 21 century’s era of the microbiome, this is a particularly egregious omission, because the human microbiome occupies what are known toxicologically as the routes of human exposures (the skin for dermal exposures, the airways for inhalation exposure, the gastrointestinal tract for oral exposures, the urogenital tract for urogenital exposure). Additionally, the human microbiome has massive metabolic activity. As a result, it is not surprising that the microbiome exerts a major influence over precisely what chemicals in what concentrations are delivered across barriers to our mammalian cells. The microbiome affects the internal exposure dose to potential toxicants (and ultimately the exposome over the life course). The critical role of the microbiome in environmental health risk assessment for human health protection has made National Research Council’s prior 1987 model (and a continuing guide) increasing irrelevant [55].

Table 1, Dogma 4 points out that continuing into the 21st century, regulated safety testing has remained focused on the single-species human mammal rather than the human superorganism. Furthermore, the legacy of failure to identify prior risk to the human microbiome, as drugs, food, food additives and environmental chemicals were approved for use, means that countless drugs, food and food additives, and environmental chemicals are utilized that are toxic for human commensal microbiota. It means that we must think well beyond just antibiotics for products that damage/destroy the human microbiome and promote both communicable diseases and NCDs [55-62].

Dogma #5

One of the major 20th century dogmas (Table1, Dogma 5) regarding human disease is that all diseases may be divided into two distinct categories: communicable (infectious) diseases and noncommunicable (or non-infectious) diseases and conditions. In a stunning reversal of the way of categorizing disease, the boundary between communicable and noncommunicable diseases has been shown to be soft rather than hard and, quite possibly, non-existent [63-67]. This means that while the ever-expanding number of medically-coded NCDs (driven by expansion in the number of autoimmune diseases and conditions) is contracting when it comes to cause/core underlying dysfunction (i.e., misregulated inflammation) [68,69], there is a convergence between communicable and noncommunicable disease categories [63-67]. The reality is that human disease is not as overwhelming and complex as previously thought. This raises serious questions as to whether we really need the ever-expanding plethora of prescription drugs and complex treatment protocols or if simpler core cures eliminating multiple disease conditions are within reach? That would be a significant step toward sustainable healthcare.

Dogma #6

One of the gross misrepresentations of microbiome-immune dysbiosis and the loss of resiliency (via loss of colonization resistance) is the recent public health supposition that humans are ill-suited for life within earth’s environments. This is Dogma #6 in Table 1 [70-80]. We are constantly told that we have to be protected from Earth, its dangerous microbes, and its unhealthy environments. The reality is that we should be immersed in that which makes us complete and strong as superorganisms. We need more microbes not fewer. We need more exposure to soil and farm-associated microbes [81-83]. The suggestions that we should fear microbes and pursue more medical care, more drugs (increased polypharmacy), more protective gear, an increasingly sanitized living environment, and less human-human contact would only further damage our microbiomes and make us increasingly immunologically compromised as an outcome. This dogma must be rejected if we are ever to pursue sustainable healthcare. Transhumanism is only the illusion of health. Instead, the solutions are within earth, its microbial life, and its environments and in the human-human, human-animal, and human-nature contacts that helped our indigenous peoples/ancestors to thrive.
Akkermansia muciniphila

The immune system was not asked to mount any assessment. Tier 1 screening is performed using an unchallenged developmental toxicity as a priority over immune functional assessment. Tier 1 toxicity screening lacks direct immuntoxicity testing and, in particular, the lack of functional immune assessment is problematic.

A second problem concerns the default testing protocols when immunotoxicity testing is required. There is a significant reliance on one functional immune test: the T-dependent antibody response or TDAR [95]. In this case, the TDAR (which came into favor during the HIV-AIDS era) is designed to detect suppressed antibody production as opposed to elevated or inappropriate antibody production as might occur with allergic or autoimmune diseases. Of course, the immune biomarkers that are associated with today’s most prevalent life-threatening diseases are connected to inappropriate inflammatory responses [69]. One example of these would be: the cytokine storm, an immune response problem experienced as a serious complication of Covid-19 infection [96]. Note that immunotoxicity testing can be performed that would detect inflammation-based problems arising during a pathobiont challenge. An example would be host resistance-immune assays in lab animals using influenza challenge [97]. However, while highly relevant to current day concerns and permitted under second tier analyses by the U.S. FDA, these types of immune functional analyses during pathobiont challenge in mucosal tissues have not been routinely required in regulated safety assessment.

As a result, the mystifying relegation of immune health risk assessment to an evaluation of secondary importance and the predominant use of non-disease-relevant functional biomarkers (i.e., TDAR) when the assessment was required does little to flag potential immunotoxic risk factors contributing to metabolic syndrome, cardiovascular disease, or cancer. We can and should do better to ensure that when toxicological assessment is required to be performed, it has relevance to the dysfunction that promotes human disease. Our knowledge of commonalities among NCDs should drive a revolution in regulated safety testing that focuses first on the microbiome and immune interconnection in mucosal tissues (e.g., the microimmunosome).
Conclusions

Sustainable healthcare can be within reach. But the regulatory, medical, pharmaceutical, healthcare, and public health communities must be willing to:

a) Reject outdated scientific dogmas,

b) Embrace the human superorganism as both the patient and the target for environmental protection, and

c) Fully implement prime directive policies that protect human microbiomes and the human immune system. They must be willing to protect the microbiome and immune system and to first and foremost correct dysbiosis in the microimmunosome.

The end result of such changes by these communities is that there would be a reduction in healthcare needs. Those communities could shrink in size and influence because there would be a reduced demand for pharmaceuticals, doctor visits, and hospital visits. The potential future impact of disease-empowered organizations (e.g., World Health Organization, Centers for Disease Control and Prevention, CDC, National Institutes for Health, National Health Service, UK, and the U.S. Food and Drug Administration) would be reduced. Are we willing to accept that?

Such change in thinking and operations is a critical part of achieving sustainable healthcare.

There are ample reasons to soundly reject the current healthcare system and its status quo. It features:

1. An ever-expanding number of medically-coded human diseases,

2. Increasing numbers of new drugs specific for each disease,

3. Increasing treatment protocols specific for each new disease,

4. Increasing prevalence of co-morbid NCDs, and

5. Increasing human vulnerability to infectious diseases/ pandemics.

Of course, we now know that these negative outcomes for human health are based, at least in part, on current preventative and therapeutic medical treatments, regulatorily-approved environmental chemical use, and the predominant foods on grocery store shelves that all contribute to the destruction of the human microbiome. Combined, this healthcare/health protection system has increased human disease, increased medical needs, increased human suffering, and reduced human quality of life. As humans, we are superorganisms and a reflection of all life on earth. The healthcare system needs to treat us as such.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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