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GERM THEORY AND MICROBIOTA: REINTERPRETING CONCEPTS AND DEFINITIONS IN HEALTH AND DISEASE

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NEW INSIGHT INTO THE NATURE OF THE MICROBIOTA

According to *Merriam-Webster*, microbiota refers to the microscopic organisms inhabiting a particular environment[1]. The older term "flora," used by Metchnikoff in 1908, is now considered a misnomer because it originally described plants rather than microbes[2]. Microbiota may be understood as a community of organisms — whether living cells or nonliving replicators such as viruses, viroids, and prions — that inhabit a given habitat. This community comprises several sub-communities, including the bacteriobiota, mycobiota, archaeaobiota, protozoobiota, virobiota, and others, and its mere presence does not inherently indicate disease[3,4].

Traditionally, the term microbiota referred only to commensal and mutualistic organisms. However, since the pioneering work of Joshua Lederberg and Alex T. McCray, the concept has expanded ecologically to encompass the entire microbial community associated with the host. This broader perspective recognizes multiple sub-types, including commensals, mutualists, opportunists, pathobionts, dormant forms, and latent organisms[5,6]. From this viewpoint, microbes are not inherently pathogenic but function primarily as ecological participants, often beneficial. At the same time, pathogenicity arises secondarily when the host-microbe-environment balance becomes disrupted (i.e., condition- or context-dependent). Several species, including *Streptococcus pyogenes, Staphylococcus aureus*, *Candida albicans, Streptococcus pneumoniae, Escherichia coli, Enterococcus spp*., and *Neisseria meningitidis*, typically reside harmlessly[7]. Yet under unfavorable ecological conditions, these same organisms can misbehave and become pathogenic, illustrating the dynamic, context-dependent nature of microbial behavior[8].

THEORIES OF DISEASE ORIGIN

Since the earliest times, humans have sought to understand the origin of disease to explain suffering, predict outcomes, and identify means of prevention or cure. In ancient cultures, disease was frequently attributed to supernatural forces or divine punishment[9]. Gradually, naturalistic explanations emerged and replaced these earlier beliefs. This ongoing search for causation gave rise to successive "frameworks" including miasma theory "bad air causation"[10], germ theory "microbe centered causation"[11], terrain theory "host's internal environment"[12], ecological theory "external environment"[13], socioecological theory "ecosystem and social determinants"[14], and most recently the One Health concept (integrating human, animal, and ecosystem health)[15]. Each reflects the scientific knowledge and societal priorities of its era.

GERM THEORY: AN OBSOLETE AND REDUCTIONIST CONCEPT

Germ theory, though revolutionary in its time, is now regarded by many scholars as obsolete, oversimplified, reductionist, over-inclusive, and outdated[16,17,18,19]. Within this framework, microbes are assumed to colonize the host, multiply, and directly produce diseases.

Clinically, germ theory led to transformative medical practices, including sterilization, disinfection, antibiotic therapy, and vaccination. However, it also initiated an enduring and relentless war against the microbial world. However, while these measures have saved countless lives, their extensive and indiscriminate application has produced profound long-term health consequences, including the emergence of antibiotic resistance and multidrug-resistant (MDR) strains, persistent treatment failure of microbe-associated diseases, and, in some cases, organ failure and other serious complications. In contrast, contemporary insights from the discovery of the human microbiota reveal a different perspective: microbes are not inherently enemies to be eliminated but vital partners whose restoration and ecological rehabilitation are essential for health[20].

A critical shortcoming of germ theory is its disregard for beneficial microbes and its failure to account for the host-microbe-environment interaction. Instead, it portrayed all microbes as fixed enemies that had to be eradicated for health to be maintained[10].

Conceptually, this reductionist framework also produced many misleading terms, such as contagion, contagious diseases, infection, infectious diseases, pathogen, pathogenicity, virulence, virulence factors, and microbial eradication. Despite its limitations, this outdated perspective continues to influence modern medicine and public health discourse[11,21].

KOCH'S POSTULATES AND MICROBIOTA

Robert Koch developed his postulates as a practical framework to support germ theory by linking a specific microbe to a particular disease. However, these postulates contain several fundamental flaws that render them oversimplified, misleading, reductionist, and largely unacceptable today[16,22]. The discovery of the human microbiota — present in both health and disease without producing clinical manifestations — undermines the validity of the first postulate[16,22]. The existence of slow-growing, fastidious, and unculturable microbes makes it impossible to fulfill the second postulate in many cases. Furthermore, host factors, the neglected role of the microbiota, and the context-dependent nature of disease, combined with the impracticality of the latter postulates, render the third and fourth postulates unrealistic and unachievable[22,23].

REALITY OF PATHOGENS

Scientists have long debated the proportion of microbes that are pathogenic to humans. Some estimates suggest that human pathogens account for far less than 1% of all microbial species on Earth. In contrast, others argue that only about 1 in 1,000,000 microbial species can cause disease in humans. A pathogen is simply defined as a microbe capable of causing disease.

However, modern medicine has revealed a more nuanced reality: no microbe is inherently pathogenic. Even organisms traditionally considered commensals can act as pathogens, a coin with two sides under certain conditions[24]. Whether a microbe causes disease depends on host factors (such as immunity, age, genetic makeup, microbiota balance, and nutrition), microbial characteristics (including virulence factors, route of entry, and microbial dose), and environmental influences (including stressors and ecological context)[25].

As a result, concepts such as pathogenicity (the capability of a microbe to cause disease), virulence (the degree of harm or tissue damage induced), and disease outcome (clinical manifestations) are all context- or condition-dependent. From this perspective, the notion of a strict pathogen is obsolete. Instead, microbes exist along a spectrum of potential interactions with their hosts, shaped continuously by internal and external environments. Moreover, life without microbes is impossible; they act as immune tutors, training and educating the immune system, supporting metabolism, and maintaining health[26-28].

MICROBIOTA AND BENEFITS TO HUMAN BEINGS

Every human being harbors a unique community of trillions of microorganisms in and on the body, collectively known as the microbiota or the "hidden organ"[29]. Far from being a passive or static collection of microbes, the microbiota is a dynamic ecosystem that plays fundamental roles in human health[30].

Microbiota are not villains; rather, they are profoundly and essentially beneficial. They educate the immune system and support the maturation of both innate and adaptive immune responses. Gut microbiota, for example, helps establish oral tolerance and train immune cells to distinguish between harmless antigens and real threats[20,31,32].

The microbiota also contributes to restoring and maintaining microbial diversity after disturbances. In addition, it modulates numerous host functions, including structural integrity (reinforcing the gut barrier), physiological regulation (gut-brain signaling), metabolic processes (fermentation of dietary fibers into short-chain fatty acids such as butyrate, acetate, and propionate), and protective defenses (colonization resistance against invading microbes).

It is also essential for vitamin synthesis (e.g., vitamin K and several B vitamins), bile acid metabolism (conversion of primary to secondary bile acids), and cholesterol balance. Beyond immediate host functions, the microbiota provides an ecological and evolutionary role, serving as a vast reservoir of genetic diversity[33].

This reservoir enables rapid microbial adaptation and innovation within the host environment, contributing to resilience against changing diets, exposures, and ecological pressures. In this light, the microbiota should not be viewed through the outdated concepts of infection and pathogens, but rather as a dynamic partner essential for human health[34,35].

MICROBIAL NEWCOMERS, MICROBIOTA DYNAMISM, AND BIODIVERSITY

Microbiota generally originate from either exogenous or endogenous sources. Exogenous acquisition (ecological seeding) usually requires microbial transmission through air, food, direct and indirect contact, vectors, or parenteral routes[36]. In contrast, endogenous microbial exposure does not depend on transmission or entry processes.

The steps by which microbial newcomers are exogenously introduced mirror those required for contagion: microbial shedding (from animate or inanimate sources), transmission, exposure, entry, and subsequent interactions with the host, ranging from coexistence and co-adaptation to colonization or infection (a specialized form of colonization). The outcome may be the incorporation of a new commensal member of the microbiota or pathogenic activity causing tissue damage and disease if the ecological balance is disrupted[36].

Introducing newcomers increases microbial diversity, which contributes to the biodiversity of the microbiota[37]. Yet, biodiversity itself is a relatively static concept — more like a catalogue of microbial presence than a process in motion[35].

MICROBIOTA BIODIVERSITY

Human beings are increasingly viewed as superorganisms composed of an amalgam of both microbial and *H. sapiens* cells[38]. Vaginal delivery, perineal contact, and breastfeeding represent uncontrolled, unintentional sources of microbial newcomers for newborn infants, enriching the developing microbiota and broadening its biodiversity. In contrast, deliberate enrichment and seeding practices after birth include cultural and medical interventions. A traditional Muslim practice, Tahneek (oral seeding), and more recent strategies, such as vaginal seeding for infants delivered by cesarean section, are examples of uncontrolled but deliberate microbial transfer. On the therapeutic side, controlled, deliberate enrichment, such as fecal microbiota transplantation and probiotic administration, is applied to patients with dysbiosis or other gut-related disorders[39].

In this context, the term *zoonotic* is a relic of germ theory, a misnomer and misleading concept, because it implies direct transmission of diseases. In reality, what occurs is the transmission or exchange of microbes among different species, and only under specific host-microbe-environment interactions might this microbial exchange lead to illness[11].

DYSBIOSIS OVER CONTAGION

Dysbiosis—the imbalance among microbial communities, whether bacteria, viruses, protozoa, fungi, or archaea within a specific niche—offers a more comprehensive explanation for many diseases than the traditional concept of contagion. The idea of contagion is oversimplified as it reduces disease to exogenous sources while overlooking the endogenous ones. In reality, microbial proliferation or activation may occur endogenously when resident microbial communities (microbiota) are disrupted. For instance, oral candidiasis (thrush) or vaginal candidiasis (vaginal moniliasis) often follow antibiotic therapy or immune suppression (e.g., diabetes or pregnancy). At the same time, dysbiosis of the pharyngeal virobiota may result in viral pharyngitis arising from resident viral populations[40].

Beyond clearly microbe-related conditions, such as irritable bowel syndrome, metabolic disorders, asthma, and autoimmune diseases, where microbial disturbance plays an indirect but pivotal role, many bacterial, fungal, and viral, and even non-microbial conditions may be better understood as outcomes of dysbiotic states. This perspective emphasizes microbial equilibrium as a cornerstone of health and disease[29,39-41].

Collectively, current evidence indicates that disease development is more often endogenous than exogenous, as internal dysbiosis can be readily induced by factors such as antibiotics, dietary shifts, stress, immune suppression, or aging. Such microbial imbalance enforces resident communities to shift toward pathogenic behavior[42].

CONTAGION: AN IMPOSSIBLE AND PROLONGED JOURNEY

Contagion, a social and epidemiological concept rather than a precise microbiological one, is fundamentally an oversimplified and reductionist process. Rooted in germ theory, it implies that disease spreads through direct or indirect contact from a diseased person to an apparently healthy one. Before the 19th century, contact with a sick person was simply believed to cause illness. In the 19th century with the rise of germ theory, contagion came to represent microbial spread, meaning that microbial transmission by contact is necessarily followed by disease transmission. However, many additional routes of microbial transmission other than contact were later recognized, rendering contagion only one limited pathway among many[16,36,43-45].

It is impossible to prove the absence or presence of an implicated microbe in a susceptible host before disease develops[24]. Furthermore, germ theory and Koch's postulates, once considered foundational, are insufficient today, especially after discovering that most microbes are harmless or beneficial[33]. Viewing germ theory as an outdated concept implies that the idea of contagion is scientifically limited and incompatible with modern microbiology[22,23]. Moreover, even if close contact occurs and a microbe is transmitted, disease may not follow; disease outcome depends on a complex interplay between host factors, environmental influences, and microbial characteristics. For contagion to succeed, each step of its long journey must occur without interruption.

That journey begins with microbial shedding from an infected person, contaminated surfaces, or fomites in sufficient numbers. Some people may shed the microbes without showing any symptoms. If microbial shedding is minimal, this very step fails, preventing progression to the next one. If shedding is adequate, transmission occurs, carrying the microbe to a susceptible host through air, contact, vectors, fluid, and other routes.

Yet transmission itself may fail because of environmental inactivation or poor transfer efficiency. If transmission succeeds, the microbe must next encounter the host (exposure) at the host entry sites. Should it fail to adhere to or remain on these external surfaces due to host defenses, it will be expelled from the host. Even if it crosses these barriers (entry), innate immunity may still eliminate it before establishment. If the microbe persists, coexistence begins, involving interactions with both the host and the resident microbiota. This coexistence may also fail due to displacement, competition for nutrients, or incompatible ecological niches.

Suppose coexistence succeeds, co-adaptation follows, though this too may fail due to immune rejection or niche incompatibility. When co-adaptation is successful, colonization or infection begins, and the microbe may either become a new member of microbiota or act as a pathogen that damages host tissues, producing disease.

In conclusion, the path from a microbial source to clinical disease is complex, multifactorial, and filled with checkpoints — most of which fail before the endpoint is reached. For contagion to truly succeed, every step must occur in sequence, and every barrier must be overcome, making it a fragile and improbable process. Thus, the journey of a contagion is better seen as an impossible, long journey rather than an inevitable outcome[11,45].

REALITY OF INCUBATION PERIOD

The concept of the incubation period is another flaw of germ theory, reinforcing the linear, reductionist assumption that one microbe causes one disease. Traditionally, the incubation period is defined as the time elapsed between the entry of a microbe and the onset of clinical manifestations. Yet in reality, no one can prove the exact moment of microbial entry except under artificial experimental conditions. The supposed causative microbe may even arise endogenously, rendering the notion of a fixed incubation period meaningless. Thus, the incubation period is inherently blurred, uncertain, and variable.

A fundamental ambiguity remains: what is being incubated, the microbe or the disease? If it is the microbe, the definition becomes unreliable because microbial presence, behavior, and activity depend on interactions with the existing microbiota, its dynamic fluctuations, and host-microbe-environment interactions that remain insufficiently understood. Moreover, many microbes persist in a latent, dormant, or harmless state long before clinical manifestations appear, making it impossible to define their incubation period. On the other hand, if it is the disease that is incubated, then by the same logic, non-microbe-associated diseases should also have an incubation period, which they do not[46-49].

In conclusion, the incubation period is a misleading, non-fixed, blurred, and profoundly context-dependent concept[50].

MEDICAL PRACTICE

Many clinical approaches remain strongly influenced by germ theory. Routine reliance on culture and sensitivity tests—performed on urine, stool, pharyngeal swabs, nasal swabs, ear swabs, conjunctival swabs, and skin lesion swabs—often overlooks the broader host-microbe-environment interaction. Furthermore, *in vitro* antibiotic sensitivity testing does not necessarily reflect the complex reality in vivo, where host immunity, microbiota interactions, and internal environmental conditions all shape therapeutic outcomes[51].

In conclusion, germ theory does focus solely on the microbe, neglecting the surrounding microbial ecosystem. The isolated fast-growing organism is typically considered the culprit; however, other "suspects" must also be considered. Meaning that every possible player, whether microbe (bacteria, viruses, fungi, protozoa, archaea) or non-microbe (metabolic, immune, stress-related factors), should be evaluated before attributing causality. Importantly, microbial behavior is context-dependent: a microbe may shift from a beneficial to a harmful role when the environmental or host conditions are disrupted[52,53].

REALITY OF VIRULENCE FACTORS

Current research emphasizes microbes as direct causative agents of disease, frequently based on the detection of so-called virulence factors. Traditionally, virulence factors – including adhesins (pili- fimbriae), invasins, toxins, capsules, iron acquisition systems, and others – were considered biological "weapons" or defensive tools that allow microbes to invade, attack, evade immune responses, and damage host tissues in a seemingly hostile conspiracy for survival. This perspective has shaped much of modern research, leading to diagnostic and therapeutic efforts that focus on identifying and targeting these factors[53].

In reality, however, many of these factors are equally present in commensals as in those historically labeled as pathogens[54]. The key difference lies not in their mere presence but in the regulatory context in which their activity is carried out. These traits are more accurately understood as microbial fitness factors or ecosystem modulators, features that enhance survival, adaptation, and coexistence within complex microbial communities[55,56]. Rather than being strictly destructive, these traits help maintain balance among microbial co-inhabitants and may even indirectly benefit the host.

For instance, microbial lipases and proteases facilitate nutrient acquisition from their environment. Adhesins enable commensals to achieve stable colonization, promote biofilm formation, and mediate niche-specific crosstalk, while invasins enable microbes to enter host cells, a specialized form of colonization. Toxins can shape microbiota communities by suppressing the overgrowth of competitors, thereby maintaining ecological balance. Commensals may employ secretion systems to educate or train the host immune system or to modulate inflammation.

Moreover, microbial cells are intrinsically dynamic; none of their genes or products is truly silent. Rather, it is the quantity, timing, and functional direction of expression that determine the outcome of host-microbe interaction. This perspective highlights the limitation of focusing solely on microbial traits while neglecting the host and environmental context. A more comprehensive approach is therefore essential—one that examines the dynamic interplay among host, microbe, and environment as the true determinants of disease outcome. In conclusion, virulence factors—often considered purely pathogenic—are in fact dual-purpose adaptation tools, whose activity reflects a contextual expression of standard microbial capacities rather than fixed, inherent properties[21,54,57].

MEDICAL OUTREACH

Organizations, such as the World Health Organization (WHO), ministries of health, and diverse media platforms, should work together to educate both healthcare professionals and the public about the dual nature of microbes. The goal is to reduce unnecessary fear of microbial transmission and to encourage practices that promote a balanced host-microbe-environment interplay, rather than focusing solely on microbial eradication. For a healthy environment, emphasis should be placed on simple hygiene measures, such as cleaning with water and soap, and ensuring access to clean drinking water, while discouraging excessive use of disinfectants that may disrupt microbial balance. For a healthy host, life adjustments are crucial, including adequate sleep, balanced nutrition, proper hydration, and moderation of caffeine-containing foods and beverages. Maintaining healthy microbes, promoting the responsible use of probiotics, and avoiding the misuse of antibiotics are essential strategies to support and restore microbial equilibrium[42,58,59].

THE REALITY AND MISUSE OF THE TERM ''INFECTION''

The term infection originates from the Latin *infectio,* derived from *inficere*, meaning “to put in”, “to dye”, “to stain”, or “to taint”[60]. Historically, it carried no implication of disease but rather described a process of interaction or entry. Its later association with pathology reflects the dominance of germ theory and its focus on microbial invasion.

In its strict biological sense, the term infection denotes a process by which a microbe colonizes or establishes itself within host tissues through invasion, growth, and multiplication[61]. The origin of infection may be exogenous, when a microbe arrives from outside, or endogenous, when a resident or latent microbe shifts into an invasive phase. Importantly, infection does not imply disease. It is a process that may or may not lead to disease, depending on the complex interactions among host, microbe, and environment[62]. Invasion alone does not necessarily imply pathogenicity; for example, virobiota – a component of the microbiota – can establish intracellular residence without causing harm under balanced conditions[25,26].

In conclusion, infection is unique and context-dependent, and should not be conflated with disease, transmission, or contagion[11,21,57]. It simply refers to a special type of colonization, often involving both intracellular and intercellular (extracellular) microbes, characterized by invasion, growth, and multiplication of a microbe within living tissues.

Similarly, the term *“infectious diseases”* is misleading as it presumes that diseases are caused solely by infectious microbes. Not all microbes are truly infectious, and the label “infectious” is not an intrinsic feature of a pathogen. For this reason, it is more accurate to use the term microbe-correlated diseases (MCDs). These can be described as falling into three types: obligate infectious MCDs, caused by microbes that actively invade host tissues (such as viruses, intracellular bacteria, and intracellular fungi); non-infectious MCDs, which are influenced by microbes that do not invade host tissues; and facultative infectious MCDs, in which microbes may invade tissues only under abnormal conditions.

Diseases with no identifiable microbial implication or with unknown microbial correlation should be termed non-microbe-correlated diseases (NMCDs), such as diabetes mellitus, metabolic disorders, obesity, Alzheimer's disease, and many cancers. In reality, MCDs and NMCDs are deeply intermixed, and the boundaries between them are blurred rather than strictly binary (not two sharply separated)[33,37,42].

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Ethics Approval and Informed Consent

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