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'Germ Theory of Diseases' A Historical and Immunological Perspective

Alisan Yildiran MD*

Professor of Pediatrics Ondokuz Mayis University, School Of Medicine, Department of Pediatric Immunology-Allergy, Samsun-Turkiye, Turkey

***Corresponding Author**: Alisan Yildiran, Professor of Pediatrics Ondokuz Mayis University, School Of Medicine, Department of Pediatric Immunology-Allergy, Samsun-Turkiye, Turkey, Tel: 00903623121919, Email: yildiran@omu.edu.tr

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Summary

This article revisits the "Germ Theory of Diseases" from historical, philosophical, and immunological perspectives. Although the theory, shaped by the pioneering work of Henle, Pasteur, and Koch, became a cornerstone of modern medicine, scientists such as Virchow, Dubos, and Casanova argued that microbes alone cannot fully explain diseases, emphasizing the decisive role of host factors. Today, the concepts of the microbiome and virome reveal that microorganisms are not only harmful but also essential for human health. The gut flora, in particular, plays a critical role in immunity, metabolism, and the nervous system, demonstrating that microbes are indispensable for maintaining bodily balance. The origins of viruses, their modes of transmission, and the immunological functions of bacteriophages remain subjects of debate, while discoveries such as CRISPR highlight the evolutionary importance of microbial immune mechanisms. Furthermore, prions, transposons, and horizontal gene transfer show that genetic diversity and disease mechanisms extend far beyond the germ theory. In conclusion, I argue that the classical germ theory is insufficient in light of modern knowledge, that viruses must be redefined, and that microbiology and immunology should adopt a more integrative approach to understanding the role of microbes.

Keywords: Germ Theory; Microbiome; Virus, Bacteriophage; Mobile genetic Elements; Chirality

Introduction

‘Science has to be understood in its broadest sense, as a method for comprehending all observable reality, and not merely as an instrument for acquiring specialized knowledge.

Alexis Carrel from Rockefeller Institute, Nobel laureate

In this article, with the perspective of a 'clinical' immunologist, and with attention to its compatibility with history and philosophical logic, the following topics and their connections are discussed in order. It is tried to explain how important the place of 'microbiology', which started with germ theory, in our genetic knowledge is, but how it has not been explained correctly and sufficiently. The subject was much broader and more important than I had imagined. As the famous immunologist Janeway said forty years ago, perhaps immunologists need to "rediscover microbiology".

The classical germ theory is insufficient in light of modern knowledge, that viruses must be redefined, and that microbiology and immunology should adopt a more integrative approach to understanding the role of microbes in human health.

Germ Theory of Diseases before Microbiome Era

The "miasma" (Greek for poisonous vapor, equivalent to Latin for "virus") believed to cause diseases in Europe was first proposed by Henle in 1840 as the organisms we know today as microbes. In fact, there were others who proposed the theory of contagion vivum (infectious organism) before Henle. Pasteur was inspired by Casimir Davaine, who first demonstrated the pasteurization technique, which prevents infection by heating, and the agent of anthrax, but this information is not widely known (1).

The causal link between the agent and the disease was still unknown. Pasteur, who was not a doctor but a chemist, proposed that fermentation was caused by germs (microbes) and that diseases were also caused by germs. This led pathologists to become germ-microbe hunters (2).

Dr. Robert Koch, who discovered the tuberculosis bacillus, published his theory (Koch's postulates) in 1890, which contained criteria for describing the causative agent of an infectious disease. According to this theory, a specific disease must be diagnosed in every patient, the resulting agent must be cultureable, and the same disease must occur when administered to a healthy individual. This theory (Koch's postulates) has remained a cornerstone of microbiology and medicine to this day (3, 4).

The famous founder of molecular pathology (and therefore of today's modern medicine) Virchow, and von Pettenkofer, rejected Koch's theory. Von Pettenkofer even publicly drank the then-deadly cholera agent and didn't even get sick. Virchow, on the other hand (though unaware of molecular ischemia-reperfusion injury), believed that capillary occlusion and the accumulation of toxins in the tissue disrupted cell function (and I still believe he was absolutely right today) (5).

The theory suffered its first serious blow in 1936 the distinguished virologist Rivers said; Viruses could be identified with three negatives: they cannot be captured in bacterial strainers, cannot be seen under a light microscope, and cannot be grown in culture. He claimed that viruses could be indirectly identified by seroconversion, that is, by antibodies specific to that virus (4). Rivers' claim, seroconversion, continues to be the fundamental basis of vaccine production to this day.

However, viruses were abundant in the environment and in humans, and could also be present within cells (endogenous retroviruses). It was only in 1957 that Huebner realized this and determined that epidemiological findings needed to be added to Koch's theory to demonstrate a causal link between the disease and the agent. Huebner described this situation as a virologist's dilemma (4).

Microbiome

Hippocrates said 2,000 years ago, "All diseases begin in the gut." The term "microbiome" was first coined in 2001 by Lederberg, who described bacterial conjugation and transduction. Then, in 2006, O'Hara et al. brought it up under the name "intestinal flora: a forgotten organ." The microbiota was given to the community of microorganisms (1011/g) found in the large intestine, and their metabolites were understood to be essential to human physiology. Short-chain fatty acids (butyrate, propionate and acetate) are produced by anaerobic metabolism in the microbiome, of which butyrate may be promutagenic (6, 7). Disruption of the balance between the bacteria, bacteriophages, and human epithelial cells that make up the microbiome (dysbiosis, its opposite, symbiosis) must lead to the emergence of diseases (8). In short, microbes (germs) are essential for a healthy body (9). Dubos's views on the relationship between microorganisms and the host actually reveal his doubts about the germ theory (9), which will be discussed again below.

Germ-free mouse models showed that bacteria are necessary for the healthy functioning of the immune, respiratory, gastrointestinal, metabolic, endocrine, and nervous systems of the organism (10).

Here, an important question is whether the microbiome is present in the fetus. In the study of Stinson et al. they recruited 50 women undergoing non-emergency cesarean section deliveries with no evidence of intra-uterine infection and collected first--pass meconium and amniotic fluid samples. Full-length 16S rRNA gene sequencing was performed to allow high resolution profiling of the fetal gut and amniotic fluid bacterial microbiomes. All meconium samples and most amniotic fluid samples (36/43) contained bacterial DNA (11).

The question is whether the blood is sterile. In the early 1900's, Béchamp claimed that animal body fluids contained subcellular living particles (i.e., microzymas) that transformed into bacteria upon death and decay of the host. Also, Enderlein described small entities called endobionts and protits in human blood. Some recent live blood analysis studies suggest that pleomorphic bacteria exists in the blood of healthy people. However, Martel et al. study refuted these claims. Their findings showed that the phenomena observed during live-blood analysis are therefore consistent with time-dependent decay of cells and body fluids during incubation ex vivo (12). But, at least it has been shown that the bladder has a microbiome (13).

Virus (Formerly Miasma)

A filterable agent in tobacco mosaic disease (TMV) was first described in the 1890s (14). However, the concept of the virus has evolved considerably in virology since Stanley demonstrated what this agent resembled through crystallography in the 1930s. In the 1990s, Grmek defined virology as "an autonomous discipline at the intersection of genetics, cytology, bacteriology, and oncology" (15). It was even announced in the popular press that "a virus has been visualized for the first time" (16).

Viruses have long been neglected by evolutionary biologists and are thought to be derived from cells (17). Even as recently as the 1990s, there was debate about whether viruses were endogenous or exogenous, whether bacteriophages were viruses, and whether they were subject to natural selection. Because they lack ribosomes, their place on the Tree of Life remains unclear (15). How viruses spread also needs to be considered. Airborne transmission has never actually been demonstrated, so when describing airborne transmission, the term "according to current belief" is used (18).

Where did viruses come from? (What was their origin?) Three hypotheses have been proposed to explain the existence of viruses lacking the ribosomes and ATP necessary for protein production: the progressive, regressive, and virus-first hypotheses, which posit that the cell emerged first (19). The inclusion of bacteriophages in viruses also seems implausible. They do not infect humans and, in fact, only transduce bacteria (20).

Bacterial-sized viruses were first identified in nature and in patients in 1981. Their genomes were found to contain genes for

the cytochrome P 450 enzyme found in mitochondria, glycolysis, the tricarboxylic acid cycle, and the cytoskeleton. A similar family of giant viruses, the megaviricetes, is unique in containing genes related to DNA repair not found in other viruses. Why would a protein that replicates itself in another organism contain a repair gene? (21). who knows?

Virome

The genetic and transcriptional identity of mammals is defined in part by our coevolved virome, a concept with profound implications for understanding health and disease. The major components of the virome are the eukaryotic virome, endogenous viral elements, and the prokaryotic virome. Members of the virome influence the phenotype of the host in a combinatorial manner by interacting with other members of the microbiome and by interacting with individual variations in host genetics (Figure 1) (22). This figure was given for the purpose of visualizing what is said in the article.

Bacteriophages are the most common biological entities found in the gut virome (90%) and on Earth. Because their genes are so variable, it is difficult to find two bacteriophages with identical genomes (23).

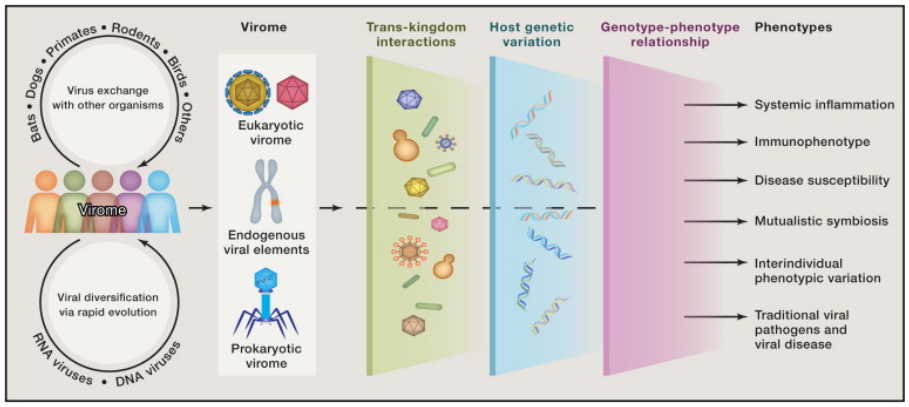

Figure 1: Components of the Virome and Their Relationship to the Genotype/Phenotype Relationship (22).

Bacteriophages and d'Herrelle

In 1952, the Hershey-Chase experiment proved that genetic information was contained in DNA, bacteriophages also entered the bacteria but, they leaved their sheaths outside (24). So, d'Herrelle was right whereas, Jules Bordet, who would win the Nobel Prize for his work on bacterial lysis, believed that this agent was a "self-sustaining catalytic enzyme." Another Nobel laureate, John Northrop, also supported Bordet's idea (25).

As a basic reminder, the lytic cycle of bacteriophages serves to reduce bacterial populations in the environment, while the lysogenic cycle alters the bacterial genome. While marine phages are mostly lytic, gastrointestinal phages are lysogenic. The innate immune system recognizes gastrointestinal phages using toll-like receptors and nucleic receptors (like RIG-1). Since bacteriophages (as the name suggests) do not infect mammalian cells, why does this phage recognition system exist? Bacteriophages have not yet been shown to replicate in eukaryotic cells (e.g., human cells). Do bacteriophages have more important immune-related functions in metazoans? It's noteworthy that Portillo and his colleagues also ask this question (26). Researchers are only now starting to suspect that phages actively contribute to the homeostasis of the bacterial flora (27). Bacteriophages are the most common biological entities found in the gut virome (90%) and on Earth. Because their genes are so variable, it is difficult to find two bacteriophages with identical genomes (23).

Let's talk about what happened to d'Herrelle who was actually a very important, yet unfortunate, figure in immunology and microbiology. The phage therapy he developed was widely used in infections until the 1930s, and he even commercialized it. Famous novel "Arrowsmith" inspired him was even written about these developments. However, he was quickly forgotten be-

cause he sided with the founders of immunology like Metchnikoff, Bordet, and Erlich because of he opposed vaccines. He particularly argued that BCG and cholera vaccines (which only make people sick) were dangerous. This jeopardized the production of antibiotics and vaccines (28).

Are bacteriophages virus? I think it has nothing to do with. Strathdee et al wrote that 'phages are viruses and have all the common viral properties: they do not replicate outside of their host, they have relatively small genomes, they make extensive use of host machinery for their replication, and they exhibit tight host cell specificity' (29). However, bacteriophages inject their genetic material to the bacterial cytoplasm leaving their envelope outside (Hershey Chase experiment). There is no eukaryotic virion like this. Also, bacteriophage virion could be cultivated and isolated via plating method easily but eukaryotic viruses not (30). The discovery of CRISPR, the mechanism by which prokaryotes and archae develop immunity against bacteriophages, was awarded a Nobel Prize in 2020. However, it was previously thought that immunity existed only in vertebrates. A region of prokaryotic DNA, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), is a system that provides protection against viruses and other mobile genetic elements through its effects on DNA and RNA, acting on a single cell. The point I want to draw your attention to here is the use of the word "virus," yet these are not viruses as we (currently) understand them, but bacteriophages (31).

In addition to protecting bacteria from phage invasion, the CRISPR-Cas system has been shown to play a role in genome evolution, DNA repair, and altering bacterial virulence. Therefore, the potential use of this system in the treatment of genetic diseases has been raised (31). Could this mechanism also be used in gene flow between species in nature? Otherwise, how can we explain the presence of 223 bacterial genes in the human genome (32)?

Our cells also have an intrinsic immunity similar to the immunity of bacteria, but this is not discussed separately in basic immunology textbooks. Intracellular immunity is used particularly against retroviruses (33). Intrinsic immunity against viruses begins with recognition by pattern recognition receptors TLR and RLR and continues with type I interferon response (IKBKB, NFKB, interferon stimulating genes and JAK-STAT pathway). Another important intracellular mechanism is ubiquitination. This is the addition of ubiquitin (post-translational modification) to a protein chain produced from mRNA at the ribosome, which determines the protein's degradation by the proteasome, its localization within the cell, and its interaction with other proteins. Viruses have evolved to antagonize the host immune response by interfering with host ubiquitin-dependent signaling pathways or hijacking the cellular ubiquitination machinery to promote viral replication and pathogenesis (34).

Prions

In the eighteenth century, proteins were first named "protein" by Berzelius, from the Greek word "prota" (meaning "very important"), considering them to be the primary substance. In 1732, "Scrapie" (transmissible spongiform encephalopathy) that a progressive, fatal, and contagious disease affecting the nervous system of sheep and goats, first described. Later, in 1875, Cohn published the first classification of bacteria, and in 1891, Koch's postulates (actually published by Henle in 1846, AY) were published. Erlich first proposed antibody proteins against pathogens in 1891. In 1898, Ivanovski identified the pathogenic infectious agent that could be separated by a sieve and named it "contugium vivum fluidum" (living fluid), or simply "virus" (poisonous fluid). Stanley, who first crystallized a virus and characterized its properties, defined the virus as an "infection protein." The neurological disease identified by Jacob and Creutzfeld in 1920 remained unknown for the next 60 years. However, scrapie was suggested as a slow viral infection (due to its long incubation period) as early as 1938. Fraenkel-Conrat and Williams discovered in 1955 that nucleic acids not only encoded genetic information but also could be 'infectious'. In 1946, Gordon had shown that other viruses were inactivated by formaldehyde and could not cause disease, but scrapie could still cause disease, so the transmissible pathogen could not be virus.

In 1967, Alper demonstrated that the agent was also resistant to ultraviolet radiation. In 1983, Prusiner isolated the infectious

protein-based amyloid substance in sick animals, defining it as a prion (protein only), and won the Nobel Prize. But what was the source of this protein? Ultimately, prions were shown to be infectious misfolded proteins, while normally folded proteins did not cause disease (35). Thus, the prion hypothesis proposed a new system for information storage and transmission. Also, Koonin et al. recently grouped all infectious-material-containing nucleic acids as either selfish elements and/or viruses and used these terms synonymously (17).

Mobile Genetic Elements, Horizontal Gene Transfer and De Novo Genes

Barbara McClintock, who should be considered the mother of genetics after Gregor Mendel, the father of genetics, was only able to receive the Nobel Prize in 1983 for transposons, which she described as jumping genes in her studies on corn in the 1940s. Unfortunately, we will only learn the reason of delayed award in 2033 (36). Also in the 1940s, Avery demonstrated that genetic information in pneumococci is transferred by transformation. In bacteria, genetic information is also transferred by transduction and conjugation (37).

Transposons are found in all living organisms and regulate gene expression during development and adaptation. They have been called evolutionary machines because they can cause intragenomic chromosomal rearrangements (deletions, translocations, inversions, segmental duplications) and intragenic mutations. Transposons are divided into two groups: retrotransposons (LINE (long terminal repeat, LTR) and SINE (non-LTR)] and DNA transposons. Due to their high mutagenicity, transposons could be the source of viruses (38). Multicellular organisms have evolved in association with various mobile genetic elements, such as transposons. Fifty percent of the mammalian genome consists of these. Furthermore, the RAG1 and 2 genes of the adaptive immune system, which rely on VDJ recombination, are said to be related to the Transib transposon in vertebrates (39).

The exchange of genes between viruses and eukaryotes through horizontal gene transfer (HGT) is a key evolutionary driver capable of facilitating host manipulation and viral resistance. Host-derived genes are known to be employed by viruses for replication and cellular control. These transfers have important evolutionary, ecological and health implications; nonetheless, we lack a general understanding of the mode and functional importance of viral–eukaryotic gene exchange, largely due to the absence of standardized analyses across diverse taxa (40).

As early as the 1930s, J.B.S. Haldane and others suggested that copies of existing genes may lead to new genes with novel functions. In 1970, Susumu Ohno published the seminal text Evolution by Gene Duplication. For some time subsequently, the consensus view was that virtually all genes were derived from ancestral genes. De novo gene birth is the process by which new genes evolve from DNA sequences that were ancestrally non-genic. De novo genes represent a subset of novel genes, and may be protein- coding or instead act as RNA genes (41).

Eventually, some genetic mechanisms like alternative splicing and polyadenylation of messenger RNAs (mRNAs) provide additional layers of diversity to gene regulation. These processes and others contribute to transcriptome and proteome diversity, expanding the coding potential of the genome (42). So, the human genome possess approximately 20,000 protein-coding genes, yet the body produces over 100,000 distinct proteins. Although only ~2% of the human genome encodes proteins, ~80% of it is transcribed to RNA. Thus, the idea of the existence of 'junk DNA' was debunked, and many of the transcribed non-coding RNAs were shown to be involved in almost every level of gene expression regulation, with their expression being quickly adjusted to environmental changes. Various classes of non-coding RNAs, such as miRNAs, lncRNAs, piRNAs, etc., and the factors involved in their biogenesis, show variations in their levels in response to stressful stimuli (43).

Endosymbiosis, Ribosomes and Archeae

Lyn Margulis, who was labeled a denier for saying that AIDS was not caused by a virus and was shown among the top 50 wom-

en in science, put forward the theory of symbiosis (living together and benefiting from each other) and the bacterial origin of mitochondria in her book "The Origin of Eukaryotic Cells" published in 1970, despite not knowing the microbiome and DNA content (44).

Interestingly, from this view, a virus is similar to an intracellular organism, which therefore further blurs the boundary between cellular organisms and viruses. Carl Woese discovered the existence of three different ribosomes in the living world, which replaced the old prokaryote–eukaryote dichotomy with a trinity — archaea, bacteria and eukarya. All cellular organisms could thus be placed together in a universal tree of life. Thus, viruses were missing from this picture (45).

In addition to the bacteria and eukaryote groups in the analysis, there was a third group of methane-producing microbes. These methanogens were already known to be chemical oddities in the microbial world, since they were killed by oxygen, produced unusual enzymes, and had cell walls different from all known bacteria. While bacteria and eukaryotes have D-glycerol in their membranes, archaeans have L-glycerol in theirs. This is more than a geometric difference. Chemical components of the cell have to be built by enzymes, and the "handedness" (chirality) of the molecule is determined by the shape of those enzymes.

The side chains in the phospholipids of bacteria and eukaryotes are fatty acids, chains of usually 16 to 18 carbon atoms. Archaea do not use fatty acids to build their membrane phospholipids. Instead, they have side chains of 20 carbon atoms built from isoprene.

Isoprene is the simplest member of a class of chemicals called terpenes that beta-carotene (a vitamin), natural and synthetic rubbers, plant essential oils (such as spearmint), and steroid hormones (such as estrogen and testosterone) can be built (46).

No single archaeal pathogen has been discovered to date. Furthermore, it has been hypothesized that the development of numerous autoimmune, systemic, and allergic diseases, such as IBD, diabetes, or asthma, may be due to microbial dysbiosis rather than the presence of a single pathogenic microorganism (47). Isn't it worth thinking about?

Chirality

In chemistry, a molecule or ion is called chiral if it cannot be superposed on its mirror image (geometrically like our hands). This geometric property is called chirality. The terms are derived from Ancient Greek (cheir) 'hand'.

A chiral molecule or ion exists in two stereoisomers that are mirror images of each other, called enantiomers. While Pasteur was working on yeast at the age of 25, he discovered tartaric acid molecules must be chiral, due to some three-dimensional feature of their molecular structure, and that they are non-superposable-mirror-image (i.e., enantiomeric) molecules. In 1886, Italian chemist Piutti discovered enantioselectivity in what is considered today ‘receptor-mediated biological activity’. Chiroselectivity in biology and the intimate relationship between structure and function is important to understand organic molecules (48).

How the enantiomers are discriminated in several important biochemical pathways and why? The answers to the fundamentally important questions of how life (or biomolecules) originated on Earth and how the homochirality in biological system evolved remain largely unresolved at present. After the thalidomide disaster. It is recognized that the knowledge of effective chirality of a drug is must and now single enantiomeric drugs constitute a billion dollar industry (49).

Organisms use l-amino acids (l-aa) for most physiological processes. Unlike other organisms, bacteria chiral-convert l-aa to d--configurations as essential components of their cell walls and as signaling molecules in their ecosystems. Mammals recognize microbe-associated molecules to initiate immune responses, but roles of bacterial d-amino acids (d-aa) in mammalian immune systems remain largely unknown.

Proteinogenic amino acids other than glycine have chiral centers at the α carbon, with d- or l-configurations. Although d- and l-amino acids (d-/l-aa) have equivalent chemical properties, organisms exclusively use l-aa in ribosomal protein synthesis in all domains of life. To maintain l-aa predominance, metabolic pathways for amino acids are mostly chiral selective for l-enantiomers.

Unlike eukaryotes and archaea, bacteria have evolved a variety of amino acid racemases to stereo-convert l-aa into d-aa. Bacteria release d-aa to modulate diverse cellular processes, such as cell wall (peptidoglycan) homeostasis, growth, and biofilm formation in the bacterial ecological niche. Peptidoglycans are degraded by metazoan lysozyme, and degraded fragments, categorized as pathogen- or microbe-associated molecular pattern (PAMP or MAMP), activate innate immune responses via pattern recognition receptors (PRRs). These signals, mediated by PRRs, also modulate acquired immunity in mammals. Thus, bacterial structures containing d-aa are closely associated with antibacterial responses.

Mammals maintain l-aa dominance by expressing two flavin adenine dinucleotide– dependent oxidoreductases that degrade d-aa, d-aa oxidase (DAO), and d-aspartate oxidase (DDO) (50).

Little is known about the identity of microbiota-derived molecules that contribute to hepatic gluconeogenesis and lipogenesis. In a new study, it was shown that a chiral molecule microbial-derived D-lactate could contributes to host glucose and lipid metabolism and can be trapped to improve metabolic disease during obesity (51).

Another Problems

Single Cell Analysis, Virus Connection

It is estimated that more than 99% of microorganisms in nature are not cultivated. This situation is referred to as the "dark matter of biology." To study this biological matter, the culturing step is bypassed and metagenomics, that is, the method of obtaining the total DNA of the sample, is used. A challenge in metagenomics is the inability to obtain information specific to a single member of the complex microbiota. Single Cell Sequencing analysis has been developed for like this purpose (44, 45). When I searched for single virion genome extraction, the protocol article I found described phage extraction, but again, there was no eukaryotic virus extraction (52). Viruses cannot be obtained, but they can be cultivated in cell cultures, and in each passage, a 'virus' with a genome different from the previous one is obtained (53). Cultivation of viruses in cell cultures carries the risk of contamination, especially mycoplasma even bacteriophages (54, 55). To prevent this, antibiotics must be added to the culture, but this also leads to other problems in cell metabolism, such as apoptosis and protein degradation (56). Hilleman's observation is spot on and very important. 'Vaccines produced in cell culture are full of foreign genetic material and foreign viruses belonging to the cell culture in which they were produced, and also this could be carcinogenic (56, 57).

Sick cell and Extracellular Vesicles

Diseased cells, such as tumour cells, and injured or stressed tissues release molecules into the bloodstream, and these extracellular vesicles (EV) can be used to monitor the status of different tissues and organs without obtaining an invasive biopsy, and blood samples are, therefore, often referred to as a "liquid biopsy". EVs are small (40–800 nm) membrane-enclosed vesicles that are released by all cells into the extracellular space and they contain RNA, lipids, proteins, and DNA that can be shuttled to other cells to influence the recipient cell's phenotype. So they are exactly the size of the viruses. Including EVs, but also a dominating pool of lipid particles such as chylomicrons and multiple types of lipoprotein particles and plasma proteins, making blood one of the most difficult body fluids to isolate EVs from (57).

Craig Venter's Synthia

When considering germ theory, it's important to understand how humans impact the germline, or microbial world, and why microbes are so important. John Craig Venter, a lazy student with ADHD (attention deficit hyperactivity disorder), became a biologist and, after working at the NIH (National Institutes of Health), became one of the world's leading scientists and very wealthy. He deciphered the human genome (his own) and founded a longevity company with his friends. He attempted to patent genes with the 'expressed sequence tag' he developed, but gave up after a huge backlash (I wonder?). Venter is also the first person to succeed in producing a microbe that contains the minimum genes necessary for an organism. This is, of course, the 'mycoplasma', whose genome (consisting of around 500 genes) was first fully sequenced in 1995. Let us also remind you that Venter, the bad boy of biology, conducted plankton research on his yacht named Sorcerer in the Galapagos Islands, where Darwin acquired his ideas about evolution, and that he tried to create a new life form right after the human genome project (58). When it comes to the Sorcerer, it's hard to miss out on a mention. Did you know that Isaac Newton, the famous scientist and alchemist who gave his name to the "cell" and gave life to cell theory, and who was in competition with Robert Hooke, the so--called "Da Vinci of England," and who was even accused of plagiarizing him, was called "The Last Sorcerer" (59, 60)?

In fact, before Venter's synthetic bacteria, it is necessary to mention the 'chemical virus' that was formed by combining nucleotides that ensure viral replication; Wimmer obtained a genome-length double-stranded complementary DNA (cDNA) of about 7,500 base pairs that contained all the genetic information of the viral RNA genome. This synthetic cDNA was transcribed into viral RNA using a specific RNA transcriptase (van der Werf et al, 1986), thereby yielding infectious viral RNA (61). Therefore, viruses other than bacteriophages should be considered chemical substances that can be synthesized in a test tube; in other words, they are not pathogens but toxic substances. Therefore, could it be said that airborne transmission has not been demonstrated?

What Does Rockefeller University Say About Germ Theory?

Edgar Crookshank, who first discussed the importance of germ theory and the need for caution in the literature before Rockefeller University, but was forgotten because he was an anti-vaccine advocate. In his 1888 article, he accurately stated that while some infections are undoubtedly caused by microorganisms, this does not apply to all infectious diseases and is misleading. He also Host-microbe cross-talk controls amino acid chirality to regulate survival and differentiation of B cells approved the idea of Lawson Tait, Lister's teacher and opponent of vivisection, considered the founder of modern gynecological surgery, that microorganisms are often the post-product of morbid lesions (62). Many people don't know, but two of the editors of the Journal of Experimental Medicine, one of the most prestigious journals of this institute and medicine, have voiced differing views on germ theory in exceptionally important articles. Moreover, both of them are French and have worked in the field of microbiology.

René Dubos's new thoughts on germ theory

Dubos, who was actually a field agriculturalist and focused on soil bacteria and later on tuberculosis (9), talked about rabbit plague, which was an important problem at that time, in his article titled "New thoughts on germ theory" in 1955, he questioned why the disease did not always occur and for the first time said, "Everyone harbors microbes, but not everyone gets sick. This means that microbes are less important than other factors affecting the host" (63). This article is very simple compared to our current knowledge, but it is important because it is the first of its kind. Why is it important? It is also important that JL Casanova (who prefers to be called JL), who declared himself an admirer, shared his position, and was also a role model for the poor, explain it under the title "From second thoughts on germ theory to full-blown host theory" (64).

Jean Laurent Casanova's 'full-blown host theory' instead of germ theory

If I remember correctly, I had the opportunity to meet JL (Casanova) at a J project meeting in 2013. We have some work underway with him and his team in France. Let us review the following information given by JL, who was a student, compatriot and successor of Dubos, and who was obviously not satisfied with the germ theory even in 2007 (65); they describes 'infection': the multiplication of a microbe in a host. Primary infection: the first infection of a specific microbe in a host. Even they defined recently 'Infection Enigma' as immense interindividual clinical variability in the course of any infection, ranging from silent infection to lethal disease (66).

Why is a primary infection different for everyone? As can be understood, the two are different things, and the importance of primary infection is the danger of the immune system failing to respond appropriately and adequately to the infection encountered for the first time. He mentions that until the end of the nineteenth century, half of children under the age of 15 died from fever, and the average "life expectancy" was 20-25 years (67). However, life expectancy does not mean average lifespan, life span is one thing, life expectancy is another.

Infectious diseases, with the exception of plague in the 17th century and tuberculosis in the 19th century, had a very low fatality rate. Even those who died had an underlying genetic cause. This (still ongoing) is something microbiologists and infectious disease specialists overlooked because they focused on vaccine and drug development. At the same time, immunologists focused on the antibody conundrum, focusing on responses to non-infectious antigens. However, the presence of human determinants of infection was unprecedented due to the effects of immunosuppression, a situation that remained unchanged until the discovery of HIV. Furthermore, fatal primary infections could not be explained by acquired immunodeficiency, and these infections should be labeled "idiopathic—of unknown cause" rather than "opportunistic." JL and Abel argued that while the belief in the intrinsic cause of infectious diseases was growing, paradoxically the belief in the extrinsic cause was becoming more established, attributing this to the effects of vaccines. However, this only applied to secondary infections, not to primary infections (68).

In their last paper they deal with the extrinsic causes. Enhanced susceptibility can be driven directly by mutations in genes essential for control of the virus or indirectly via the production of autoantibodies against components of host defense. However, little is known about the impact of these human genotypes on the natural history of viruses, including not only persisting but also emerging viruses (69).

Different Opinions

Carlsson et al Opinion

Carlsson et al. consider the factors that determine disease severity using established knowledge concerning evolutionary biology, microbial pathogenesis, and host–pathogen interactions. They also defined that the available data support a non-centric view that recognizes key roles for both the causative microbe and the host in dictating infection outcome. They also note that the hypothesis of Casanova et al regarding so-called covert immunodeficiencies—which are assumed to exist but remain unknown—represents an unscientific conjecture as it cannot be falsified. They discuss what pathogen is, but they do not consider the molecular properties given above (70).

Another Opinion 'Contract Theory' of Dr. Konuralp

The preservation of life and the continuation of the species, whether single-celled or multicellular, on the planet we inhabit (the biosphere), and indeed throughout the universe, depends fundamentally on two main factors: 1. Providing sufficient and appropriate nutrients (needed substances). 2. Removing waste (harmful substances). In biology, every waste product has a recipient. In other words, what is harmful to you or unusable is food for someone else or a substance they can use. Newborns and the production of vitamin K by bacteria is a typical example of this intercourse. They can also collect dead and disintegrated cells belonging to the host or other foreign organisms for us, like scavengers. In other words, they perform wound debridement (me-

chanical cleaning) at the micro level. The result of the agreement being disrupted, usually epigenetically, for any reason is infection and/or inflammation (71).

Conclusion

In conclusion, I believe that, despite advances in microbiology, immunology, and genetics, germ theory has been consigned to obscurity by the molecular developments and some strong objections described above. I also believe that knowledge and definition about viruses needs to be revised, and their classification with bacteriophages should be abandoned. I hope that the information presented here can be used as a foundational tool, particularly in the field of molecular immunology.

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